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Clinical Review Criteria
Intraperitoneal Hyperthermic Chemotherapy (IPHC)

- Hyperthermic Intraperitoneal Chemotherapy (HIPEC)
- Intraoperative Chemo Hyperthermic Peritoneal Perfusion (CHPP)
- Intraperitoneal Hyperthermic Chemoperfusion (IHCP)

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Hyperthermia for Treatment of Cancer (110.1) **Per NCD: Covered in connection with radiation therapy for certain types of malignancies, not covered in connection with chemotherapy*
Local Coverage Determinations (LCD)	None

For Non-Medicare Members

Service	Criteria Used
Cytoreductive Surgery Perioperative Hyperthermic Intraperitoneal Chemotherapy	Cytoreductive surgery and perioperative hyperthermic intraperitoneal chemotherapy may be considered **medically necessary** for the treatment of: • pseudomyxoma peritonei • diffuse malignant peritoneal mesothelioma • ovarian cancer Cytoreductive surgery and perioperative hyperthermic intraperitoneal chemotherapy is considered **investigational** for: • peritoneal carcinomatosis from colorectal cancer, gastric cancer, or endometrial cancer; • all other indications, including goblet cell tumors of the appendix.
Intraperitoneal chemotherapy without hyperthermic methodology	Intraperitoneal chemotherapy without hyperthermic methodology is considered standard therapy and is not subject for review and is covered.

If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist

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Background

Colon Cancer

In the United States, approximately 108,070 patients are diagnosed with colon cancer (CRC) per year, and between 10-30% of these patients will develop peritoneal carcinomatosis (PC) at some point after their initial diagnosis. PC is characterized by intraperitoneal spread of tumor nodules in the peritoneum which may occur as a result of growth of the tumor and its invasion through the serosal lining of the bowel lumen, or as result of iatrogenic manipulation during surgical procedures. PC of colorectal origin has poor survival and is the second most frequent cause of death in patients with colorectal cancer (CRC), after metastatic liver disease. It has always been regarded as a terminal condition and was commonly treated only with palliative therapies (Franko 2012, Macri 2010, Ripley 2010, Chua 2012).

Over the last two decades, significant advances made in the field of cytotoxic chemotherapy and biological agents have changed the treatment of PC from a palliative to a potentially curative approach. Modern chemotherapeutic regimens have increased the response rate and median survival of patients with PC. However, few patients experience long-term survival with chemotherapy alone. In the 1980s a multimodal technique was developed to manage PC based on cytoreduction of the primary tumor, peritonectomy, and hyperthermic antiblastic peritoneal perfusion (HIPEC). Theoretically cytoreductive surgery (CRS) treats the macroscopic residual disease and intraperitoneal (IP) chemotherapy treats the microscopic residual disease. IP chemotherapy is based on the principle that a high concentration of chemotherapy within the abdominal cavity will kill the tumor cells on the surface with less diffusion into the tissues and thus are less toxicity. Hyperthermia with IP chemotherapy optimizes the process as heat has direct cytotoxic effects on cancer cells and increases the cytoactivity and penetration of certain cytotoxic drugs (Verwaal 2008, Macri 2010, Ripley 2010, Vaira 2010, Glehen 2010, Mizumato 2012, Chua 2012, Miceli 2012).

HIPEC is achieved by the intraperitoneal administration of a large volume of chemotherapeutic agents in a carrier solution through an open or closed technique. It involves the placement of one inflow and three outflow catheters in the abdominal cavity after the cytoreduction surgery. The cytotoxic agent is applied through the inflow drainage using a roller pump and heat exchanger in a closed system that allows perfusion circulation. The intraperitoneal temperature should reach 41-42oC and is monitored by two sensors placed in the inflow catheter and in the Douglas pouch. At the end of the procedure the solution is drained, and the abdominal wall is closed. There is no standardized procedure for HIPEC and there are variations between the centers in the combinations and/ or concentrations for the cytotoxic agents used, as well as the intraabdominal temperature and duration of the treatment which ranges from 30 minutes to 2 hours depending on the protocol of the drug used. The combination therapy of cytoreductive surgery and HIPEC is complex, has a steep learning curve, and is associated with significant morbidity and mortality. Preoperative selection of patients to achieve complete cytoreduction plays a crucial role for the success of therapy regarding the clinical and ontological outcomes as well as the patient quality of life (Glockzin 2009, Mizumato 2012).

There is controversy around the use of cytoreduction therapy and HIPEC for peritoneal surface disease from CRC, and the procedure is not widely accepted despite the Consensus Statement (issued by representatives from the major Peritoneal Surface Malignancy Centers from around the world) on the role of cytoreductive surgery and HIPEC in the management of peritoneal surface malignancies of colonic origin (Esquivel 2007).

Ovarian Cancer

Ovarian cancer is the fifth leading cause of death in women in the US and the most common cause of death from gynecological cancer in the Western World. It was estimated that around 22,280 women will be diagnosed with ovarian cancer and that 15,500 women will die of the disease in the US in 2012. Approximately two thirds of the women are diagnosed at an advanced stage due to the nonspecific nature of the presenting symptoms of ovarian cancer and its high tendency for early peritoneal spread. Peritoneal carcinomatosis occurs through exfoliation of malignant cells into the peritoneal fluid and their dissemination along the abdominal and pelvic peritoneum. Traditionally these patients with extensive peritoneal carcinomatosis were often labeled as having terminal disease and were only given palliative therapy with no curative intent (Chua 2009, Spiliotis 2011, Chan 2012, de Bree E 2012, Mulier 2012, Siegal 2012, Tentes 2012).

The standard therapy for patients with ovarian cancer is maximal cytoreductive surgery (CRS) followed by systemic chemotherapy with a platinum-based agent and a taxane combination. Ovarian cancer is one of the most chemosensitive tumors, and its response to this initial therapy is high, but the disease often recurs, mostly locoregionally, involving the peritoneum and adjacent intra-abdominal organs. The sensitivity of epithelial ovarian

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cancer to chemotherapy and its tendency to remain confined to the peritoneal cavity through much of its natural history, have led the researchers to investigate regional treatment such as intraperitoneal (IP) administration of chemotherapy (IPC). The theoretical benefits include the achievement of a high drug concentration in the peritoneal cavity without the toxic effects of the systemic chemotherapy. IP chemotherapy has been investigated in clinical trials including the Gynecologic Oncology Group (GOG-172) phase III trial that showed approximately 16 months improvement in the median survival of women treated with a combination intravenous (IV) and IP chemotherapy compared to those treated with IV chemotherapy alone, but on the expense of the increased risk of toxicity and catheter-related complications. Based on the results of this as well as other trials, the National Cancer Institute (NCI) issued a clinical announcement in 2006 recommending that women with optimally debulked stage III ovarian cancer and their physicians consider a combination of intravenous (IV) and intraperitoneal chemotherapy (IPC). IPC has limited tissue penetration and may be indicated only following optimal resection of peritoneal disease when there is either no or very small macroscopic disease remaining (<1.0 cm). The use of IPC however, is controversial and is not widely accepted by the medical community as a standard treatment in the management of advanced epithelial ovarian cancer, due to its high toxicity, catheter-related complications, and negative impact on the patients' quality of life (Almadrones 2007, Trimble 2008, Runowicz 2008, Lim 2009, Spiliotis 2011, Tentes 2012, Chan 2012, de Bree 2012).

In the last two decades researchers investigated the synergistic effect of combining regional hyperthermia and intraperitoneal chemotherapy (hyperthermic IPC, or HIPEC) together with the CRS. Theoretically, in addition its tumoricidal effect, hyperthermia increases the permeability of the drug to the tumor cells (up to 5-6 mm compared to 2-3 mm of the conventional IPC). Hyperthermia may also alter the cellular metabolism, and cellular drug pharmacogenetics. A potential advantage of administrating HIPEC intraoperatively is providing superior and homogenous exposure of the seroperitoneal surface to the drug and heat before the development of adhesions. The disadvantage of HIPEC compared to IPC is the shorter tumor exposure time and its administration only once during the surgery or at the most twice when a secondary surgery is performed (de Bree 2012).

Other primary peritoneal malignancies or secondary dissemination from gastrointestinal tract or other pelvic organs.
Primary peritoneal malignancies such as peritoneal mesothelioma or papillary serous carcinoma are rare, but peritoneal dissemination form gastrointestinal tract and ovarian carcinomas are common. In the past these carcinomatosis were regarded as terminal and the patients were only treated with palliative measures. Over the last 30 years however, novel more aggressive treatment strategies that combine cytoreductive surgery with intraperitoneal (IP) chemotherapy were explored. Hyperthermic intraperitoneal chemotherapy (HIPEC) and early postoperative IP chemotherapy emerged as the most commonly used IP adjuvant therapies. Theoretically cytoreductive therapy treats the macroscopic disease, and intraperitoneal chemotherapy (IP) treats the microscopic disease and the residual or free tumor cells left in the peritoneal cavity after surgery, in order to prevent and control peritoneal dissemination. IP chemotherapy is based on the principle that a high concentration of chemotherapy within the abdominal cavity will kill the tumor cells on the surface with less diffusion into the tissues and less toxicity. Hyperthermia with IP chemotherapy optimizes the process as heat has direct cytotoxic effects on cancer cells and increases the cytotoxicity and penetration of certain cytotoxic drugs. Hyperthermia is also believed to modulate the cells of the innate and adaptive immune system, thereby improving effectiveness (Shen 2009, Glehen 2010, Mizumoto 2012, Sun 2012, MI 2013).

Medical Technology Assessment Committee (MTAC)

Intraperitoneal Hyperthermic Chemotherapy (IPHC)

04/02/2007: MTAC REVIEW

Evidence Conclusion: *Prevention of peritoneal carcinomatosis* Two randomized controlled trials from Japan, conducted among patients who underwent surgery for T2-T4 gastric carcinoma with serosal involvement, found a significant benefit from including HIPEC treatment. The study with the stronger methodology (Yonemura et al., 2001) found a higher estimated 5-year survival in the group receiving cytoreduction and HIPEC (61%), compared to two other groups (cytoreduction and normothermic intraperitoneal chemotherapy, 44%; and surgery alone 42%). The other RCT (Fujimoto et al., 1999) had poorly described methodology, and also found a significantly higher estimated survival rate in a group receiving cytoreduction plus HIPEC compared to surgery alone. The first study had a minimum of 2.4 years of follow-up; length of follow-up was not reported in the Fujimoto study. Findings from studies on Japanese gastric cancer may not be generalizable to the United States. *Treatment of peritoneal carcinomatosis* There is evidence from one reasonably valid randomized controlled trial that HIPEC is beneficial as a treatment for peritoneal carcinomatosis (Verwaal et al., 2003). The study, which included 105 patients with histologically proven peritoneal metastases of colorectal adenocarcinoma, compared an experimental treatment (cytoreduction and HIPEC, plus adjuvant chemotherapy) to standard treatment (outpatient chemotherapy, surgery only if necessary). After a median follow-up of 22 months, the survival rate was

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significantly higher in the experimental treatment group (56% vs. 39%). Sub-group analyses suggest that survival was lower in patients with extensive residual disease or involvement of more than 5 regions of the abdominal cavity. A case series by the same research group found an estimated one-year survival of 75% and three-year survival of 28% with the experimental treatment. There were no long-term survival data for the standard treatment group. The evidence base would be strengthened with additional comparative studies.
Articles: *Prevention of peritoneal carcinomatosis* Three RCTs were identified: all were conducted by Japanese investigators. The two trials with the larger sample sizes (n=139 and n=141) were critically appraised. The third study was smaller (n=82) and had limitations including a non-significant finding with no discussion of statistical power. *Citations for the reviewed studies are as follows:* Yonemura Y, deAretxabala X, Fukimura T et al. Intraoperative chemohyperthermic peritoneal perfusion as a adjuvant to gastric cancer: Final results of a randomized controlled study. Hepato-Gastroenterology 2001; 48: 1776-1782. See Evidence Table. Fujimoto S, Takahashi M, Mutou T et al. Successful intraperitoneal hyperthermic chemoperfusion for the prevention of postoperative peritoneal recurrence in patients with advanced gastric carcinoma. Cancer 1999; 85: 529-534. See Evidence Table. *Treatment of peritoneal carcinomatosis:*
One RCT from the Netherlands was identified and critically appraised (Verwaal et al., 2003). There have also been a number of case series, most had sample sizes under 100. The largest case series was a multicenter study by Glehen et al., 2004 and included 506 patients. This study was limited in that it combined data from different centers that had different protocols and patient populations. All of the centers used perioperative intraperitoneal chemotherapy, but it appears that not all used hyperthermic treatment. As a result, the Glehen article was excluded from further review. The next largest case series available in English was by Verwaal et al., 2005. This article reported long-term follow-up on 117 patients, 48 of whom were included in the 2003 RCT, and was critically appraised. *The two studies reviewed were as follows:* Verwaal VJ, van Ruth S, de Bree E et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol 2003; 21: 3737-3743. See Evidence Table. Verwaal VJ, van Ruth S, Witkamp A et al. Long-term survival of peritoneal carcinomatosis of colorectal origin. Ann Surg Oncol 2005; 12: 65-71. See Evidence Table

The use of intraperitoneal hyperthermic chemotherapy (IPHC) in the treatment of peritoneal carcinomatosis does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Intraperitoneal Hyperthermic Chemotherapy (IPHC)
10/16/2012: MTAC REVIEW
Evidence Conclusion: Verwaal and colleagues (2003, 2008) conducted a randomized controlled trial in one center in the Netherlands to compare the efficacy of cytoreductive surgery (CRS) and HIPEC versus systemic chemotherapy and surgery in the management of peritoneal carcinomatosis of colorectal origin. The study randomized 105 patients younger than 71 years of age, with peritoneal metastases of CRC to undergo CRS in combination with hyperthermic intraperitoneal therapy (HIPEC) or systemic chemotherapy and surgery. The authors published the results after a median of 21.6 months, and later after an extended follow-up of 91 month. The initial results of the trial showed a significantly higher median survival of the patients treated with CRS and HIPEC vs. standard therapy (22.3 months and 12.6 months respectively). After 8-years of follow-up, 9 patients were still alive. This long-term follow-up showed a median progression-free survival of 12.6 months in the CRS and HIPEC group and 7.7 months in the standard therapy group. Subgroup analyses of the results showed that patients with 6-7 regions had a very poor survival (median 5.4 months) compared to those with 0-5 regions (median >29 months), and that survival was significantly higher with success of surgical procedure i.e. complete cytoreduction. The trial had generally valid methodology; it was randomized and controlled. However, it was conducted over a decade ago and significant progress in chemotherapy has been accomplished since then. The systemic therapy with 5-FU and leucovorin used in the control group is outdated, and mitomycin-C, the HIPEC drug used in the experimental group is not the most effective drug for used for CRC. In addition, the experimental group underwent both cytoreduction and HIPEC and it is difficult to determine whether the survival benefit was due to one of the two treatment modalities or their combination, and whether heating of the chemotherapy had an additive effect to the IP therapy.
Articles: The search revealed one meta-analysis, one randomized controlled trial with long-term follow-up, and a number of observational studies with or without comparison groups. The randomized trial was selected for critical appraisal. The meta-analysis pooled the results of that RCT together with a retrospective study and was not critically reviewed. Verwaal VJ, van Ruth S, de Bree E, et al Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol 2003;21:3737-3743 See Evidence Table. Verwaal VJ, Bruin S, Boot H, et al 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. Ann Surg Oncol.2008; 15:2426-2432 See Evidence Table.

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The use of intraperitoneal hyperthermic chemotherapy (IPHC) in the treatment of peritoneal carcinomatosis does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Intraperitoneal Hyperthermic Chemotherapy (IPHC)

02/11/2013: MTAC REVIEW

Evidence Conclusion: There is insufficient published evidence to determine the efficacy and safety of hyperthermic intraperitoneal chemotherapy for the treatment of patients with ovarian cancer whether as an initial therapy, consolidation therapy, or for the treatment of a persistent or recurrent disease. The published studies on HIPEC for ovarian cancer are all prospective or retrospective case series. The studies included heterogeneous groups of women of different ages, different disease characteristics, stages, and tumor load, previous use of systemic chemotherapy regimens, chemo resistance, and with different indications for HIPEC therapy (primary, consolidation, persistent, or recurrent disease after initial therapy). In addition, the published studies recruited patients over long periods of time and used different HIPEC protocols and chemotherapeutic regimens some of which were outdated by the time the studies were completed and their results published. In a small observational study, Spiliotis and colleagues (2011, evidence table 1) compared survival benefit of HIPEC for ovarian cancer among two case series: one with 24 patients treated with CRS followed by HIPEC and systemic chemotherapy, and the other with 24 were treated with CRS and systemic chemotherapy alone without HIPEC for various reasons not explained by the authors. The results of the study show that the median survival was significantly higher for those who received HIPEC vs. those who did not (19.4 months vs. 11.2 months). The 1-year and 3-year survival rates were also significantly higher among patients treated with HIPEC. Within each of the two groups survival outcomes were better among patients with less extensive peritoneal disease and more complete cytoreduction. Due to the study design, the potential selection bias and confounding, it is difficult to determine whether improved survival was due to HIPEC, successful cytoreduction, or other confounding factors. An earlier observational study (Gori et al, 2005) compared the outcomes of a second look surgery and HIPEC (4-8 weeks after standard CRS and systemic chemotherapy) in 29 patients, to the outcomes for 19 patients who refused the second look and HIPEC. All patients had stage III ovarian cancer and had undergone a primary complete or optimal cytoreductive surgery (residual lesion <2cm) and 6 cycles of systemic chemotherapy. After a median follow-up of 73 months (range 24-134 months) the results showed a higher but statistically insignificant median survival patients treated with HIPEC vs. those who refused to undergo the treatment. The results of a larger retrospective case series with a historical comparison group (Ryu et al 2004, evidence table 2) show that HIPEC may be associated with better disease response and survival in patients with ovarian cancer. However, these results must be interpreted cautiously due to the limitations of the study including but not limited to potential selection bias, confounding, and other inherent limitations of case series and the use of retrospective data.
Conclusion: Overall the results of the published observational studies suggest, but do not provide sufficient evidence to conclude, that HIPEC is feasible and may improve survival in women with advanced ovarian cancer. Due to the inherent limitations of the observational studies, it is hard to ascertain the extent at which the reported survival benefit resulted from selection bias, and whether it was due to the intraoperative intraperitoneal therapy, the hyperthermia, the aggressive cytoreduction therapy, the systemic chemotherapy regimens used, or other confounding factors. It is also difficult to determine whether complications occurring after major cytoreduction surgery and HIPEC were due to the surgery itself or the HIPEC. Only well conducted, adequately powered, randomized controlled trials with long-term follow-up may determine the net clinical benefit of incorporating HIPEC in the management of patients with ovarian cancer. Currently, at least three randomized controlled trials are ongoing to investigate the efficacy and safety of adding HIPEC to primary or secondary cytoreductive surgery in women with stage III or relapsing ovarian cancer. Among these trials are the OVIHIPEC trial in the Netherlands, the CHIPOR trial in France, and the HORSE trial in Italy. Their results may answer many questions about the role of HIPEC in treating ovarian cancers, its indications, efficacy, morbidity, and net clinical benefits.
Articles: The literature search did not reveal any randomized controlled trial that compared the efficacy of HIPEC to standard therapy for treatment of women with ovarian cancer. The published studies were mainly prospective or retrospective observational studies. The search identified one retrospective review and three case series that compared the outcomes of patients undergoing HIPEC to those who refused to undergo the procedure or did not receive the HIPEC therapy for various other reasons.
Two case series that compared the outcomes of patients who received HIPEC to those of patients who did not were selected for critical appraisal. Spiliotis J, Vaxevanidou A, Sergouniotis F et al. The role of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of recurrent advanced ovarian cancer: a prospective study. J Buon 2011; 16:74-75. See Evidence Table. Ryu KS, Kim JH, et al. Effects of intraperitoneal hyperthermic chemotherapy in ovarian cancer. Gynecol Oncol. 2004; 94:325–332. See Evidence Table.

The use of intraperitoneal hyperthermic chemotherapy (IPHC) in the treatment of ovarian cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

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Intraperitoneal Hyperthermic Chemotherapy (IPHC)

08/19/2013: MTAC REVIEW

Evidence Conclusion: The current review focuses on the safety and efficacy of HIPEC therapy for non-ovarian, non-colorectal cancers with serosal invasion or peritoneal carcinomatosis. Perioperative HIPEC in combination with cytoreductive surgery was evaluated in small, randomized controlled trials and a number of meta-analyses for patients with gastric cancer. The search did not identify any RCTs or large prospective studies that evaluated HIPEC for the treatment of peritoneal mesothelioma, pseudomyxoma peritonei, or for peritoneal carcinomatosis secondary to urinary bladder cancer, or uterine leiomyosarcoma. *HIPEC for Gastric cancer:* Mi DH and colleagues' meta-analysis (2013) pooled the results of 16 trials that examined the effectiveness and safety of radical surgery (RS) combined with HIPEC vs.RS without HIPEC in 1,906 patients with histologically diagnosed, primary, locally advanced gastric cancer with macroscopic serosal invasion, but with no peritoneal or distant metastases. The primary outcome of the analysis was overall survival. The pooled results indicate that compared with surgery alone, the combination of surgery with HIPEC was associated with a significant improvement in survival rate at 1,2,3,5 and 9 years. It was also associated with a significant reduction in recurrence rates at 2, 3, and 5 years. There was however, a significantly higher incidence of abdominal pain with HIPEC. The rates of other adverse events were too small to show a significant difference. Sun and colleagues' meta-analysis (2012) also examined the effectiveness and safety of gastrectomy combined with HIPEC versus gastrectomy alone in patients with advanced gastric cancer with serosal invasion but without distant metastases or peritoneal carcinomatosis. The analysis included 10 trials with a total of 1,062 patients. The primary outcome was overall survival defined as the time from treatment to the last follow-up or death. Similar to MI et al's analysis, the pooled results indicate that surgery combined with HIPEC may improve the overall survival for patients and prevent peritoneal local recurrence. There pooled results do not show a significantly higher risk of complications associated with HIPEC, but again the numbers were too small to provide sufficient statistical power. The two meta-analyses had had generally valid methodology and analysis. However, they had only 5 trials in common despite almost similar literature search dates. The trials included were small, all were conducted in Asia, and many were performed in the late 1980s and early 1990s and the procedures used may be currently outdated. In addition, there was no standardized agent or dose used for HIPEC; different chemotherapeutic agents were used among the trials and at different doses. The most commonly used agents in the trials were mitomycin C and cisplatin given alone, in combination together, or in combination with other agents. A small phase III RCT (Yang et al, 2011) conducted in Japan, evaluated the efficacy and safety of cytoreductive surgery (CRS) in combination with hyperthermic intraperitoneal therapy (HIPEC using mitomycin C and cisplatin) for the treatment peritoneal carcinomatosis (PC) from gastric cancer. The study randomized 68 participants to receive CRS combined with open HIPEC or CRS alone. The primary outcome was overall survival. After a median follow-up of 32 months (range 7.5-83.5 months), the results showed that patients in the CRS and HIPEC had significantly better overall survival compared to those who underwent CRS with no HIPEC. The numbers of serious adverse events were higher in the HIPEC group but were too small to allow any conclusion. *HIPEC for diffuse malignant peritoneal mesothelioma (DMPM)*: Baratti and colleagues (2009) analyzed data from a prospective database for 70 patients with DMPM who were treated with cytoreduction surgery and HIPEC by the same surgical team from 1996 to 2008 at a cancer institute in Italy. Disease progression was the primary outcome of the study. This occurred among 38 (54.28%) of the participants after a median follow-up of 43 months. The median time to disease progression (TTP) among these patients was 9 months and the median survival from progression was 8 months. Failure pattern was categorized as peritoneal progression, which occurred among 31(81.58%) patients, liver metastasis in one patient, abdominal lymph node involvement in 2, and pleural seeding in 4 patients. Residual tumor $\leq$2.2 mm was the only independent risk factor for disease progression. Progressive disease was treated with second HIPEC in 3 patients, debulking in 4, systemic chemotherapy in 16, and supportive care in 15. A multivariate analysis showed that time to progression <9 months, poor performance status, and supportive care correlated to reduced survival from progression. These results should be interpreted with caution as the study was small, observational, conducted in a single center, and had no comparison or control group. *HIPEC for Pseudomyxoma peritonei (PMP)* In a retrospective study, Chua and colleagues (2012) reported on the outcome of nearly 2,300 patients from 16 institutions worldwide that were treated with cytoreductive surgery (CRS) and HIPEC over an 18-years period for pseudomyxoma peritonei (PMP) that arose from the appendix. The study was based on data from the Peritoneal Surface Oncology Group International registry. The median survival was 16.3 years, and the median progression-free survival was 8.2 years, with 10-year survival rate of 63% and a 15-year survival rate of 59%. The postoperative mortality rate after cytoreductive surgery and HIPEC was low (2%), but 24% of patients experienced major complications and 10% of patients required surgery for their complications. Data on quality of life were not provided. A multivariate analysis indicated that prior chemotherapy treatment, peritoneal mucinous carcinomatosis (PMCA) histopathological subtype, major postoperative complications, high peritoneal cancer index, and debulking surgery were independent predictors for a poorer progression-free survival. Use of HIPEC was associated with a favorable progression- free survival. Older age, major postoperative complications, debulking surgery, prior chemotherapy treatment, and PMCA histopathological subtype were independent predictors of a poorer overall survival. Elias and colleagues (2010) also conducted a retrospective

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analysis of data from a registry with 301 patients with PMP treated with CRS and HIPEC between 1993 and 2007 in 18 French speaking centers in Europe and Canada. The mean follow-up was 88 months, the 5-year and 10-year overall survival rates were 73% and 54.8% respectively. The 5-year disease-free survival was 56%. 4.4 % of the patients died postoperatively, 40% had a grade 3-4 complication. 17.5% of all patients required a re-operation due to complications. These results of these retrospective analyses should be interpreted with caution due to the methodological limitations of retrospective studies, and lack of control groups. Conclusion: There is some evidence from small RCTs conducted in Asia, and meta-analyses pooling their results that cytoreductive surgery combined with intraperitoneal hyperthermic chemotherapy may improve the overall survival in patients with advanced gastric cancer without macroscopic
peritoneal carcinomatosis or distant metastases. There is insufficient evidence to determine the subgroup of patients with gastric cancer who would benefit most from HIPEC as the effectiveness of HIPEC may depend on size and depth of micrometastases. There is insufficient evidence to determine the optimal regimen for HIPEC. There is insufficient evidence to determine the efficacy of HIPEC in patients with peritoneal carcinomatosis from gastric cancer. There is insufficient evidence to determine the safety of HIPEC or its effect on the quality of life in patients with gastric cancer with or without dissemination to the peritoneum. There is insufficient evidence to determine the safety and efficacy of HIPEC for the treatment of other peritoneal malignancies, whether of a primary origin or peritoneal carcinomatosis secondary to cancer in other organs within the peritoneal cavity.
Articles: The literature search for studies on the efficacy and safety of HIPEC in patients with pseudomyxoma peritonei, GI cancers (other than colorectal cancer) identified two recent meta-analyses of RCTs, two older ones, and a phase III RCT on HIPEC for patients with gastric cancer. The search did not reveal any RCTs that evaluated HIPEC for primary peritoneal malignancies, or other peritoneal disseminations from other cancers evaluated in this review. The published studies were mainly small prospective or retrospective case series with no comparison or control groups. The two more recent meta-analyses and the RCT that evaluated the efficacy and safety of HIPEC for gastric carcinoma were selected for critical appraisal.
Mi DH, Li Z, Yang KH, et al. Surgery combined with intraoperative hyperthermic intraperitoneal chemotherapy (IHIC) for gastric cancer: a systematic review and meta-analysis of randomized controlled trials. Int J Hyperthermia. 2013; 29:156-167. See Evidence Table. Sun J, Song Y, Wang Z, et al. Benefits of hyperthermic intraperitoneal chemotherapy for patients with serosal invasion in gastric cancer: a meta-analysis of the randomized controlled trials. BMC Cancer. 2012; 12:526. See Evidence Table. Yang XJ, Huang CQ, Suo T, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improves survival of patients with peritoneal carcinomatosis from gastric cancer: final results of a phase III randomized clinical trial. Ann Surg Oncol. 2011; 18:1575-1581. See Evidence Table.

The use of intraperitoneal hyperthermic chemotherapy (IPHC) in the treatment of Gastric, DMPM, and PMP cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Medicare – Considered not medically necessary for use of hyperthermia with chemotherapy
Non-Medicare - Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® Codes	Description
77600	Hyperthermia, externally generated; superficial (ie, heating to a depth of 4 cm or less)
77605	Hyperthermia, externally generated; deep (ie, heating to depths greater than 4 cm)
77610	Hyperthermia generated by interstitial probe(s); 5 or fewer interstitial applicators
77615	Hyperthermia generated by interstitial probe(s); more than 5 interstitial applicators
77620	Hyperthermia generated by intracavitary probe(s)

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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04/19/2007	04/02/2007, 04/16/2007 MDCRPC, (reinitiated policy document) 11/06/2012 MDCRPC, 03/05/2013 MDCRPC,10/01/2013 MPC, 01/07/2014 MPC, 11/04/2014MPC, 09/01/2015MPC, 07/05/2016MPC, 05/02/2017MPC, 03/06/2018MPC, 03/05/2019MPC, 03/03/2020MPC, 03/02/2021MPC, 03/01/2022MPC, 03/07/2023MPC	03/01/2022

MDCRPC Medical Director Clinical Review and Policy Committee

MPC Medical Policy Committee

Revision History	Description
08/02/2016	Removed the diagnosis, Pseudomyxoma Peritonei (PMP), from the non-covered list
05/22/2020	Added CPT codes 77600, 77610, 77615, 77620 and removed 96446.
03/01/2022	Added ovarian cancer to the list of medically necessary diagnoses.

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Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Intense Pulsed Light (IPL) for Meibomian Gland Dysfunction

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article	None
Kaiser Permanente Medical Policy	Due to the absence of a NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Clinical Review Criteria, **Intense Pulsed Light (IPL) for Meibomian Gland Dysfunction,** for medical necessity determinations. Use the Non-Medicare criteria below.

For Non-Medicare Members

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

If requesting review for this service, please send the following documentation:

- Last 6 months of clinical notes from requesting provider &/or specialist

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Background

Meibomian glands are located in the eyelids and secrete lipids into the surface of the eye. These lipids prevent the tears from evaporating rapidly. Meibomian gland dysfunction (MGD) is an abnormality or obstruction of meibomian glands leading to evaporation of the tears which in turn results in dry eye. Increased evaporative loss results in tear film instability, hyperosmolarity and lacrimal system inflammation (https://www.uptodate.com/contents/dry-eye-disease).

Meibomian gland dysfunction affects 70% of the population in some parts of the world (Craig, Chen, & Turnbull, 2015). Risk factors include age (the risk of MGD increases with age), ethnicity (Asians have high risk of MGD), eye makeup, contact lenses. The pathophysiology of MGD is multifactorial; it includes inflammation, bacterial overgrowth, abnormal blood vessel growth around the meibomian gland, and abnormal meibum production (Sabeti, Kheirkhah, Yin, & Dana, 2019).
Clinical symptoms include dryness, red eyes, general irritation, gritty sensation, burning, paradoxical excessive tearing, and decreased visual acuity (https://www.uptodate.com/contents/dry-eye-disease).

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Treatment of MGD includes artificial tears, heat application, manual gland expression, warm compresses, lubricants with fatty acids, omega-3 supplementation, topical antibiotics, oral antibiotics, corticosteroids, or topical cyclosporine (Craig et al., 2015; Dell, Gaster, Barbarino, & Cunningham, 2017). However, these therapies come with adverse events, are temporarily effective and both physicians and patients are unsatisfied (Craig et al., 2015). IPL has garnered interest due to its concomitant effectiveness on ocular and dermatological manifestations in patients with rosacea. However, the mechanism by which this occurs is not well understood (Rennick & Adcock, 2018).

The most common indication for IPL has been skin disorders such as rosacea and acne. Regarding this treatment, the skin is exposed to the light with wavelengths from 500 to 1200 nm. The targeted tissue absorbed the light. This generates heat which destroys the lesions (Craig et al., 2015). In addition, the wavelengths stimulate melanin and hemoglobin in the skin causing coagulation and ablation of blood vessels ((Gao et al., 2019); Rennick & Adcock, 2018) and suppressing inflammation. IPL can also eliminate bacteria on treated zones of the skin. The theory is that IPL should improve MGD. There are several mechanisms by which IPL enhances MGD: heating, occlusion of abnormal blood vessels, liquefaction of meibum improving secretion and excretion, reduction in epithelial turnover, local photomodulation, activation of fibroblasts, enhancement of collagen synthesis, and destruction of Demodex mites (Sabeti et al., 2019).

The procedure starts with placement of shields over the eyes. This serves as protection from the light. A cooling gel is then applied to the area followed by administration of pulsed light around the eyelids. Manual gland expression is then performed, and normal oil flow is restored in the tear film. The procedure lasts approximately 20 minutes and is performed once a month for four months (https://www.theeyeinstitute.com/dry-eye/intense-pulsed-light-ipl-treatment/). Gao et al., 2019 (Gao et al., 2019) applied lidocaine cream for anesthesia for 30 minutes before placing the protective shield and administering IPL. Indications include rosacea, acne, MGD. Other indications include hypertrichosis, benign cavernous hemangiomas, benign venous malformations, telangiectasia, and pigmented lesions. It is also used in the cosmetic industry (Craig et al., 2015). IPL can only be used for patients whose skin is Fitzgerald type four or below (https://www.reviewofophthalmology.com/article/intense-pulsed-light-for-treating-dry-eye).

Medical Technology Assessment Committee (MTAC)

Intense Pulsed Light (IPL) for the treatment of meibomian gland dysfunction (MGD)

01/13/2020: MTAC REVIEW

Evidence Conclusion:

The evidence consists of six small randomized controlled trials. One RCT compared intense pulsed light (IPL) to tobramycin/dexamethasone, three RCTs compared IPL plus meibomian gland expression to meibomian gland expression alone, and two other RCTs compared IPL vs sham. Statistically significant reduction of symptoms was found in each study. In addition, IPL appears to be safe as no serious adverse events were reported. However, the studies have small sample size, short follow-up, the risk of bias is not low, power calculations were not consistently provided. High-quality studies with large sample size and long-term follow-up are warranted. The findings are promising.

Overall, the evidence is not sufficient to draw overarching conclusions on the effectiveness and safety of intense pulsed light for the treatment of meibomian gland dysfunction.

Articles: PubMed search was conducted up to December 2, 2019 with the search terms (intense pulsed light OR intense-pulsed-light OR intense pulse light OR intense-pulse-light OR IPL) AND (dry eye OR DED OR meibomian OR MGD OR meibomian gland dysfunction). The search was limited to English language publications and human populations. The reference lists of relevant studies were reviewed to identify additional publications. Non-randomized controlled trials were excluded. Only randomized controlled trials were included in the review. The search yielded several articles. However, seven RCTs were retained and reviewed. See Evidence Table**.**

The use of Intense Pulsed Light (IPL) for the treatment of meibomian gland dysfunction (MGD) does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Considered Not Medically Necessary:

CPT® Codes	Description
0207T	Evacuation of meibomian glands, automated, using heat and intermittent pressure, unilateral

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0507T	Near-infrared dual imaging (ie, simultaneous reflective and trans-illuminated light) of meibomian glands, unilateral or bilateral, with interpretation and report
0563T	Evacuation of meibomian glands, using heat delivered through wearable, open-eye eyelid treatment devices and manual gland expression, bilateral
May be submitted with unlisted code 17999 and ICD-10 codes H02.88-H02.88B	Unlisted procedure, skin, mucous membrane and subcutaneous tissue
	Meibomian gland dysfunction of eyelid

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
03/03/2020	03/03/2020[MPC], 03/02/2021[MPC], 03/01/2022[MPC], 03/07/2023[MPC], 03/12/2024[MPC]	09/11/2020

[MPC] Medical Policy Committee

Revision History	Description
03/03/2020	MPC approved to endorse a non-coverage policy for IPL.
09/11/2020	Added CPT codes 0207T, 0507T, 0563T and 17999 w dx codes H02.88-H02.88B

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Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Islet Cell Transplantation for Type I Diabetes

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Islet Cell Transplantation in the Context of a Clinical Trial (260.3.1)
Local Coverage Determinations (LCD)	None

For Non-Medicare Members

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

If requesting review for this service, please send the following documentation:

- Last 6 months of clinical notes from requesting provider &/or specialist

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Some patients with Type I diabetes fail to obtain adequate glucose control despite insulin treatment. Pancreas allo-transplantation can restore metabolic control, but this procedure is limited by a shortage of donor organs and a complex surgical procedure with associated morbidity and mortality. Transplantation of pancreatic islet cells is a possible alternative treatment. The islet of Langerhans cells contains insulin-secreting *b* cells and make up only about 1% of the whole pancreas.

In the early 1970s, researchers found that islet cell transplantation could be used to treat diabetes in rats. Since that time, there have been attempts to apply this treatment to humans. Most of the applications of this procedure were unsuccessful; the Islet Transplant Registry estimated in 1996 that only 6 percent of islet transplantations done between 1990-1996 were successful (success defined as not needing insulin treatment for a year after transplantation).

Medical Technology Assessment Committee (MTAC)

Islet Cell Transplantation

10/11/2001: MTAC REVIEW

Evidence Conclusion: To date, there has been one report of some success with islet cell transplantation in 7 patients; only 3 of these were followed-up for at least a year. The effectiveness of islet cell transplantation for type 1 diabetes cannot be determined based on the current published scientific evidence. A randomized controlled trial, which will provide higher-quality data, was recently initiated by the Juvenile Diabetes Foundation and the National Institutes of Health to study the effectiveness of islet cell transplantation.

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Articles: The searches yielded 60 articles. These were predominantly review articles and articles on technical aspects of the procedure. There were no randomized controlled trials or meta-analyses. There were 3 empirical articles with clinical outcomes; all were case series studies with sample sizes less than n=10. An evidence table was done for the case series that used the most up-to-date techniques: Shapiro AMJ, Lakey JRT, Ryan EA, Korbutt GS, Toth E, Warnock GL, Kneteman NM, Rajotte RV. Islet cell transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. NEJM 2000; 343: 230-8. See Evidence Table.

The use of Islet Cell Transplantation in the treatment of diabetes does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Considered not medically necessary

CPT® Codes	Description
0584T	Islet cell transplant, includes portal vein catheterization and infusion, including all imaging, including guidance, and radiological supervision and interpretation, when performed; percutaneous
0585T	Islet cell transplant, includes portal vein catheterization and infusion, including all imaging, including guidance, and radiological supervision and interpretation, when performed; laparoscopic
0586T	Islet cell transplant, includes portal vein catheterization and infusion, including all imaging, including guidance, and radiological supervision and interpretation, when performed; open
HCPC Codes	**Description**
S2102	Islet cell tissue transplant from pancreas; allogeneic ***S codes not covered by Medicare***

Medicare - Considered Medically Necessary when criteria in the applicable policy statements listed above are met
Non-Medicare - Considered not medically necessary

HCPC Codes	Description
G0341	Percutaneous islet cell transplant, includes portal vein catheterization and infusion
G0342	Laparoscopy for islet cell transplant, includes portal vein catheterization and infusion
G0343	Laparotomy for islet cell transplant, includes portal vein catheterization and infusion

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Creation Date	Review Date	Date Last Revised
11/17/2000	05/03/2011 MDCRPC, 08/02/2011 MDCRPC, 06/05/2012 MDCRPC, 04/02/2013 MDCRPC, 02/04/2014 MPC,12/02/2014 MPC, 10/06/2015MPC, 08/02/2016MPC, 06/06/2017MPC, 04/03/2018MPC, 03/05/2019MPC, 03/03/2020MPC, 03/02/2021MPC, 03/01/2022MPC , 03/07/2023MPC	06/23/2020

MDCRPC Medical Director Clinical Review and Policy Committee
MPC Medical Policy Committee

Revision History	Description
06/23/2020	Added CPT codes 0584T, 0585T and 0586T

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Clinical Review Criteria
Jaw Motion Rehabilitation Device (Jaw Stretch Device)

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article (LCA)	None
Kaiser Permanente Medical Policy	Due to the absence of a NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Clinical Review Criteria, "***Jaw Motion Rehabilitation Device***," for medical necessity determinations. Use the Non-Medicare criteria below.

For Non-Medicare Members

Jaw motion rehabilitation system is medically necessary to treat mandibular hypomobility when caused by radiation therapy in persons with head and neck cancer.

It is **not medically necessary** for any other indication, as there is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

If requesting these services, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist
- Last 6 months of radiology notes if applicable

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Background

Trismus, defined as a tonic spasm of the muscles of mastication from diseases of the trigeminal nerve, is often used to describe mandibular hypomotility of any cause. Mandibular hypomotility is a common symptom in patients suffering from temporomandibular disorders as well as variety pathologies of the masticatory system. It may be related to intra- or extra-articular conditions such as synovitis, osteoarthritis, fibrosis, facial space infections, coronoid hyperplasia, fibrosis following radiation therapy, and tumors involving the head and neck regions. Patients with mandibular hypomotility experience limitations during eating, speaking, and with oral hygiene (Israel 1997, Cohen 2005, Melchers 2009).

The temporomandibular joint (TMJ) is a synovial joint that functions according to the same biological rules as other synovial joints and follows the same principles of joint motion and rehabilitation. Several manual, mechanical, and electromechanical approaches have been used for TMJ mobilization and increasing mouth

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opening. The most common methods used are isometric and range of motion exercises, tongue depressor therapy, and mechanical stretching devices (Israel 1997).

The Therabite System (Therabite Corporation, Bryn Mawr, PA) is a handheld patient controlled, mechanical device with two mouthpieces that are inserted between the teeth of the upper and lower jaw. By squeezing the handles, the mouthpieces open and assist the opening of the mouth. The horseshoe-shaped surfaces on the arms come in contact with the teeth and spread the load across 10 anterior teeth in each jaw. This generates less force on the incisors than spatulas or screws and makes the Therabite appliance more comfortable to use. The force applied by squeezing and releasing the handle stretches the fibrosis intermittently. Maximum device opening can be adjusted between 25 and 45 mm using a single screw and can be sequentially increased by the patient or clinician. Similar to other exercise regimens and physiotherapy, the patient must be motivated and must use the device correctly and regularly. Adherence to exercise regimens has a positive effect on outcome, and poor adherence may be a barrier to treatment success (Buchbinder 1993, Gibbons 2007, Melchers 2009).

Medical Technology Assessment Committee (MTAC)

Jaw Motion Rehabilitation Device

04/16/2012: MTAC REVIEW

Evidence Conclusion: In a relatively small unblinded, randomized, controlled trial, Maloney and colleagues (2002) compared the effectiveness of a passive jaw motion device (Therabite) and wooden tongue depressors (WTD) in patients with temporomandibular joint and muscle disorders that did not respond to manual manipulation and bite plane therapy. The authors did not discuss the cause of mouth opening restriction. After undergoing manual manipulation of the mandible combined with flat bite plane therapy for 4 weeks, eligible patients were randomly assigned to one of three treatment groups: Therabite group, wooden tongue depressor group, or control group. Patients in the first 2 intervention groups received treatment for 4 weeks, and the control group received a total of 8 weeks of flat bite plane therapy only. The authors did not discuss compliance with therapy or completeness of follow-up. The results of the trial show that passive jaw motion therapy using Therabite was more effective than using wooden tongue depressor in reducing pain and increasing the maximum interincisal opening.

In a smaller RCT, Buchbinder and colleagues (1993) compared the use of Therabite system plus unassisted exercise vs. tongue blade therapy plus unassisted exercise, or unassisted exercise only for 10 weeks in 21 patients with decreased interincisal opening secondary to radiation therapy after head and neck cancer resection. The initial average maximum interincisal opening (MO) was 21.6 mm. All three groups showed an initial increase in the MO in the first 4 weeks, after which there was only minimal further gain in the unassisted exercise group with or without tongue blade therapy. After 6 weeks of treatment, the net increase in MO in the Therabite group was significantly greater than either of the other 2 groups. In conclusion, evidence from two small RCTs suggest that passive jaw motion rehabilitation using Therabite device may be more effective than unassisted exercise, manual manipulation, and bite plane therapy with or without tongue blade therapy in reducing pain and improving maximum interincisal opening in patients with mandibular hypomobility.

Articles: The literature on the use jaw motion rehabilitation devices for patients with mandibular hypomotility is limited. Only two small RCTs comparing TheraBite to other treatment were identified and critically appraised, Maloney GE, Mehta N, Forgione AG, et al. Effect of a passive jaw motion device on pain and range of motion in TMD patients not responding to flat plane intraoral appliances. Cranio. 2002; 20:55-66. See Evidence Table**.** Buchbinder D, Currivan RB, Kaplan AJ, et al. Mobilization regimens for the prevention of jaw hypomobility in the radiated patient: a comparison of three techniques. J Oral Maxillofacial Surg. 1993; 51:863-867.

The use of jaw motion rehabilitation device for mandibular hypomobility does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPC Codes	Description
E1700	Jaw motion rehabilitation system
E1701	Replacement cushions for jaw motion rehabilitation system, package of 6
E1702	Replacement measuring scales for jaw motion rehabilitation system, package of 200

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
05/01/2012	05/01/2012[MDCRPC], 06/05/2012[MDCRPC], 04/02/2013[MDCRPC], 02/04/2014 [MPC], 12/02/2014 [MPC], 10/06/2015[MPC], 08/02/2016[MPC], 06/06/2017[MPC], 04/03/2018[MPC], 04/02/2019[MPC], 04/07/2020[MPC], 04/06/2021[MPC], 04/05/2022[MPC], 04/04/2023[MPC], 01/09/2024[MPC]	06/06/2017

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
06/06/2017	Adopted Kaiser Permanente policy for Medicare members

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Clinical Review Criteria
Ketamine for the Treatment of Depression and Other Psychiatric Disorders

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article (LCA)	None
Kaiser Permanente Medical Policy	Due to the absence of an active NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Clinical Review Criteria, "***Ketamine for the Treatment of Depression and Other Psychiatric Disorders"*** for medical necessity determinations. Refer to the Non-Medicare criteria below.

For Non-Medicare Members

Ketamine (intranasal, intravenous, or subcutaneous) is considered experimental and investigational as its clinical value has not been established. Non-covered diagnoses include but are not limited to:

- Chronic pain
- Depression
- Generalized anxiety and social anxiety disorders
- Substance use disorder
- Suicidal ideation

*Esketamine nasal spray (Spravato) has separate criteria for pharmacy review:
https://wa-provider.kaiserpermanente.org/static/pdf/provider/clinical-review/list-officeinject.pdf

For non-covered criteria

If requesting review for this service please send the following documentation:

- Last 6 months of clinical notes from requesting provider &/or specialist

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Hayes Review

Ketamine Infusion for Treatment-Resistant Bipolar Depression

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Conclusion - D[2]
A small body of very low-quality evidence found that ketamine infusion rapidly reduces symptoms of severe bipolar depression. Although the antidepressant effects appear to last for only a few days, this can be clinically significant if it improves the mood of severely depressed, potentially suicidal patients. In all of the studies, only a single dose of ketamine was administered; the safety and effectiveness of repeated administration of ketamine for treatment of bipolar depression is unknown. The evidence suggests that ketamine is reasonably safe. Additional large, well-designed studies with adequate follow-up are needed to evaluate the long-term effects of prolonged ketamine treatment.
Insights

- Ketamine is administered by infusion because it does not have good bioavailability via alternative routes, such as oral or intramuscular injection.
- The low oral bioavailability and potential for abuse makes ketamine an unlikely first- or second-line therapy for bipolar depression.
- Persons with bipolar disorder are more apt to seek medical attention when they are depressed; therefore, a careful medical history must be obtained to avoid misdiagnosis of the patient's disorder as major depression.
- None of the reviewed payers had policies available for the use of ketamine to treat bipolar depression.

Ketamine as Primary Therapy for Treatment-Resistant Unipolar Depression Or Posttraumatic Stress Disorder
Conclusion- C (For ketamine as a treatment for treatment-resistant unipolar depression)
D2 (For ketamine as a treatment for posttraumatic stress disorder (PTSD).
A moderate-size body of low-quality evidence has consistently found that ketamine reduces symptoms of severe treatment-resistant unipolar depression, symptoms of PTSD, or suicidal ideation at short-term follow-up of 1 to 3 days posttreatment; however, the findings at longer-term follow-up of 1 to 4 weeks are mixed. The majority of the studies administered only a single dose of ketamine; the safety and effectiveness of repeated administration of ketamine for treatment of depression or PTSD is unknown. The evidence suggests that ketamine is reasonably safe if complications are properly managed. Additional large, well-designed studies with adequate follow-up are needed to evaluate the long-term effects of prolonged ketamine treatment, to assess simplified ketamine administration via intranasal or subcutaneous routes, to determine the efficacy and safety of ketamine for PTSD treatment, and to evaluate the efficacy and safety of ketamine relative to ECT for unipolar depression.
Insights

- The low oral bioavailability and potential for abuse makes ketamine an unlikely first- or second-line therapy for treatment-resistant unipolar depression or PTSD.
- The reviewed studies found that ketamine is consistently beneficial for 24 hours posttreatment; however, the durability of results at 1 to 4 weeks posttreatment are mixed. Thus, it is unclear whether ketamine provides durable relief of depression or PTSD symptoms.
- As the beneficial effects of ketamine may be limited to 24 hours posttreatment, it is important to establish the safety and effectiveness of repeated administration of ketamine. There is currently a paucity of studies investigating repeated administration of ketamine for unipolar depression or PTSD.
- Several representative payer organizations do not have coverage policies for ketamine monotherapy for unipolar depression or PTSD.

Applicable Codes

Considered Not Medically Necessary - experimental, investigational or unproven:

CPT® or HCPCS Codes	Description
J3490	Unclassified drugs
Commonly submitted with CPT code(s) 96365, 96366, 96367, or 96368	
ICD-10 Codes	**Description**
F01-F09	Mental disorders due to known physiological conditions
F10-F19	Mental and behavioral disorders due to psychoactive substance use
F20-F29	Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders
F30-F39	Mood [affective] disorders
F40-F48	Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders

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F50-F59	Behavioral syndromes associated with physiological disturbances and physical factors
F60-F69	Disorders of adult personality and behavior
F70-F79	Intellectual disabilities
F80-F89	Pervasive and specific developmental disorders
F90-F98	Behavioral and emotional disorders with onset usually occurring in childhood and adolescence
F99-F99	Unspecified mental disorder
T14.91XA	Suicidal behavior with attempted self-injury
R45.89	Suicidal behavior without attempted self-injury
T65.92XA	Suicidal deliberate poisoning
R45.851	Suicidal ideation
R45.851	Suicidal ideations
R45.851	Suicidal intent
T50.902A	Suicidal overdose
T50.902A	Suicidal overdose, initial encounter
T50.902S	Suicidal overdose, sequela
T50.902D	Suicidal overdose, subsequent encounter
R45.89	Suicidal risk
R45.851	Suicidal thoughts
R45.851	Feeling suicidal
T40.602A	Narcosis due to narcotic, purposeful, non-suicidal
Z71.1	Concern about becoming suicidal without diagnosis
F32.A, R45.851	Depression with suicidal ideation
Z91.52	History of non-suicidal self-harm
Z91.51	History of suicidal behavior
G89.21	Chronic pain due to trauma
G89.22	Chronic post-thoracotomy pain
G89.28	Other chronic postprocedural pain
G89.29	Other chronic pain
G89.3	Neoplasm related pain (acute) (chronic)
G89.4	Chronic pain syndrome
G90.511	Complex regional pain syndrome I of right upper limb
G90.512	Complex regional pain syndrome I of left upper limb
G90.513	Complex regional pain syndrome I of upper limb, bilateral
G90.519	Complex regional pain syndrome I of unspecified upper limb
G90.521	Complex regional pain syndrome I of right lower limb
G90.522	Complex regional pain syndrome I of left lower limb
G90.523	Complex regional pain syndrome I of lower limb, bilateral
G90.529	Complex regional pain syndrome I of unspecified lower limb
G90.59	Complex regional pain syndrome I of other specified site

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
11/10/2021	12/07/2021[MPC], 12/06/2022[MPC], 12/09/2023[MPC]	12/07/2021

[MPC] Medical Policy Committee

Revision History	Description

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12/07/2021	MPC approved to adopt a policy of non-coverage for IV Ketamine for mental diagnoses including chronic pain, depression, generalized anxiety and social anxiety disorders, substance use disorder and suicidal ideation.
06/21/2022	Updated the 60-day notice to 12/1/2022 and removed “oral” per Pharmacy

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KAISER PERMANENTE®

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PATIENT REFERRAL GUIDELINES
Kidney Transplant

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Criteria

For Medicare Members

Source	Policy
Chapter Manual	Medicare Benefits Manual Chapter 11 – End Stage Renal Disease Section 140 - Transplantation
National Coverage Determination (NCD)	Thoracic Duct Drainage (TDD) in Renal Transplants (20.3) Dental Examination Prior to Kidney Transplantation (260.6) Nonselective (Random) Transfusions and Living Related Donor Specific Transfusions (DST) in Kidney Transplantation 110.16
Local Coverage Determination (LCD)	None

For Non-Medicare Members

Transplantation may be considered for patients with end-stage or life-threatening disease who have no prospect for prolonged survival, or whose quality of life is severely impaired. Kidney transplantation is the preferred renal replacement therapy for almost all patients with chronic kidney disease. Most patients with chronic kidney disease or end stage renal disease should be considered for kidney transplant evaluation. However, the patient must have adequate social support systems and a proven record of adherence to medical treatment. These guidelines for referral for transplant evaluation are not intended as an automatic inclusion or exclusion of a candidate for referral. Referral to a regionally contracted transplant center for kidney transplant does not guarantee that the patient will be listed or transplanted. These are decisions made at the Transplant Center's discretion.

1. GENERAL PRINCIPLES

a. If clinical parameters of end-stage or life-threatening disease indicate the need for transplantation, then early referral should be made.
b. Patients with a history of malignancy with a moderate to high risk of recurrence (as determined after consultation with oncologist considering tumor type, response to therapy, and presence or absence of metastatic disease) may be unsuitable candidates for transplantation. Patients with low risk of recurrence may be considered.
c. Uncontrollable active infection is a contraindication to transplant.
d. Candidates with a history of substance abuse must be free from alcohol and other substance abuse for six (6) months and have been evaluated by a substance abuse program. The risk of recidivism, which has been documented to negatively impact transplant outcomes, must be addressed and considered to be low.[1,2,3] Exceptions may be made on a case-by-case basis.
e. Candidates for thoracic organ (heart, lung and heart/lung) transplants must be free from tobacco use for the previous six (6) months. Routine monitoring may be required. Specific programs for abdominal organs (liver, intestines, and kidney) may require abstinence from tobacco products in order to be actively listed.
f. Candidates must have adequate social support systems and display a proven record of adherence to medical treatment.
g. Patients must be willing and able to travel within short notice to the KP approved transplant Center of Excellence and, if necessary, return for treatment of complications.

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h. Patients must have a care giver or care givers who are physically and cognitively able to assist the patient with self- care activities and are available to travel within short notice to the KP approved transplant Center of Excellence.
i. The presence of significant irreversible neurologic dysfunction, active psychological and/or psychiatric conditions, and/or other social behaviors that prevent adherence with a complex medical regimen, are considered contraindications for referral for transplant.
j. Evidence of such nonadherence may be failure to keep appointments, failure to make steady progress in completing pre-transplant evaluation requirements, failure to accurately follow medication regimens or failure to accomplish the activities required for maintenance on the waiting list.
k. Whenever transplant is considered as an option and discussed with the patient and/or family, consultation with Advanced Life Care Planning/Palliative Care resources is strongly recommended.

2. INDICATIONS FOR KIDNEY TRANSPLANT

Most patients with kidney failure can be considered for transplantation. It is important to note that these are guidelines and should be applied together with careful clinical judgment. The aim is to perform pre-emptive renal transplantation without initiation of standard kidney replacement therapy (hemodialysis/peritoneal dialysis).

a. All pediatric and adult patients who require dialysis or are expected to require dialysis within the next 12 months can be considered candidates. If possible, patients should be evaluated prior to this time to discuss options for renal replacement therapy.
    1. Patients with an estimated GFR ≤ 30 should be informed of, educated about, and considered for potential referral for transplantation.[4]
b. Known Type 2 diabetes patients, sometimes referred to as type 1.5 diabetes, with BMI <28, who require low-dose insulin, may be considered for SPK. Input from endocrinology may be needed.
c. Patients cannot be listed on the UNOS waiting list for a deceased donor kidney until their estimated GFR, calculated by the CKD-EPI creatinine equation (2021) that are refitted without race or the CKD-EPI creatinine-cystatin equation (2012) that are refitted without race, is less than 20ml/min.[5,6,7]
d. Estimated GFR for the pediatric population using the Schwartz formula of 10 – 15, or sooner if symptomatic. Symptomology is defined as poor growth/failure to thrive and suboptimal energy level despite adequate caloric support. Patients with estimated GFR <30 may be referred early.

CONTRAINDICATIONS FOR KIDNEY TRANSPLANT

a. Significant irreversible coronary artery disease and/or left ventricular dysfunction, and irreversible pulmonary disease.
b. Irreversible peripheral vascular disease, including carotid vascular disease. (Amputation alone is not a contraindication)
c. Uncontrolled hypertension.

RELATIVE CONTRAINDICATIONS FOR KIDNEY TRANSPLANT

a. Patients with a BMI ≥ 40 may be referred to the COE for individual consideration and concurrently referred for weight loss intervention.
b. Active nicotine abuse.
c. Age: There is no firm upper limit cut-off for kidney transplantation.
d. When considering candidacy, close attention should be paid to concurrent conditions, such as frailty, that would increase the risk of morbidity and mortality.
e. Presence of other significant, permanent, irreversible organ failure.

Footnotes

1. *Liver Transplantation* 2006, .12:813-820. Alcohol consumption patterns and predictors of use following liver transplantation for alcoholic liver disease.
2. *Liver Transplant Surg*. 1997, Vol 3, 304 – 310. The natural history of alcoholism and its relationship to liver transplantation.
3. Alcohol abstinence prior to liver transplantation for Alcoholic Liver Disease (G110807), *TPMG New Medical Technology*
4. KDIGO Clinical Practice Guideline on the Evaluation and Management of Candidates for Kidney Transplantation. Transplantation. 2020;104: S1 – S103.
5. Inker, Lesley A., et al., "New Creatinine- and Cystatin C–Based Equations to Estimate GFR without Race." N Engl J Med 2021; DOI: 10.1056/NEJMoa2102953
6. Hsu, Chi-yuan, et.al., "Race, Genetic Ancestry, and Estimating Kidney Function in CKD." N Engl J Med 2021; DOI: 10.1056/NEJMoa2103753
7. National Kidney Foundation, eGFR Calculator: https://www.kidney.org/professionals/kdoqi/gfr_calculator

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If requesting this service, please send the following documentation to support medical necessity:

- Copy of final summary report from multidisciplinary transplant team

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Background

Kidney transplant is a surgical procedure to implant a healthy kidney into a patient with kidney disease or kidney failure. The kidney transplant may be taken from a living donor or from a recently deceased donor.

The transplant is conducted when the patient has non-reversible, end stage renal failure with a glomerular filtration rate 20 mL/min/1.73m2 (0.33 mL/sec/1.73m2) or less. There are several causes for renal failure, but the most common cause is diabetes or hypertension.

Evidence and Source Documents

See evidence document for HIV patients: Organ Transplant for HIV Positive Patients

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® Codes	Description
50300	Donor nephrectomy (including cold preservation); from cadaver donor, unilateral or bilateral
50320	Donor nephrectomy (including cold preservation); open, from living donor
50323	Backbench standard preparation of cadaver donor renal allograft prior to transplantation, including dissection and removal of perinephric fat, diaphragmatic and retroperitoneal attachments, excision of adrenal gland, and preparation of ureter(s), renal vein(s), and renal artery(s), ligating branches, as necessary
50325	Backbench standard preparation of living donor renal allograft (open or laparoscopic) prior to transplantation, including dissection and removal of perinephric fat and preparation of ureter(s), renal vein(s), and renal artery(s), ligating branches, as necessary
50327	Backbench reconstruction of cadaver or living donor renal allograft prior to transplantation; venous anastomosis, each
50328	Backbench reconstruction of cadaver or living donor renal allograft prior to transplantation; arterial anastomosis, each
50329	Backbench reconstruction of cadaver or living donor renal allograft prior to transplantation; ureteral anastomosis, each
50340	Recipient nephrectomy (separate procedure)
50360	Renal allotransplantation, implantation of graft; without recipient nephrectomy
50365	Renal allotransplantation, implantation of graft; with recipient nephrectomy
50370	Removal of transplanted renal allograft
50380	Renal autotransplantation, reimplantation of kidney
50547	Laparoscopy, surgical; donor nephrectomy (including cold preservation), from living donor

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Revised	Date Last Revised
05/1996	10/05/2010 MDCRPC, 08/02/2011 MDCRPC, 06/05/2012 MDCRPC, 04/02/2013 MDCRPC, 02/04/2014 MPC, 12/02/2014 MPC, 10/06/2015MPC, 08/02/2016MPC,	01/10/2022

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	06/06/2017[MPC], 04/03/2018[MPC], 04/02/2019[MPC], 04/07/2020[MPC], 04/06/2021[MPC], 04/05/2022[MPC], 04/04/2023[MPC]	

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
05/07/2019	MPC approved to adopt KP National criteria for Kidney transplant.
03/03/2020	MPC approved the proposed changes from KP National Transplant Services.
04/06/2021	Per National Transplant Guidelines: 1.3 added “active”
01/10/2022	MPC approved the proposed changes from KP National Transplant Services. 60-day notice is not required.

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PATIENT REFERRAL GUIDELINES
Kidney/Pancreas Transplant

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	Medicare Benefits Manual Chapter 11 – End Stage Renal Disease Section 140 - Transplantation
National Coverage Determinations (NCD)	Pancreas Transplants (260.3)
Local Coverage Determinations (LCD)	None

For Non-Medicare Members

Note: Simultaneous Pancreas Kidney Transplantation (SPK)[1]

Transplantation may be considered for patients with end-stage or life-threatening disease who have no prospect for prolonged survival, or whose quality of life is severely impaired. These guidelines for referral for transplant evaluation are not intended as an automatic inclusion or exclusion of a candidate for referral. It is important to note that these are guidelines and should be applied together with careful clinical judgment. Patient and treating physician should understand the uncertain benefits of successful pancreas transplantation beyond glucose control.

1. **GENERAL PRINCIPLES**
   a. If clinical parameters of end-stage or life-threatening disease indicate the need for transplantation, then early referral should be made.
   b. Patients with a history of malignancy with a moderate to high risk of recurrence (as determined after consultation with oncologist considering tumor type, response to therapy, and presence or absence of metastatic disease) may be unsuitable candidates for transplantation. Patients with low risk of recurrence may be considered.
   c. Uncontrollable active infection is a contraindication to transplant.
   d. Candidates with a history of substance abuse must be free from alcohol and other substance abuse for six (6) months and have been evaluated by a substance abuse program. The risk of recidivism, which has been documented to negatively impact transplant outcomes, must be addressed and considered to be low[2,3,4]. Exceptions may be made on a case-by-case basis.
   e. Candidates for thoracic organ (heart, lung and heart/lung) transplants must be free from tobacco use for the previous six (6) months. Routine monitoring may be required. Specific programs for abdominal organs (liver, intestines, and kidney) may require abstinence from tobacco products in order to be actively listed.
   f. Candidates must have adequate social support systems and display a proven record of adherence to medical treatment.
   g. Patient must be willing and able to travel within short notice to the KP approved transplant Center of Excellence and, if necessary, return for treatment of complications.
   h. Patient must have a care giver or care givers who are physically and cognitively able to assist the patient with self-care activities and are available to travel within short notice to the KP approved transplant Center of Excellence.
   i. The presence of significant irreversible neurologic dysfunction, active psychological and/or psychiatric conditions, and/or other social behaviors that prevent adherence with a complex medical regimen, are considered contraindications for referral for transplant.

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j. Evidence of such non adherence may be: failure to keep appointments, failure to make steady progress in completing pre-transplant evaluation requirements, failure to accurately follow medication regimens or failure to accomplish the activities required for maintenance on the waiting list.
k. Whenever transplant is considered as an option and discussed with the patient and/or family, consultation

2. INDICATIONS FOR SPK TRANSPLANT

a. Type 1 (as verified by stimulated C-peptide testing or presence of antibodies to glutamic acid decarboxylase, islet cell, insulin, etc.) diabetes mellitus with or approaching end stage renal disease. A diagnosis of Type 1.5 diabetes mellitus may be needed by endocrinology.
    1. In selective situations, known Type 2 Diabetes Mellitus patients (also referred to as Type 1.5 DM) with low C peptide and a low BMI (<28), requiring low dose insulin with end stage renal disease or advanced CKD may be considered for SPK.
b. Optimally and intensively managed by an endocrinologist for at least 12 months for Type 1 diabetes mellitus.[5]
c. Age 18-55, except under special clinical circumstances.
d. Must be a candidate for kidney transplantation. Patients cannot be listed on the UNOS waiting list for a deceased donor kidney until their estimated GFR, calculated by the CKD-EPI creatinine equation (2021) that are refitted without race or the CKD-EPI creatinine-cystatin equation (2012) that are refitted without race, is less than 20ml/min.[6,7,8]

CONTRAINDICATIONS FOR SPK TRANSPLANT

a. Significant irreversible coronary artery disease and/or left ventricular dysfunction, and irreversible pulmonary disease.
b. Irreversible peripheral vascular disease, including carotid vascular disease. (Amputation alone is not a contraindication)
c. Uncontrolled hypertension.

RELATIVE CONTRAINDICATIONS FOR SPK TRANSPLANT

a. BMI ≥ 35. Patients may be referred to the COE for individual consideration
    i. May be concurrently referred for weight loss intervention.
b. Cachexia and/or malnourishment

Footnotes

1. In certain situations where the NTS COE recommends, in discussion with the patient, to proceed with a staged transplant procedure (living donor kidney followed by cadaveric pancreas transplant) due to organ availability, the patient will need to meet the indications for a SPK transplant.
2. *Liver Transplantation* 2006, .12:813-820. Alcohol consumption patterns and predictors of use following liver transplantation for alcoholic liver disease.
3. *Liver Transplant Surg*. 1997, Vol 3, 304 – 310.The natural history of alcoholism and its relationship to liver transplantation.
4. Alcohol abstinence prior to liver transplantation for Alcoholic Liver Disease (G110807), *TPMG New Medical Technology*
5. National Coverage Determination (NCD) for Pancreas Transplants (260.3) version 3. http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?
6. Inker, Lesley A., et al., "New Creatinine- and Cystatin C–Based Equations to Estimate GFR without Race." N Engl J Med 2021; DOI: 10.1056/NEJMoa2102953
7. Hsu, Chi-yuan, et.al., "Race, Genetic Ancestry, and Estimating Kidney Function in CKD." N Engl J Med 2021; DOI: 10.1056/NEJMoa2103753
8. National Kidney Foundation, eGFR Calculator: https://www.kidney.org/professionals/kdoqi/gfr_calculator

If requesting this service, please send the following documentation to support medical necessity:

- Copy of final summary report from multidisciplinary transplant team

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage

Background

This service is covered when it is medically necessary and identified as a benefit in the consumer's coverage contract. The Kaiser Permanente Nephrologists in collaboration with the Kaiser Permanente Transplant Committee and the Transplant Centers define the Kaiser Permanente patient referral guidelines.

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Evidence and Source Documents

Kaiser Permanente Committee on Emerging Technology
Transplant, simultaneous Pancreas/Kidney (SPK) - 7/11/1990
Simultaneous pancreas/kidney transplantation is approved for diabetic patients who otherwise would be candidates for a kidney transplant, subject to review in six months.

The University of Washington transplant criteria set are used as a source document and updated when new efficacy data becomes available by the Kaiser Permanente Nephrology section with approval by the Kaiser Permanente Transplant Committee.

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® Codes	Description
50300	Donor nephrectomy (including cold preservation); from cadaver donor, unilateral or bilateral
50320	Donor nephrectomy (including cold preservation); open, from living donor
50323	Backbench standard preparation of cadaver donor renal allograft prior to transplantation, including dissection and removal of perinephric fat, diaphragmatic and retroperitoneal attachments, excision of adrenal gland, and preparation of ureter(s), renal vein(s), and renal artery(s), ligating branches, as necessary
50325	Backbench standard preparation of living donor renal allograft (open or laparoscopic) prior to transplantation, including dissection and removal of perinephric fat and preparation of ureter(s), renal vein(s), and renal artery(s), ligating branches, as necessary
50327	Backbench reconstruction of cadaver or living donor renal allograft prior to transplantation; venous anastomosis, each
50328	Backbench reconstruction of cadaver or living donor renal allograft prior to transplantation; arterial anastomosis, each
50329	Backbench reconstruction of cadaver or living donor renal allograft prior to transplantation; ureteral anastomosis, each
50340	Recipient nephrectomy (separate procedure)
50360	Renal allotransplantation, implantation of graft; without recipient nephrectomy
50365	Renal allotransplantation, implantation of graft; with recipient nephrectomy
50370	Removal of transplanted renal allograft
50380	Renal autotransplantation, reimplantation of kidney
50547	Laparoscopy, surgical; donor nephrectomy (including cold preservation), from living donor
48550	Donor pancreatectomy (including cold preservation), with or without duodenal segment for transplantation
48551	Backbench standard preparation of cadaver donor pancreas allograft prior to transplantation, including dissection of allograft from surrounding soft tissues, splenectomy, duodenotomy, ligation of bile duct, ligation of mesenteric vessels, and Y-graft arterial anastomoses from iliac artery to superior mesenteric artery and to splenic artery
48552	Backbench reconstruction of cadaver donor pancreas allograft prior to transplantation, venous anastomosis, each
48554	Transplantation of pancreatic allograft
48556	Removal of transplanted pancreatic allograft
HCPC Codes	**Description**
S2065	Simultaneous pancreas kidney transplantation ***S codes not covered by Medicare***

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Created		Revised
07/11/1997	04/05/2010[MDCRPC], 08/02/2011[MDCRPC], 06/05/2012[MDCRPC], 04/02/2013[MDCRPC], 02/04/2014 [MPC], 12/02/2014[MPC], 10/06/2015[MPC], 08/02/2016[MPC], 06/06/2017[MPC], 04/03/2018[MPC], 04/02/2019[MPC], 04/07/2020[MPC], 04/06/2021[MPC], 04/05/2022[MPC], 04/04/2023[MPC]	01/10/2022

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
04/07/2020	MPC approved to adopt Kaiser Permanente National coverage policy
06/12/2020	Added “Patient Referral Guidelines” to title; changed background from patient selection criteria to patient referral guidelines
04/06/2021	Per National Transplant Guidelines: 1.3 added “active”
01/10/2022	MPC approved the proposed changes from KP National Transplant Services. 60-day notice is not required.

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Clinical Review Criteria

Vertebroplasty + Kyphoplasty

- Percutaneous Vertebroplasty with Polymethylmethacrylate
- Radiofrequency Ablation with Vertebral Augmentation for Painful Spinal Metastases

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	Percutaneous Vertebral Augmentation (PVA) for Osteoporotic Vertebral Compression Fracture (VCF) (L34106)
Local Coverage Article	Billing and Coding: Percutaneous Vertebral Augmentation (PVA) for Osteoporotic Vertebral Compression Fracture (VCF) (A56573)

For Non-Medicare Members

Kaiser Permanente has elected to use coverage guidance from the Noridian Local Coverage Determination (LCD) L34106 *Percutaneous Vertebral Augmentation (PVA) for Osteoporotic Vertebral Compression Fracture (VCF)* for medical necessity determinations for non-Medicare members.

*Note: Provisions in the LCD and related coding article only address Vertebral Augmentation for Osteoporotic Vertebral Compression Fracture (VCF). Coverage will remain available for medically necessary procedures for other conditions not included in the LCD, such as other pathologic vertebral compression fractures.

Percutaneous vertebral augmentation is not covered if the procedure includes the following:

A. Radiofrequency-assisted vertebral augmentation with ultrahigh viscosity cement, including but not limited to Radiofrequency-Targeted Vertebral Augmentation™ (RF-TVA™) with the StabiliT® System
B. Mechanical vertebral augmentation using any device other than a balloon device, including but not limited to use of the following:
    1. Use of the Kiva®

Percutaneous Sacroplasty – there is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

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Vertebral compression fractures (VCFs) occur when the bones of the spine become compressed and break. It is estimated that about five million new vertebral fractures occur worldwide each year. Most common in elderly populations and females, osteoporosis is responsible for more than 1.5 million fractures annually, the majority of which are vertebral. Other potential causes of VCFs include trauma, steroid use, malignancy in the vertebrae, and haemangioma. In any case, VCFs can be asymptomatic and resolve without treatment, however, they are frequently associated with pain, disability, and reduced quality of life (QoL). To add to this, VCFs are a risk factor for subsequent fractures which can lead to additional complications such as kyphosis, impairment of mobility or balance, and increased mortality to name a few (Chitale and Prasad 2013).

The majority of patients with VCFs are successfully treated with conservative management aimed to alleviate symptoms via external bracing, decreased activity and analgesics. Some patients, however, will experience persistent pain and symptoms refractory to medical therapy and may require additional intervention.

Over the last twenty years, two minimally invasive techniques to augment the vertebral bodies and reduce pain have been developed as a treatment option for refractory VCFs. The first technique, percutaneous vertebroplasty, was first introduced in France by Deramond and colleagues in 1984 and later, in 1993, was introduced into clinical practice in the United States (US). The procedure, initially performed to strengthen vertebrae weakened by angiomas, involved injection of polymethylmethacrylate (PMMA) into a collapsed vertebral body under fluoroscopic guidance (Deramond, Depriester et al. 1998). Since then, however, indications for vertebroplasty have expanded to include metastatic vertebral cancer, multiple myeloma, as well as, osteoporotic VCFs that have not responded to conservative therapy. The second procedure, kyphoplasty, was devised in 1998 after mounting concerns over flaws in the vertebroplasty technique. With the same aims and desired outcomes as vertebroplasty, kyphoplasty employs the use of inflatable balloon tamps to restore vertebral height and reduce kyphotic deformity before stabilization with PMMA. It is believed that the cavity formation and the use of more viscous cement introduced with less pressure, compared to vertebroplasty leads to lower risk of cement extravasation (Atalay, Caner et al. 2005; Wardlaw, Cummings et al. 2009).

Medical Technology Assessment Committee (MTAC)

06/07/2001: MTAC REVIEW
Kyphoplasty
Evidence Conclusion: The published evidence consists of one poorly described case series that is insufficient to draw conclusions about the safety and efficacy of kyphoplasty.
Articles: The literature search yielded one published article. The article reported on a study using cadavers and does not have data appropriate for MTAC review. One other published article was received from Kyphon. This was largely a review article; it included one paragraph about the use of the kyphoplasty procedures. No details on study methodology were given so that this study also could not be evaluated. There is also one article documented to be in-press in Spine. An evidence table was created for this case series. Lieberman IH, Dudeney S, Reinhardt M-K, Bell G. Initial outcome and efficacy of “kyphoplasty” in the treatment of painful osteoporotic vertebral compression fractures. Spine 2001; in-press. See Evidence Table.

Kyphoplasty for the treatment of vertebral body compression fractures refractory to maximal medical management does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

07/14/2004: MTAC REVIEW
Kyphoplasty
Evidence Conclusion: The evidence is insufficient to draw conclusions about the safety and efficacy of kyphoplasty. It consists of two small (fewer than 30 patients) case series, one published in 2001 and one with the abstract published electronically in April 2004 ahead of the print version.
Articles: The search yielded 41 articles, most of which were discussion pieces and technical reports. The single new empirical study was an “electronic publication ahead of print” and was not yet available. An inspection of the abstract showed that this was a case series with 27 patients.

Kyphoplasty for the treatment of vertebral body compression fractures refractory to maximal medical management does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

06/06/2005: MTAC REVIEW
Kyphoplasty
Evidence Conclusion: There are no randomized controlled studies that compared the short and long-term

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outcomes of kyphoplasty with those of the more conservative standard therapies. The Grohs' study compared kyphoplasty head to head with vertebroplasty however, it was small, nonrandomized and unblinded. Postoperative comparison was made versus baseline condition for each intervention with no direct comparison between the two techniques. The results of the study show that both procedures offered significant pain relief, which was maintained at a lower level with the kyphoplasty. The functional disability on the other hand was significantly improved only with kyphoplasty and not vertebroplasty. The observed improvement was statistically significant for the first year only. The results of the study also indicate that the rate of fracture of an adjacent vertebra seems to be higher with the kyphoplasty vs. vertebroplasty (21% vs. 4%). The other article reviewed was a case series with some advantages: it was relatively large, had inclusion/exclusion criteria, and had objective outcomes. However, like all case series it lacks a control or comparison group and has potential selection and observation bias. Overall its results showed that the pain was completely relieved in 78% of the patients, and, that the vertebral height significantly improved after kyphoplasty. There were no long-term follow-up data to determine the long-lasting effects or late complications of the intervention. In conclusion, the published literature does not provide sufficient evidence to determine the effects of the procedure on the spine, or its long-lasting effect on pain relief. A European multicenter prospective randomized controlled trial comparing kyphoplasty with the standard pharmacological therapy is underway (Ohlin 2004).
Articles: The search yielded 70 articles, most of which were review articles, discussion pieces and technical reports. There was no randomized controlled trial that compared the short and long-term outcomes with conservative therapies. The search revealed a recent nonrandomized study that compared kyphoplasty head-to head with percutaneous vertebroplasty, as well as several small prospective case series, and retrospective reviews of cases that underwent the procedure. *The following controlled study, as well as the largest case series (N=222), were selected for critical appraisal:* Grohs JG, Matzner M, Trieb K, et al. Minimal invasive stabilization of osteoporotic vertebral fractures. A prospective nonrandomized comparison of vertebroplasty and balloon kyphoplasty. *J Spinal Disord Tech* 2005; 18:238-242. See Evidence Table. Majd ME, Farley S, and Holt RT. Preliminary outcomes and efficacy of the first 360 consecutive kyphoplasties for the treatment of painful osteoporotic vertebral compression fractures. *Spine J.* 2005; 5:244-255. See Evidence Table.

Kyphoplasty for the treatment of vertebral body compression fractures refractory to maximal medical management does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

08/04/2008: MTAC REVIEW
Kyphoplasty
Evidence Conclusion: The body of evidence on the safety and efficacy of balloon kyphoplasty (BKP) in the treatment of vertebral compression fractures consisted of multiple case series and few non-randomized studies that compared BKP to either vertebroplasty or the standard conservative therapy. Several authors pooled the results of these comparative and non-comparative series in a number of meta-analyses. However, the quality of meta-analyses and the strength of their conclusions depend on the quality of the included studies. The studies included in the published meta-analyses for BKP were too small, and had their methodological flaws and potential selection and observation bias. The comparative studies were non-randomized and the authors did not discuss how and why patients were selected for each of the procedures. There was evidence of publication bias as well as significant heterogeneity between the studies included in the meta-analyses. The studies differed their inclusion/exclusion criteria, outcome measures, scales used, and scoring systems, as well as duration and completeness of follow-up. Moreover, the results were unblinded and many of the outcomes were subjective.
The comparative studies published after the meta-analyses were also too small, non- randomized, unblinded, with relatively short follow-up duration, as well as other validity threats and do not allow making conclusions as regard the efficacy and safety of the procedure. In conclusion, the published literature does not provide sufficient evidence to determine the benefit of the procedure in relieving pain, improving function, and reducing rate of vertebral fractures. There is also insufficient evidence to determine its long-lasting effect on pain relief or its adverse effects on the spine. Large well conducted randomized controlled trials, with long term follow-up duration are needed to objectively compare balloon kyphoplasty to conventional treatment and other percutaneous techniques, and to determine its long-term safety and efficacy in improving function and reducing pain, disability, and complications associated with vertebral compression fractures.
Articles: The search yielded over 90 articles on balloon kyphoplasty. Many were reviews and technical reports. No randomized controlled trials that compared the procedure with vertebroplasty or conservative therapy were identified. There were four meta-analyses of non-randomized controlled studies and case series. All four included almost the same studies, and two were performed by the same group of authors. The search also revealed two non-randomized comparative studies published after the meta-analyses. One (N=21) compared kyphoplasty to vertebroplasty for the treatment of painful osteoporotic or traumatic VCFs, and the other (N=60) compared kyphoplasty with standard medical treatment of osteoporotic or traumatic VCF. The studies on the use of

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kyphoplasty for severe back pain due to metastatic disease were small case series with no control or comparison groups. The most recent meta-analysis and the two comparative studies were critically appraised. Taylor RS, Fritzell P, Taylor RJ. Balloon kyphoplasty in the management of vertebral compression fractures: an updated systematic review and meta-analysis. *Eur Spine J* 2007; 16:1085-1100. See Evidence Table. De Negri P, Tirri T, paternoster G, et al. Treatment of painful osteoporotic or traumatic vertebral compression fractures by percutaneous vertebral augmentation procedures. *Clin J Pain.* 2007; 5:425-430. See Evidence Table. Grafe IA, Fonseca KD, Hillmeier J, et al. Reduction of pain and fracture incidence after kyphoplasty: 1-year outcomes of a prospective controlled trial of patients with osteoporosis. *Osteoporos Int* 2005; 16:2005-2012. See Evidence Table.

Kyphoplasty for the treatment of vertebral body compression fractures refractory to maximal medical management does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

12/07/2009: MTAC REVIEW
Kyphoplasty
Evidence Conclusion: A recently published RCT (Wardlaw et al 2009) compared kyphoplasty plus standard medical therapy to medical therapy alone in 300 patients from 21 sites in eight countries. The trial was randomized and controlled, however kyphoplasty was not compared to a sham procedure or an alternative invasive or noninvasive surgical procedure. The medical therapy was not standardized and varied according to the standard practices of the participating centers, and neither the patients nor the investigators were blinded to the treatment received. Medtronic Spine LLC, the manufacturer of the kyphoplasty balloon technology was involved in the study design, data monitoring, analysis, and reporting of the results. The results of the trial shows that patients in the kyphoplasty group experienced greater reduction in pain and improved function at one month compared to the control group. The significant improvement observed at one month in the short form -36 physical component summary (SF-36 PCS) scale, the primary outcome the trial, declined along the following months and was statistically insignificant by the 12th months, when the controls showed improvement. The results also show a higher rate of vertebral fractures and/or worsening of fractures among the patients in the kyphoplasty group vs. the controls. The difference was not statistically significant, but the study was not powered to detect significant differences in fracture rates. The authors did not report on any cement leakage associated with kyphoplasty.
In conclusion, the published literature does not provide sufficient evidence to determine that kyphoplasty is a safe and an appropriate procedure for relieving pain, improving function, reducing rate of vertebral fractures and disability in patients with vertebral compression fractures.
Articles: The search identified one recent randomized controlled trial (Wardlaw et al 2009) that compared balloon kyphoplasty with non-surgical care for vertebral compression fracture No randomized controlled trials that compared the procedure with a sham treatment were identified. A relatively small RCT with only 6 months of follow-up compared the kyphoplasty to vertebroplasty in patients with osteoporotic vertebral fractures. Wardlaw et al's RCT was selected for critically appraised. Wardlaw D, Cummings SR, Van Meirhaeghe J. Efficacy and safety of balloon kyphoplasty compared with non-surgical care for vertebral compression fracture (FREE): a randomized controlled trial. Lancet. 2009; 373:1016-24. See Evidence Table.

Kyphoplasty for the treatment of vertebral body compression fractures refractory to maximal medical management does meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

02/09/2015: MTAC REVIEW
Kyphoplasty
Evidence Conclusion: *Effectiveness* In 2009, Wardlaw and colleagues reported results from an RCT comparing kyphoplasty to non-surgical management (NSM) in 300 patients from 21 sites in eight countries. The results of the trial indicate that patients in the kyphoplasty group experienced greater reduction in pain and improved function at one month compared to the control group. The significant improvement observed at one month in the short form- 36 (SF-36) physical component summary (PCS) scale, the primary outcome the trial, declined along the following months and was statistically insignificant by 12 months. The kyphoplasty group also experienced statistically significant reductions in back pain and improvement in both back function and quality of life scales early on, however, this effect diminished over time (Wardlaw, Van Meirhaeghe et al. 2012). In 2010, Boonen and colleagues expand on the results of the FREE-trial including an additional 12 months of follow-up. With the exception of pain and QoL, most criteria were no longer statistically significant at 24 months indicating that any benefit for both groups occurs within the first year. The investigators do note that averaged scores, across the 24 month period, did show significance when compared with NSM in physical symptoms, as assessed by the SF-36 PCS (3.24 points, 95% CI 1.47-5.01, p=0.0004), and on the QoL scale as assessed by the Euro quality-of-life questionnaire (EQ-5D) (0.12 points, 95% CI, 0.06 to 0.18, p=0.0002). The investigators concluded that, compared with NSM, kyphoplasty rapidly

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reduces pain and improves function, disability, and QoL over the course of two years (Boonen, Van Meirhaeghe et al. 2011). [Evidence Table 1] *Safety* At 24 months, the investigators report that the overall frequency of patient with adverse events (AE) and serious adverse events (SAE) was similar between treatment groups. With that said, the investigators did report two serious adverse events, hematoma and urinary tract infection (UTI), that were considered to be related to the procedure. In addition, the investigators identified cement leakage in one patient who had undergone kyphoplasty. Finally, the kyphoplasty group had a higher rate of subsequent vertebral fractures when compared with the NSM group (47.5% vs. 44.1%; 3.4% difference, 95% CI -16.5 to 9.9, p=0.68), however, this difference was not statistically significant, and the study was not powered to detect significant differences in fracture rates. The FREE-trial has the advantage of being multi-centered, randomized and controlled. In addition, the analysis was based on intention-to-treat (ITT) and the study was adequately powered. Limitations of the study, however, include an inadequate comparator. Ideally, kyphoplasty should have been compared with a sham procedure or an alternative surgical procedure. Instead, the investigators compare the procedure to conservative management which, with 21 sites spanning eight different countries, was variable and not standardized. To add to this limitation, the differences in the treatment of the control and the intervention groups did not allow for blinding of both patients and the investigators opening the study up to selection and information bias. A further limitation of the study includes the investigators failure to stratify the data in analysis according to indication (osteoporosis vs. myeloma vs. metastasis) limiting the applicability of the results. Finally, it should be noted that the manufacturer of the kyphoplasty balloon technology, Medtronic Spine LLC, was involved in the study design, data monitoring, analysis, and reporting of results. For these reasons, the results of the study should be interpreted with caution and does not provide sufficient evidence to determine safety and effectiveness of kyphoplasty for treating VCF. *Conclusions:* There is insufficient evidence to support the effectiveness of kyphoplasty over non-surgical management for the treatment of VCF caused by osteoporosis, myeloma or malignancy. There is insufficient evidence to support the safety of kyphoplasty for the treatment of VCF caused by osteoporosis, myeloma or malignancy.
Articles: The literature search sought to update the evidence from the end date of the last MTAC review. The search revealed a large quantity of publications including a variety of systematic reviews and retrospective observational studies. No RCTs were identified that compared kyphoplasty to sham treatment. The largest RCT to date, the fracture reduction evaluation (FREE), included 300 patients with 12 months follow-up and was critically appraised by MTAC in 2009 (Wardlaw, Van Meirhaeghe et al. 2012). Since then, Boonen and colleagues have published a follow-up analysis reporting the 24-month outcomes of the FREE trial. The following articles were selected for critical appraisal: Wardlaw D, Cummings SR, Van Meirhaeghe J, et al. Efficacy and safety of balloon kyphoplasty compared with non-surgical care for vertebral compression fracture (FREE): a randomized controlled trial. Lancet. 2009; 373(9668):1016-1024. Evidence Table 1. Boonen S, Van Meirhaeghe J, Bastian L, et al. Balloon Kyphoplasty for the treatment of acute vertebral compression fractures: 2-year results from a randomized trial. JBMR. 2011; 26(7):1627-1637. Evidence Table 1.

Kyphoplasty for the treatment of vertebral body compression fractures refractory to maximal medical management does meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Percutaneous Vertebroplasty of Low Back Pain
02/09/2000: MTAC REVIEW
Evidence Conclusion: Efficacy of vertebroplasty in patients with osteoporotic compression fractures cannot be determined from these studies because of the likelihood of selection bias, observation bias, confounding and chance as explanations for some of, or all of, the studies' findings.
Articles: Articles were selected on the basis of study type. Because the literature revealed no randomized control trials or meta-analyses, the 14 cohort studies or case series were reviewed by abstract. The largest case series were selected for critical appraisal and evidence tables were created (Weill A, Chrias J, Simon J, et al. Spinal Metastases: Indications for Results of Percutaneous Injection of Acrylic Surgical Cement. Radiology. 1996; 199:241-247. Cortet B, Cotton A, Boutry N, et al. Percutaneous Vertebroplasty in the Treatment of Osteoporotic Vertebral Compression Fractures: An Open Prospective Study. J Rheumatol. 1999;26:2222-8.) Weill A, Chrias J, Simon J, et al. Spinal Metastases: Indications for and Results of Percutaneous Injection of Acrylic Surgical Cement. Radiology 1996; 199;241-247. See Evidence Table. Cortet B, Cotten A, Boutry N, et al. Percutaneous vertebroplasty in the treatment of osteoporotic vertebral compression fractures: An open prospective study. J Rheumatol. 1999;26:2222-8. See Evidence Table. Deramond H, Depriester C, Galibert P, et al. Percutaneous Vertebroplasty with Polymethylmethacrylate: Techniques, Indications, and Results. Radiologic Clinics of North America, Vol 36(3); May 1998:533-546. See Evidence Table.

The use of percutaneous vertebroplasty of low back pain has been approved by the FDA and therefore meets *Kaiser Permanente Medical Technology Assessment Criteria*.

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Percutaneous Vertebroplasty in Treatment of Osteoporotic Vertebral Fracture
06/06/2005: MTAC REVIEW
Evidence Conclusion: The studies reviewed do not provide sufficient evidence to determine the efficacy of the procedure, its long-term benefits, or late complications. No direct randomized studies comparing the intervention with standard, non-operative care are available.
Diamond et als study had the advantage of comparing the intervention with conservative therapy. However, it was not randomized, and conservative therapy was offered to those who denied percutaneous vertebroplasty, which might be a potential source of selection bias. The study was also subject to observation bias as it was not blinded, and all outcomes were subjective. Moreover, the follow-up duration might be insufficient to determine the long- term effects of the vertebroplasty. The Grohs' study compared kyphoplasty head to head with vertebroplasty.
However, it was small, nonrandomized and unblinded. Postoperative comparison was made vs. baseline condition for each intervention with no direct comparison between the two techniques. The results of the study show that both procedures offered significant pain relief, which was maintained at a lower level with the kyphoplasty. The functional disability on the other hand was significantly improved only with kyphoplasty and not vertebroplasty. The results of the study also indicate that the rate of fracture of an adjacent vertebra seems to be higher with the kyphoplasty vs. vertebroplasty (21% vs. 4%). Gangi's study was a case series with potential selection and observation bias, with no control or comparison group, and the authors did not provide sufficient data on patient selection for the intervention, their characteristics, and follow-up, or long-term outcomes.
Articles: The search yielded 179 articles, most of which were review articles, discussion pieces and technical reports. A nonrandomized trial comparing percutaneous vertebroplasty with conservative therapy, and another comparing it to kyphoplasty were identified, as well as several case series. *The two studies with comparison groups, as well as the largest case series (N=868), were selected for critical appraisal:* Diamond T, Champion B, and Clark W. Management of acute osteoporotic vertebral fractures: A nonrandomized trial comparing percutaneous vertebroplasty with conservative therapy. Am J Med. 2003;114:257-265. See Evidence Table.

Grohs JG, Matzner M, Trieb K, et al. Minimal invasive stabilization of osteoporotic vertebral fractures. A prospective nonrandomized comparison of vertebroplasty and balloon kyphoplasty. J Spinal Disord Tech 2005;18:238-242. See Evidence Table. Gangi A, Guth S, Imbert JP, et al. Percutaneous vertebroplasty: Indications, technique, and results. Radiographics. 2003;23:e10-e10. See Evidence Table.

The use of Percutaneous Vertebroplasty in Treatment of Osteoporotic Vertebral Fractures does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

09/04/2009: MTAC REVIEW
Percutaneous Vertebroplasty in Treatment of Osteoporotic Vertebral Fracture
Evidence Conclusion: There is fair evidence from two randomized controlled trials that vertebroplasty does not have a significant benefit over sham treatment in reducing pain and pain-related disability in patients with osteoporotic vertebral fractures. Kallmes, et al 2009 trial: Kallmes and colleagues randomly assigned 131 patients with 1-3 painful osteoporotic compression vertebral fractures (between T4 and L5), that was <1 year old and not responding to standard medical therapy, to undergo vertebroplasty or a sham treatment that simulated the procedure but without PMMA infusion. The primary outcomes were scores on the modified Roland-Morris Disability Questionnaire (RDQ) and patient's rating of average pain intensity during the preceding 24 hours at 1 month. Patients were allowed to cross over to the other study group after one month. The results of the trial show no significant differences in the primary outcome between the two groups (difference in RDQ score 0.7; 95%CI, -1.3 to 2.8, p=0.49, and difference in pain rating 0.7; 95% CI, -0.3 to 1.7, p=0.19). One serious adverse event occurred in each of the 2 study groups (injury to the thecal sac in the vertebroplasty procedure, and tachycardia and rigors in the control group) At 3 moths there was a higher rate of cross over in the control group (43%) than the vertebroplasty group (12%), p<0.001. The study had generally valid methodology, bur not without limitations. It was randomized, controlled, blinded, multicenter, with well defined inclusion/ exclusion criteria, sufficient statistical power to detect differences between the study groups, and analysis was based on ITT. The limitations of the trial included allowing cross-over between the two treatment groups after 1 month which did not allow evaluating the long-term efficacy of the procedure. Moreover, no adjustments were made for other medical treatments received, or other causes of pain all of which are potential confounders. Buchbinder, et al 2009: Buchbinder and colleagues randomized 78 patients with one or two painful. MRI confirmed unhealed osteoporotic vertebral fractures. <12 months duration to undergo vertebroplasty or a sham procedure. Patients were followed up for 6 months, and the primary outcome was overall pain at 3 months. Secondary outcomes included functional status and QoL at 1week, 1, 3, and 6 months after the procedures. The trial had generally valid methodology but was relatively small. It was randomized, controlled, blinded, multicenter, with sufficient statistical power to detect significant differences between

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the study groups, and analysis was based on ITT. The results show no significant difference between the vertebroplasty and sham treatment in any of the outcomes. The mean reduction in pain was 2.6 +2.9 and 1.9+3.3 respectively with an adjusted difference between the two groups of 0.6; 95% CI, -0.7 to 1.8. Both groups showed a significant reduction of pain at three months vs. baseline. 7 new of clinical vertebral fractures occurred during the 6-month follow-up (three in the vertebroplasty group and 4 in the control group. Conclusion: The published literature provides fair evidence that vertebroplasty has no significant benefit over a sham procedure in the treatment of patients with osteoporotic vertebral fractures.
Articles: Two trials on vertebroplasty for osteoporotic spinal fractures were recently published: Buchbinder R, Osborne RH, Ebeling PR, et al. A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. *N Engl J Med* 2009;36:557-568. Kallmes DF, Comstock BA, Heagerty PJ, et al. A randomized trial of vertebroplasty for osteoporotic spinal fractures. *N Engl J Med* 2009;36:569-579.

The use of Percutaneous Vertebroplasty in Treatment of Osteoporotic Vertebral Fractures does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

02/09/2015: MTAC REVIEW
Percutaneous Vertebroplasty in Treatment of Osteoporotic Vertebral Fracture
Evidence Conclusion: *Effectiveness:* In the first RCT, detailed in evidence table one, Buchbinder and colleagues included 78 subjects with back pain, ≤12 months in duration, who had up to two VCF evidenced by the presence of vertebral collapse, edema and/or a fracture line on MRI. Patients were randomized into either the vertebroplasty treatment group or a group that received sham procedure. Outcomes were measured at baseline and several points in time up to six months following the procedure. The primary endpoint was overall pain at three months, however, the study also included QoL measures and a survey specific to osteoporotic vertebral fractures.
Ultimately the study found no beneficial effect of vertebroplasty over the sham procedure at any time. In fact, the only significant between-group difference was seen on the Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO) total score at one week, favoring the sham group [-4.0 (95%CI -7.8 to -0.2)] (Buchbinder, Osborne et al. 2009). Evidence Table . The second study, by Kallmes and colleagues, also randomized osteoporotic patients with up to three painful VCFs (n=131) to vertebroplasty or sham procedures. After one month, if patients did not achieve adequate pain relief, the investigators allowed cross-over to the alternate therapy. The primary outcomes, pain and disability, were assessed at one month, however, investigators also describe outcomes up to three months to assess the effects of cross-over. At one month, both the vertebroplasty and sham groups demonstrated substantial improvements, however, no significant differences were seen between groups in either of the primary outcomes. The mean Roland-Morris Disability Questionnaire (RDQ) in the vertebroplasty group was 12.0±6.3 and 13.0±6.4 in the sham group (adjusted treatment effect, 0.7; 95% CI, -1.3 to 2.8; P=0.49). Similarly, the mean pain-intensity rating was 3.9±2.9 in the vertebroplasty group and 4.6±3.0 in the sham group (adjusted treatment effect, 0.7; 95% CI, -0.3 to 1.7; P=0.19). The investigators note, however, that the control group saw a higher rate of cross-over than the vertebroplasty group (51% vs. 13%, P<0.001). Despite this significance, the investigators concluded that improvements in pain and pain-related disability associated with osteoporotic VCF in patients treated with vertebroplasty were similar to the improvements seen in the sham group (Kallmes, Comstock et al. 2009). Evidence Table. *Safety:* Adverse events were documented in both studies and included hospitalizations from the procedure, as well as, subsequent fractures. Cement leakage was not reported by Kallmes and colleagues, however, Buchbinder et al. reported 37% cement leakage rate with no symptomatic events. Neither of the studies provided extended follow-up of safety and adverse events with the longest follow-up limited to six months following procedure. Previous reviews of vertebroplasty failed MTAC criteria with the available evidence offering little value due to methodological limitations such as a lack of randomization, inappropriate comparators and the likelihood of selection bias, observation bias, confounding and chance as explanations for study findings. Currently, however, the literature is more robust with two RCTs that compare vertebroplasty to sham procedures. The design of both studies was strengthened by the use of a sham procedure replicating verbal and visual cues allowing for the blinding of patients. With that said, an additional control group receiving no treatment would have benefited the outcome comparisons. Other limitations include sample size. Despite relatively lax inclusion criteria, both of the studies experienced difficulties recruiting patients resulting in a modification of sample size in the study by Kallmes et al. and the inability to assess two year follow-up in the Buchbinder study. Ultimately, the studies provide adequate evidence to suggest that vertebroplasty is no better than sham treatment for treating patients with VCF due to osteoporosis.
Conclusions: There is evidence to suggest that vertebroplasty is no more effective than sham therapy for the treatment of vertebral compression fractures in osteoporotic patients. There is insufficient evidence to assess the safety of vertebroplasty for the treatment of vertebral compression fractures in osteoporotic patients.
Articles: The search yielded a large quantity of publications relating to vertebroplasty. The majority of the literature

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was comprised of non-randomized, observational studies, many of which sought to compare vertebroplasty with kyphoplasty. A supplemental search of the clinical trials database revealed several studies relating to vertebroplasty that are currently recruiting or on-going. Since the last MTAC review, two randomized trials comparing percutaneous vertebroplasty with a sham procedure therapy were published and selected for critical appraisal. The following articles were selected for critical appraisal: Buchbinder R, Osborne RH, Ebeling PR, et al. A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. NEJM. 2009; 361(6):557-568.
Evidence Table 1. Kallmes DF, Cornstock BA, Heagerty PJ, et al. A randomized trial of vertebroplasty for osteoporotic spinal fractures. NEJM. 2009;261(6):569-571. Evidence Table 2.

The use of Percutaneous Vertebroplasty in Treatment of Osteoporotic Vertebral Fractures does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Radiofrequency Ablation with Vertebral Augmentation for Painful Metastases
BACKGROUND
The number of patients living with cancer in the United States (US) is estimated to be 4.86 million. Virtually all cancers have the potential to spread, or metastasize, with bone being one of the more common sites of metastasis. Generally speaking, skeletal metastases are associated with debilitating symptoms such as intolerable pain and hypercalcemia compromising the quality of life. Occurrence in the vertebral column, as does with a third of all cancer patients, contributes the additional complexity of complications such as vertebral compression factors (VCF) and spinal cord or nerve root compression that can cause potentially irreversible loss of neurologic function (Coleman 2000).

Depending on the primary tumor, prognosis is variable with five-year survival ranging from 2% in patients with lung cancer to 44% in those with thyroid cancer. Treatment presents a challenge in that there is no currently available cure, nor has there been any established treatment proven to increase life expectancy. Instead, the goals of treatment aim to control pain, limit complications and preserve function. Depending on individual patient factors, management options range from medications and systemic therapy all the way to surgical resection (Dunning, Butler et al. 2012).

Due to the advanced nature of metastatic cancer and its accompanying comorbidities, populations with skeletal metastases are usually at a higher surgical risk, making minimally invasive techniques an attractive option. Vertebral augmentation (VA) techniques, aimed at stabilizing vertebral compression fractures (VCF), have been documented to provide immediate and sustained relief (Weill, Chiras et al. 1996). In the same way, radiofrequency ablation (RFA), a technique that utilizes thermal energy to destroy cancer cells, has also been demonstrated to reduce pain (Goldberg and Dupuy 2001; Kassamali, Ganeshan et al. 2011). Most recently, RFA and VA, in combination, have been considered a promising treatment option for treating metastatic lesions of the spine (Grönemeyer, Schirp et al. 2002; Schaefer, Lohrmann et al. 2002; Schaefer, Lohrmann et al. 2003).

The STAR™ Tumor Ablation System was developed by DFINE, Inc. (San Jose, CA) specifically for metastatic spinal lesions. The system itself consists of the SpineSTAR™ Ablation Instrument and the corresponding MetaSTAR™ RF Generator which work in unison to deliver energy and provide access and navigation to the tumor within the vertebrae. Subsequent to tumor ablation, stabilization is carried out with the StabiliT® Vertebral Augmentation System, also developed by DFINE, Inc. Put simply, the StabiliT® System allows for the delivery of highly viscous bone cement to the tumor bed. In combination, the procedures require a small incision under local anesthesia with conscious sedation and offer the advantages of unipedicular access, and real-time monitoring of ablation zone allowing for the targeting of tumor cells and controlled cement delivery.

04/20/2015: MTAC REVIEW
Radiofrequency Ablation with Vertebral Augmentation for Painful Metastases
Evidence Conclusion: *Effectiveness:* In a small RCT, Orgera and colleagues, sought to compare the combined techniques of RFA and VA with VA alone. Following baseline assessment, the investigators randomized 36 patients into the two treatment groups and followed them up for six weeks. Outcomes of interest included surgery success, pain relief and the amount of analgesia administered. The investigators reported a 100% technical success rate in both groups with no significant differences noted between treatment groups with regard to pain as measured on a Visual Analogue Scale (VAS) or Roland Morris Questionnaire (RMQ). In addition, medication use decreased significantly in both groups but the investigators found no significant difference between groups.
Ultimately, the results led the investigators to conclude that the addition of RFA did not offer any additional benefit (Orgera, Krokidis et al. 2014). [Evidence Table 1] A retrospective review of 128 metastatic lesions in 92 patients who

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underwent 96 procedures was carried out by Anchala and colleagues. The studies intent was to assess the safety and efficacy of RFA of malignant spinal lesions using the SpineSTAR ablation instrument. The investigators determined that RFA was 'technically successful' in all metastatic lesions. Post-operative pain rated on a Visual Analogue Scale (VAS) demonstrated significant changes at all time points when compared to baseline. The investigators also reported that within the largest institution, 54% of patients reported a decrease in pain medication. Ultimately, the investigators concluded that the STAR system was safely and effectively used in the treatment of spine metastatic osseous lesions (Anchala, Irving et al. 2014). [Evidence Table 2]
Safety Although the follow-up period was limited, Orgera and colleagues reported several complications such as cement leakage (11%), death (5%) and opioid toxicity (8%). Anchala and colleagues, on the other hand, did not explicitly report safety details, but did note asymptomatic cement extravasation in two patients. Although Orgera's study was randomized and blinded, the population size was small and the follow-up period short. Limitations of Anchala's study include the lack of an adequate comparator and retrospective design. The investigators also highlight limitations such as a heterogeneous population and variable availability of data collected from each treatment center. Finally, it should be noted that at least two of the investigators from the retrospective review disclosed financial relationships with the device manufacturer. Collectively, the body of evidence is limited in nature and should be interpreted with caution.
Conclusions: There is insufficient evidence to support the effectiveness of the combination of RFA and VA, compared with VA alone, for the management of pain in metastatic spinal tumors. There is insufficient evidence to support the safety of RFA and VA, compared with VA alone, for the management of pain in metastatic spinal tumors.
Articles: A search of the literature returned a variety of publications relating to both RFA and VA, in general. The majority of publications returned were case studies/series. One study was identified comparing the combination of RFA and VA with balloon kyphoplasty, however, this study was performed in cadaveric models (Dalton, Kohm et al. 2012). A recent study identified in the search, by Song and colleagues, investigated the use of RFA and vertebral augmentation in 12 patients, however, this study was not selected for critical appraisal due to the small sample size and lack of a comparator (Song, Gu et al. 2014). The best evidence identified was a small randomized controlled trial (RCT) comparing RFA+VA with VA alone in patients with multiple myeloma (Orgera, Krokidis et al. 2014). In addition, a retrospective analysis, by Anchala and colleagues, evaluating the combination of RFA with VA for treating metastatic spinal lesions was also included (Anchala, Irving et al. 2014). An additional search of the clinical trials database identified a few prospective observational studies sponsored by DFINE, Inc. currently in the recruitment phase. The following articles were selected for critical appraisal: Orgera G, Krokidis M, Matteoli M, et al. Percutaneous vertebroplasty for pain management in patients with multiple myeloma: is radiofrequency necessary? 2014;37:203-210. See Evidence Table. Anchala PR, Irving WD, Hillen TJ, et al. Treatment of metastatic lesions with a navigational bipolar radiofrequency ablation device: a multicenter retrospective study. Pain Physician. 2014;17:317-327. See Evidence Table.

The use of Radiofrequency Ablation with Vertebral Augmentation for Painful Spinal Metastases does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Kyphoplasty - Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® Codes	Description
22513	Percutaneous vertebral augmentation, including cavity creation (fracture reduction and bone biopsy included when performed) using mechanical device (eg, kyphoplasty), 1 vertebral body, unilateral or bilateral cannulation, inclusive of all imaging guidance; thoracic
20983	Ablation therapy for reduction or eradication of 1 or more bone tumors (eg, metastasis) including adjacent soft tissue when involved by tumor extension, percutaneous, including imaging guidance when performed; cryoablation
22514	Percutaneous vertebral augmentation, including cavity creation (fracture reduction and bone biopsy included when performed) using mechanical device (eg, kyphoplasty), 1 vertebral body, unilateral or bilateral cannulation, inclusive of all imaging guidance; lumbar
22515	Percutaneous vertebral augmentation, including cavity creation (fracture reduction and bone biopsy included when performed) using mechanical device (eg, kyphoplasty), 1 vertebral body, unilateral or bilateral cannulation, inclusive of all imaging guidance; each additional thoracic or lumbar vertebral body (List separately in addition to code for primary procedure)

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Vertebroplasty - Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® Codes	Description
22510	Percutaneous vertebroplasty (bone biopsy included when performed), 1 vertebral body, unilateral or bilateral injection, inclusive of all imaging guidance; cervicothoracic
22511	Percutaneous vertebroplasty (bone biopsy included when performed), 1 vertebral body, unilateral or bilateral injection, inclusive of all imaging guidance; lumbosacral
22512	Percutaneous vertebroplasty (bone biopsy included when performed), 1 vertebral body, unilateral or bilateral injection, inclusive of all imaging guidance; each additional cervicothoracic or lumbosacral vertebral body (List separately in addition to code for primary procedure)

Sacroplasty - Considered Not Medically Necessary:

CPT® Codes	Description
0200T	Percutaneous sacral augmentation (sacroplasty), unilateral injection(s), including the use of a balloon or mechanical device, when used, 1 or more needles, includes imaging guidance and bone biopsy, when performed
0201T	Percutaneous sacral augmentation (sacroplasty), bilateral injections, including the use of a balloon or mechanical device, when used, 2 or more needles, includes imaging guidance and bone biopsy, when performed

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
06/07/2001	04/02/2013[MDCRPC], 02/04/2014[MPC], 05/06/2014[MPC], 03/03/2015[MPC], 01/05/2016[MPC], 11/01/2016[MPC], 09/05/2017[MPC], 08/07/2018[MPC], 08/06/2019[MPC], 08/04/2020[MPC], 08/03/2021[MPC], 08/02/2022[MPC], 08/01/2023[MPC]	05/03/2022

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
09/08/2015	Revised LCD for Percutaneous Vertebral Augmentation (L34106).
08/04/2020	Added Medicare LCA A56573
05/03/2022	MPC approved to adopt Medicare criteria for Non-Commercial members for Vertebroplasty; merged Kyphoplasty and Vertebroplasty into one policy

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Clinical Review Criteria
Leadless Pacemakers

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Leadless Pacemakers (20.8.4)
Local Coverage Determinations (LCD)	None
Local Coverage Article	None
KPWA Medical Policy	None

For Non-Medicare Members

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist

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Background

Cardiac arrhythmias occur when there is interruption of the normal sinus rhythm. Symptoms include palpitations, dizziness, lightheadedness, syncope, dyspnea, anxiety, weakness, and chest discomfort. One therapeutic option is the implantation of pacemaker which provides electrical impulses to the heart. Conventional pacemakers consist of a pulse generator, which provides electrical impulses, and leads delivering electrical impulses from the generator to the heart. The pulse generator is the battery and is placed in the anterior part of the chest (pre-pectoral) while the leads are placed transvenously.

However, there are several complications associated with traditional pacemakers. Complications due to the pulse generator include hematoma, skin breakdown, and pocket infection (Udo et al., 2012). Complications due to the leads include venous obstruction, lead dislodgement, lead malfunction, lead fractures, and infection (Cheng, Wang, Curtis, & Varosy, 2010; Kirkfeldt et al., 2011; Udo et al., 2012).

Leadless pacemakers have been the center of attention due to its ability to address the limitations of traditional transvenous pacemakers. Two leadless pacemakers have been assessed for single-chamber right ventricular pacing. These include Nanostim LP (Abbott, formerly St. Jude, Lake Bluff, IL) and Micra Transcatheter Pacing System (Medtronic, Minneapolis, MN). Nevertheless, Nanostim is out of the market due to premature battery depletion (Yarlagadda et al., 2018). Leadless pacemakers are composed of a pulse generator, battery, and electrode in the same device (Reddy et al., 2015). It is placed through a catheter and is directly implanted into the right ventricle (Yarlagadda et al., 2018).

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The leadless pacemaker's (Nanostim) length is 42 mm and a maximum diameter of 5.99 mm with a battery life ranging from 8.4 to of 12.4 years (Reddy et al., 2015). A sheath is placed in the femoral vein, and with a sleeve-based catheter, the device is delivered to the right ventricle. The sleeve is then withdrawn, and the pacemaker is implanted into the endocardium while the device remains docked. The device is then undocked from the catheter but is still connected to the catheter through tether connections. This allows for device measurements and evaluation of stability without the catheter. Repositioning can be performed if the device is not well positioned. Once positioning is assured and the pacemaker parameters are optimal [(R wave amplitude ≥5.0 mV) and pacing threshold (≤2.0 V at 0.4 ms)] (Yarlagadda et al., 2018), the device is untethered from the catheter resulting in the final implant position (Reddy et al., 2015). The procedure is performed under fluoroscopy. After the procedure, patients are observed over a period of 24 hours and discharged (CADTH 2015). An external programmer is used to program Micra transcatheter pacing system.
Some differences are worth noted. The Nanostim pacemaker is smaller than the traditional pacemaker (<10%), with a battery life ranging between 8.4 years and 12.4 years. The Micra Transcatheter Pacing System pacemaker is 30% smaller than the Nanostim and its estimated battery life ranges from 10 to 15 years. Micra transcatheter pacing is 93% smaller than conventional pacemakers, about the size of a large vitamin capsule (https://www.medtronic.com/us-en/patients/treatments-therapies/pacemakers/our/micra.html). The insertion of these devices takes 20 to 45 minutes compared to 60 minutes for the conventional pacemaker (CADTH 2015).

Medical Technology Assessment Committee (MTAC)

Leadless Pacemakers for the treatment of cardiac arrhythmias

Date: 04/21/2019

Evidence Conclusion:

- In patients with cardiac arrhythmias who require single-chamber ventricular pacing, there is insufficient evidence to compare leadless pacemakers with conventional pacemakers. However, serious complications are non-negligible.
- Randomized controlled trials with longer-term follow-up and direct comparisons are warranted.

Articles: PubMed was searched through March 8, 2019 with the search terms ((Nanostim Leadless Pacemaker OR Micra Transcatheter Pacing System OR leadless pacemaker)) AND (traditional pacemakers OR conventional pacemakers). Other search terms included (Nanostim Leadless Pacemaker OR Micra Transcatheter Pacing System OR leadless pacemaker) filters: observational study. The search was limited to English language publications and human populations. The reference lists of relevant studies were reviewed to identify additional publications. Randomized controlled trials, and observational studies were included in the search. Clinicaltrials.gov was also searched. Three studies were retained and reviewed. See Evidence Table**.**

The use of Leadless Pacemakers for the treatment of cardiac arrhythmias does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Hayes Technology Assessment

Micra Transcatheter Pacing System (Medtronic Inc.) for Single Chamber Pacemaker Indications

Date: July 3, 2022

The Micra TPS is a single-chamber right ventricular pacing device. The device senses electrical activity of the heart via electrodes within the device's titanium capsule. Heart rhythm is monitored for bradycardia. Rate-adaptive pacing therapy is provided based on programmed pacing parameters. The Micra TPS is self-contained and does not require a surgical incision in the chest or intravascular leads. It is inserted via a 23-French catheter placed in the femoral vein and held in place within the right ventricle of the heart via nitinol tines that attach to the myocardium.

Conclusion

A low-quality body of evidence suggests that Micra TPS is associated with a high rate of procedural success and that pacing capture thresholds remained low and stable after implantation for up to 36 months. Major complications are comparable with and perhaps lower for Micra TPS versus TVPM, and revision and retrieval rates are lower for Micra TPS than TVPM. However, the clinical significance of any benefits introduced by use of the Micra TPS is uncertain due to the small body of evidence directly evaluating patient-centered outcomes.

Hayes Rating: C

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Hayes. Hayes Technology Assessment. Micra Transcatheter Pacing System(Medtronic Inc.) for Single-Chamber Pacemaker Indications. Dallas, TX: Hayes; July 3, 2022. Retrieved May 15, 2023, from https:// https://evidence.hayesinc.com/report/htb.micrapacing4178

Applicable Codes

Medicare - Considered Medically Necessary when criteria in the applicable policy statements listed above are met
Non-Medicare - Considered Not Medically Necessary

CPT® Codes	Description
33274	Transcatheter insertion or replacement of permanent leadless pacemaker, right ventricular, including imaging guidance (eg, fluoroscopy, venous ultrasound, ventriculography, femoral venography) and device evaluation (eg, interrogation or programming), when performed
33275	Transcatheter removal of permanent leadless pacemaker, right ventricular, including imaging guidance (eg, fluoroscopy, venous ultrasound, ventriculography, femoral venography), when performed

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Date Created	Date Reviewed	Date Last Revised
05/07/2019	05/07/2019[MPC], 05/05/2020[MPC] , 05/04/2021[MPC], 05/03/2022[MPC], 05/02/2023[MPC]	05/15/2023

[MPC] Medical Policy Committee

Revision History	Description
05/07/2019	MPC approved to adopt a non-coverage policy for leadless pacemakers
05/05/2020	Added applicable CPT codes 33274 and 33275 to policy
05/15/2023	Updated References to include Hayes Technology assessment

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Clinical Review Criteria
Peanut Challenge for Sensitized Infants

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Criteria

For Medicare Members

None

For Non-Medicare Members

Medical necessity review no longer required.

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Background

Food allergy affects 1-3% of children in developing countries, and the prevalence of food allergy has increased dramatically in the past several decades. For many years' scientists believed that delaying the introduction of allergenic foods into an infant's diet was beneficial, though more recent evidence has questioned this assumption. The "Learning Early About Peanut Allergy" (LEAP) Study, sponsored in part by FARE (Food Allergy Research and Education) and the National Institute of Allergy and Infectious Disease, hypothesized that the early introduction of peanuts into the diet of high-risk infants may prevent peanut allergy. LEAP Study design: The LEAP study enrolled 640 "high risk" infants between age 4 months and 11 months. High risk was defined as having moderate to severe eczema (persistent rash affecting > 75% of skin) and/or egg allergy since children with these problems are more likely to develop peanut allergy. All of the infants were skin tested to peanut. Those who had a strongly positive skin test (> 4 mm welt from prick test) were not allowed to continue in the study because they were assumed to have peanut allergy. The rest of the infants were randomly assigned to either consume peanut at least 3 days a week until age 5 (equivalent of 6 tsp peanut butter per week) or to avoid peanuts until age 5. Importantly, all these high-risk infants randomized to consume peanut underwent supervised oral challenge to peanut in the allergy clinic before feeding peanut at home.

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
95076	Ingestion challenge test (sequential and incremental ingestion of test items, eg, food, drug or other substance); initial 120 minutes of testing
95079	Ingestion challenge test (sequential and incremental ingestion of test items, eg, food, drug or other substance); each additional 60 minutes of testing (List separately in addition to code for primary procedure)
with dx of peanut allergy	

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Date Created	Date Reviewed	Date Last Revised
09/01/2015	09/01/2015[MPC], 06/07/2016[MPC], 04/04/2017[MPC], 02/06/2018[MPC], 01/08/2019[MPC], 01/07/2020[MPC], 01/05/2021[MPC], 01/04/2022[MPC], 01/10/2023[MPC]	09/01/2015

[MPC] Medical Policy Committee

Revision History	Description
04/04/2017	Medical necessity review no longer required.

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KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Light Therapy, for Seasonal Affective Disorder (SAD)

- Bright Light Therapy
- Dawn Simulation Therapy

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	See the Noridian Non-Covered Items for HCPC code E0203

For Non-Medicare Members

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

If requesting review for this service, please send the following documentation:

- Last 6 months of clinical notes from requesting provider &/or specialist

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Background

The term ‘seasonal affective disorder’ (SAD) was first introduced by Rosenthal and colleagues in 1984 who described a series of patients with a history or recurrent depressions that occurred in the fall or winter and spontaneously remitted in the following spring or summer. Two seasonal patterns of SAD have been described; the summer-onset SAD and the fall-onset SAD. The latter, also known as “winter depression”, is the most common pattern of the disorder. SAD affects about 5-6% of the population in the U.S. and its prevalence increases with latitude. This ranges from 1.4% in Florida to 9.7% in New Hampshire and 9.9% in Alaska. It is reported that SAD affects patients in their 20s, and that women are more likely than men to develop the disorder.

SAD was previously classified as a mood disorder in which people with normal mental health throughout most of the year experience depressive symptoms in the winter or summer. The Diagnostic and Statistical Manual of Mental Disorders DSM-IV and DSM-5 no longer classifies SAD as a unique mood disorder but describes it as a "specifier" or a subtype that can occur as part of unipolar major depression, bipolar I disorder, or bipolar II disorder. SAD is characterized by typical symptoms of major depression such as low mood, lack of drive, lack of concentration, and decrease in interest. In addition, patients exhibit more atypical depressive symptoms such as hypersomnia, increased appetite with carbohydrate craving, weight gain, irritability, and anger attacks. Symptoms usually resolve in the summer, and rarely progress to manic episodes of bipolar disorder.

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The exact mechanism of SAD is still under investigation, but it is hypothesized that it is related to natural seasonal variations in light levels. According to this hypothesis “the phase shift hypothesis” fewer daylight hours in the winter causes a circadian misalignment between the biological clock and solar cycle leading to disturbances in the melatonin levels and longer periods of its synthesis at night. Melatonin, also called circadian hormone, peeks in the darkness and promotes sleep. It is believed that its increased daytime levels contribute to the depressive symptoms of SAD. Other neurotransmitters under circadian control e.g. serotonin, norepinephrine, and dopamine are also believed to have a role in the SAD mood alterations. However, no studies have established a causal relationship between decreasing daylight and the winter SAD.

Three types of treatment are being used for patients with SAD: pharmacological therapy, cognitive behavioral therapy (CBT), and light therapy. Antidepressant medication is an accepted treatment for depression in general, and three SSRIs have shown favorable results with SAD. CBT may help reduce the risk of relapse of major depression, but only few small studies evaluated its effectiveness for SAD.

Light therapy using light boxes was introduced as a treatment for SAD when the disorder was first described in 1984, based on the phase shift hypothesis. Early studies examined the effect of bright white light on circadian rhythm. Other research investigated less intense light and showed that it may have a larger capacity to regulate the biological clock than higher intensity light. A small study showed that blue light with an intensity of about 460 m may have a significant effect on melatonin suppression and circadian phase shifting.

Currently there are a number of commercially available light therapy products. These include bright light boxes, lamps, light visors, and dawn simulators. Light boxes come in different shapes and sizes, and with varied features and intensities of light. There is no well-accepted standard protocol for light therapy. Commonly bright-light therapy (BLT) is applied using a light box containing fluorescent lamps, a reflector and a diffusing screen. For adequate treatment light intensities of 5,000-10,000 lux measured at the level of the eyes, and at a therapeutic distance of 60-80 cm from the light box is considered as a standard requirement. Patients do not need to look directly into the light source as long as the light meets the eye at an angle of 30-60o. Treatment is usually started with using a light intensity of 10,000 lux for 30 minutes. The duration of treatment may be increased in case of insufficient response or when using less powerful light boxes. It is reported that morning administration of BLT offers greater chance of remission, that compliance is the primary factor for success of the therapy, and that the therapeutic effect is demonstrated in 3-7 days and disappears shortly after the treatment is discontinued.

Light boxes are designed to be safe and effective but are not regulated as devices by the Food and Drug Administration (FDA). A number of side effects of light therapy for SAD have been reported but are generally mild and/or transient. These include headache, nausea, agitation, eye strain and blurred vision. Evening light therapy may lead to sleep disturbances. Suicidality, menstrual irregularity, and hypomania in bipolar patients have also been reported. Retinal degeneration after prolonged exposure to intensive light has been noticed in rodents but was not confirmed in humans. However, it is recommended that caution must be used with patients at higher risk of retinal damage or those who need photosensitizing medication.

Medical Technology Assessment Committee (MTAC)

Light Therapy in the Treatment of Seasonal Affective Disorder (SAD)

06/02/2008: MTAC REVIEW

Evidence Conclusion: There is evidence from a meta-analysis of placebo-controlled RCTs (Golden et al., 2005) that bright light therapy and dawn simulation are both effective for treating SAD in non-geriatric adults. Strength of the meta-analysis was that the investigators used strict criteria to ensure that studies had a valid placebo control. Limitations are that studies tended to be small (all had <100 participants) and the minimum treatment duration was 4 days. Moreover, studies had different treatment protocols and thus conclusions cannot be drawn about the effectiveness of a particular approach to light therapy (e.g. lux, frequency of sessions, length of treatment). There is currently no generally accepted protocol for light therapy. When the two RCTs in the meta-analysis with the longest treatment durations and largest sample sizes were examined closely, bright light therapy did not clearly appear to be effective. Avery et al. (2001) did not find that bright light was significantly superior to placebo. Eastman et al. (2005) did not find a significant benefit to light therapy versus placebo for the outcomes change in SIGH-SAD score and response rate. They did find a significant benefit when examining the proportion of participants classified as near complete or complete responders. All of the studies on dawn simulation in the Golden et al. meta-analysis were conducted by the same research group. As the authors pointed out, the evidence would be strengthened if their findings could be replicated by different researchers in other locations. The largest study, Avery et al., (2001) found that dawn simulation was superior to both bright light and placebo for remission of SAD. The RCTs identified that compared light therapy to medication or cognitive-behavioral therapy did not have true placebo control groups and thus, intervention effectiveness beyond the placebo effect cannot be

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determined. The Rohan et al. 2007 study found a lower post-treatment SAD score in patients receiving light therapy, CBT or their combination compared to a wait-list control. However, being on a wait-list could have a 'reverse placebo effect' since patients are not expecting to improve before receiving treatment. The Lam et al. (2006) studies did not find significant differences in response rates in groups assigned to light therapy or fluoxetine treatment.
Conclusion: A valid placebo group is important in RCTs of light therapy for SAD. A meta-analysis of placebo-controlled RCTs found a significant benefit of bright light and dawn simulation therapy. The meta-analysis was limited because studies tended to be small and of short duration. The largest RCTs in the meta-analysis did not find a significant benefit to bright light therapy. The evidence on dawn simulation is limited because all studies were done by the same research group and it is not known whether findings are generalizable. RCTs comparing light therapy to antidepressant treatment or psychotherapy did not include true placebo groups.
Articles: The ideal study would be a randomized controlled trial (RCT) or meta-analysis of RCTs that include a placebo or sham intervention. Studies comparing light therapy to medication therapy and/or psychotherapy should also have a placebo group. There was a protocol for a Cochrane review on light therapy for SAD. The protocol was published in 2003, and its status remains unchanged in Cochrane Library 2008, Issue 2. An estimated date for completion of the review is not available. One published meta-analysis was identified (Golden et al., 2005). The Golden study searched the literature to July 2003 and included only placebo-controlled studies. Golden et al. and the two RCTs in the meta-analysis with the largest sample sizes per treatment group and the longest trial duration (Avery et al., 2001; Eastman et al., 1998) were critically appraised. No large placebo-controlled RCTs published after the Golden meta-analysis was identified. There was one newer RCT comparing light therapy to fluoxetine treatment (Lam et al., 2006) and another comparing light therapy to cognitive-behavioral therapy (Rohan et al. 2007). These two new RCTs were also critically appraised. References for studies reviewed are as follows:
Golden RN, Gaynes BN, Ekstrom RD et al. The efficacy of light therapy in the treatment of mood disorders: A review and meta-analysis of the evidence. Am J Psychiatry 2005; 162: 656-662. See Evidence Table. Avery DH, Eder DN, Bolte MA et al. Dawn simulation and bright light in the treatment of SAD: A controlled study. Biol Psychiatr 2001; 50: 205-216. See Evidence Table. Eastman CI, Young MA, Fogg LF et al. Bright light treatment of winter depression. Arch Gen Psychiatr 1998; 55: 883-889. See Evidence Table. Lam RW, Levitt AJ, Levitan RD et al. The Can-SAD study: A randomized controlled trial of the effectiveness of light therapy and fluoxetine in patients with winter seasonal affective disorder. Am J Psychiatry 2006; 163: 805-812. See Evidence Table. Rohan KJ et al. A randomized controlled trial of cognitive-behavioral therapy, light therapy and their combination for seasonal affective disorder. J Consult Clin Psych 2007; 75: 489-500. See Evidence Table.

The use of light therapy in the treatment of Seasonal Affective Disorder (SAD) does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

12/21/2015: MTAC REVIEW
Light Therapy for SAD
Evidence Conclusion: The ideal study for examining the effect of bright light therapy for SAD would be a double-blind randomized controlled trial that compares light therapy to a placebo or sham intervention. Studies comparing light therapy to pharmacological therapy or psychotherapy should also have a placebo group since there is limited evidence from placebo-controlled trials on the effectiveness of antidepressants or cognitive behavioral therapy on SAD. *Light therapy versus placebo* Martensson et al's meta-analysis, 2015 (Evidence table 1), pooled the results of 8 RCTs that compared light therapy to placebo (low negative air ions, dim red light, and dawn simulator placebo) to determine the effect bright white light (BWL) therapy on SAD. The authors performed two separate sets of meta-analyses; the first analyzed the results week-by-week, and the second analyzed the final results only. The pooled results suggest that BWL had a moderate effect on SAD symptoms compared to the controls (standardized mean difference [SMD] -0.54 (95% CI -0.95, -0.03), and that it reached statistical significance at week two and week three of treatment. The authors concluded that the BWL therapy seems to be effective, but they questioned the validity of the results due to the heterogeneity of the studies, lack of an appropriate placebo or sham light therapy control group, and other methodological limitations including the small sizes, short duration, and complex design of the trials. The results of Martensson et al's meta-analysis show a smaller effect size than that found in the Golden et al's meta-analysis reviewed earlier in MTAC (effect size 0.84, 95% CI 0.60, 1.08). As noted in the 2008 MTAC report, Golden et al's meta-analysis had the advantage of using strict criteria to ensure that studies had a valid placebo control, but was limited by the inclusion of very small studies with large treatment effect, short treatment durations, and the use different treatment protocols, which makes it difficult to draw any conclusion on the effectiveness of a particular approach to light therapy. When the two RCTs in the meta-analysis with the longest treatment durations and largest sample sizes were examined closely, bright light therapy did not clearly appear to be effective. *Light therapy versus antidepressants* In a Cochrane review on second-generation antidepressants for SAD, Thaler, et al (2011), pooled the results of two small trials (total N=136 participants) that

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compared light therapy to fluoxetine and found no significant difference between the two therapies in response or remission of SAD. The trials were small, with limitations and high dropout rates, and the overall response rate (>50% improvement on 24-item HAM-D SIGH-SAD) was 68/100 in the light therapy group and 67/100 in the fluoxetine group. The authors concluded that the overall quality of evidence is a low and insufficient to draw any conclusion on the use of second-generation antidepressants for SAD. The only available RCT of fluoxetine vs. placebo showed a nonsignificant effect in favor of fluoxetine, and the two small trials that compared fluoxetine to light therapy showed no significant differences between the two therapies in the treatment of SAD. *Light therapy versus cognitive behavioral therapy (evidence table 2)* In a recent RCT, Rohan et al, 2015, compared the treatment outcomes of light therapy versus cognitive behavioral therapy for SAD. The trial randomised 177 participants to receive light therapy (using 23x15.5x3.25 in. SunRay that emits 10,000 lux of cool-white fluorescent light) immediately upon awakening, or to receive cognitive behavioral therapy (CBT-SAD) for 6 weeks. The primary endpoints of the trial were the change in depression severity SIGH-SAD during 6 weeks of therapy, and remission status after treatment. Overall, the results showed improvement in SAD symptoms in the two study groups with no significant differences between them at 6 weeks of treatment. There was no long-term follow-up to examine recurrence rates with each therapy. The trial was a relatively small, single center, RCT conducted mainly among white women. The participants were not blinded to the treatment allocation, which is a potential source of bias, and according to the authors, the primary investigator was the developer of CBT-SAD which is another potential source of bias. More importantly, light therapy was compared to CBT-SAD which has not been thoroughly investigated as a treatment for SAD. Ideally the trial would include a sham light therapy and /or a placebo group to determine the placebo effect of each of the two therapies.
Conclusion: There is insufficient evidence to determine the effectiveness of light therapy for the treatment of SAD. Several national and international guidelines recommend light therapy for SAD giving it a level 1 evidence (Canadian guideline, 2009) or level 2 evidence (AAFP, 2013), others like the British NICE guideline (2009) and the World Federation of Societies of Biological Psychiatry (WFSBP, 2013) are uncertain about the evidence supporting light therapy for SAD.
Articles: The literature search for studies on light therapy for SAD published after the last MTAC review revealed a recent systematic review with meta-analyses on bright light therapy for depression including SAD, a Cochrane review on second-generation antidepressants for SAD, a randomized controlled trial of CBT vs. light therapy for SAD, a crossover RCT investigating the rapid effects of light therapy on SAD, and a retrospective study investigating the appropriate duration of light therapy. The search also identified three small to relatively small RCTs that compared standard bright light vs. dawn simulation, low-intensity blue-enriched white light, or negative air ions, as well as a more recent trial on different intensities of transcranial bright light treatment delivered via the ear canals for SAD. The meta-analysis and the RCT comparing bright light therapy to CBT were selected for critical appraisal. The pooled results of studies comparing antidepressants vs. light therapy in the Cochrane review were included. Mårtensson B, Pettersson A, Berglund L, et al. Bright white light therapy in depression: A critical review of the evidence. *J Affect Disord*. 2015 Aug 15; 182:1-7. See Evidence Table 1**.** Rohan KJ, Mahon JN, Evans M, et al. Randomized Trial of Cognitive-Behavioral Therapy versus Light Therapy for Seasonal Affective Disorder: Acute Outcomes. *Am J Psychiatry*. 2015 Sep 1; 172(9):862-869. See Evidence Table 2.

The use of light therapy in the treatment of Seasonal Affective Disorder (SAD) does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

07/08/2019: MTAC REVIEW
Light Therapy for SAD
Conclusion:

- The search identified one study which is a follow-up of one of the studies assessed in the last review in 2015. The study is of low quality and suggests that CBT may be comparable to LT in terms of recurrence and remission status at next winter. In addition, CBT might be more effective than light therapy two winters later. Studies with higher quality are needed to draw firm conclusions on light therapy and unipolar depression with seasonal pattern in the long-term. There is insufficient (high-quality) evidence for or against the use of light therapy in patients with unipolar major depression with seasonal pattern in the long-term.
- There is insufficient evidence for or against the effectiveness of light therapy as preventive treatment for patients with a history of SAD.

Articles: The search yielded 242 items; but one RCT and one meta-analysis were retained.

The use of light therapy in the treatment of Seasonal Affective Disorder (SAD) does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

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Applicable Codes

Considered not covered:

HCPC Codes	Description
E0203	Therapeutic lightbox, minimum 10,000 lux, table top model
A4634	Replacement bulb for therapeutic light box, tabletop model

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check.**

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Date Created	Date Reviewed	Date Last Revised
07/16/2008	05/03/2011[MDCRPC], 08/02/2011[MDCRPC], 06/05/2012 [MDCRPC], 04/02/2013[MDCRPC], 02/04/2014 [MPC], 12/02/2014 [MPC], 10/06/2015[MPC], 08/02/2016[MPC], 06/06/2017[MPC], 04/03/2018[MPC], 04/02/2019[MPC], 04/07/2020[MPC], 04/06/2021[MPC], 04/05/2022[MPC], 04/04/2023[MPC]	08/06/2019

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
10/20/2015	Changed Medicare link
01/06/2016	MPC approved to retain a policy of insufficient evidence
08/06/2019	Added July 8, 2019 MTAC review

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KAISER PERMANENTE®

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PATIENT REFERRAL GUIDELINES
Liver Transplant

- Liver Transplant: Adult/Pediatric
- Living-Donor Liver Transplant: Adult – Adult
- Organ Transplantation in Members with HIV/AIDS

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Adult Liver Transplantation (260.1)
Local Coverage Determinations (LCD)	None
Local Coverage Article	None

For Non-Medicare Members

Liver transplantation may be considered for patients with end-stage liver diseases who have no prospect for prolonged survival, or whose quality of life is severely impaired. These guidelines for referral for transplant evaluation are not intended as an automatic inclusion or exclusion of a candidate for referral.

1. **GENERAL PRINCIPLES**
   a. If clinical parameters of end-stage or life-threatening disease indicate the need for transplantation, then early referral should be made.
   b. Patients with a history of malignancy with a moderate to high risk of recurrence (as determined after consultation with oncologist considering tumor type, response to therapy, and presence or absence of metastatic disease) may be unsuitable candidates for transplantation. Patients with low risk of recurrence may be considered.
   c. Uncontrollable active infection outside of the hepatobiliary tree is a contraindication to liver transplant.
   d. Candidates with a history of substance abuse must be free from alcohol and other substance abuse and have been evaluated by a substance abuse program. The risk of recidivism, which has been documented to negatively impact transplant outcomes, must be addressed and considered to be low. [1,2,3] Exceptions may be made on a case-by-case basis.
      i. For patients with a first alcohol-related / liver decompensating event, whose severity of liver disease suggests they are unlikely to survive to reach 6 months alcohol abstinence, see appendix for the "Kaiser Permanente Protocol: Reduced Duration Alcohol Sobriety Pathway to Liver Transplant Listing" (Appendix I).
   e. Candidates for thoracic organ (heart, lung and heart/lung) transplants must be free from tobacco use for the previous six (6) months. Routine monitoring may be required. Specific programs for abdominal organs (liver, intestines, and kidney) may require abstinence from tobacco products to be actively listed.
   f. Candidates must have adequate social support systems and display a proven record of adherence to medical treatment.
   g. Patients must be willing and able to travel within short notice to the KP approved transplant Center of Excellence and, if necessary, return for treatment of complications.
   h. Patients must have a caregiver or caregivers, who are physically and cognitively able to assist the patient with self-care activities and are able to travel within short notice to the KP approved transplant Center of Excellence.

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i. The presence of significant irreversible neurologic dysfunction, active psychological and/or psychiatric conditions, and/or other social behaviors that prevent adherence with a complex medical regimen, are considered contraindications for referral for transplant.
j. Evidence of such non-adherence may be failure to keep appointments, failure to make steady progress in completing pre-transplant evaluation requirements, failure to accurately follow medication regimens or failure to accomplish the activities required for maintenance on the waiting list.
k. Whenever transplant is considered as an option and discussed with the patient and/or family, consultation with Advanced Life Care Planning/Palliative Care resources is strongly recommended.

2. **INDICATIONS FOR LIVER TRANSPLANT**
   a. Acute Fulminant Hepatic Failure. Refer patient as soon as diagnosis is made.
      i. Progressive Coagulopathy
      ii. Hepatic Encephalopathy
      iii. Progressive Hyperbilirubinemia
   b. Chronic Liver Disease – referral is generally not advised until there is a MELD or PELD score of 15, with exceptions for the indications listed below: There is evidence that there is no survival benefit for patients transplanted with a MELD score <15. [4]
      i. Hepatocellular Carcinoma
         1. Patients who meet Milan/UCSF criteria for hepatocellular carcinoma may be referred to transplant centers for transplant evaluation.
         2. Patients with hepatoblastoma who exceed Milan/UCSF criteria may be considered as liver transplant candidates on a case by case basis. [5]
         3. Pediatric patients with nonmetastatic and unresectable hepatoblastoma (PRETEXT IV and complex pretext III) should be referred for LT evaluation at the time of diagnosis or no later than after 2 rounds of chemotherapy.
         4. Pediatric patients with hepatoblastoma and pulmonary metastases can be considered for liver transplant if, following chemotherapy, a chest CT is clear of metastases or, if a tumor is identified, the pulmonary wedge resection reveal the margins are free of the tumor (AASLD/NASPGHAN guidelines 2014)
      ii. Intractable Encephalopathy
      iii. Intractable Ascites/ hepatic hydrothorax
      iv. Intractable Variceal Bleeding
      v. Cholestatic Liver Disease:
         1. Intractable Pruritis
         2. Recurrent Cholangitis
         3. Intractable Bone Disease
      vi. Progressive Hepatopulmonary Syndrome
      vii. Hepatorenal Syndrome
      viii. Additional indications for liver transplant for the pediatric population: Urea cycle defects, organic acidemia and other metabolic disorder

3. **CONTRAINDICATIONS FOR LIVER TRANSPLANT**
   a. Advanced cardiopulmonary disease or any other life limiting disorder not corrected by liver transplantation. All patients should be evaluated for coronary artery disease (CAD) and occult cardiomyopathy. Hepatopulmonary syndrome and hepatorenal syndrome are not contraindications as they are correctable by transplantation.
   b. Patient whose HCC exceeds Milan criteria or whose alpha fetoprotein (AFP) level is greater than 1000 ng/ml should not be referred for transplant until they have been down staged successfully to within Milan criteria and/or an AFP level of less than 500 ng/ml. Exceptions may be made on a case by case basis for hepatoblastoma. [6, 7]
   c. Absolute contraindication of liver transplant in pediatric patients - Severe multisystem mitochondrial disease

4. **RELATIVE CONTRAINDICATIONS FOR LIVER TRANSPLANT**
   a. Pulmonary hypertension with pulmonary artery systolic pressure 50 mmHg or mean >35 mmHg (despite optimal medical management).
   b. Renal failure (excluding hepatorenal syndrome)
   c. Active infection outside the hepatobiliary system
   d. Advanced malnutrition
   e. Severe diabetic complications
   f. Inability to control HbA1C <8
   g. Massive obesity
   h. Multiple abdominal surgeries

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i. Significant irreversible neurologic dysfunction.
j. Highly selected patients with only intra-ductal cholangiocarcinoma may be considered for transplant on a case-by-case basis, at a transplant center with an established cholangiocarcinoma program. [8, 9]

5. MULTIPLE ORGAN TRANSPLANTS INCLUDING LIVER

Liver transplantation combined with another organ transplant is indicated in special circumstances in pediatric and adult patients. Examples include, but are not limited to, liver/kidney, liver/lung and liver/heart. These combined organ transplants require case by case evaluation.

6. SPECIAL CONSIDERATIONS FOR LIVING DONOR LIVER TRANSPLANT

In addition to the current KP cadaveric donor patient referral guidelines for adults, the following should be considered when presented with a potential living donor liver transplant.

a. No recipient should be considered for living donor liver transplant if in status 1 fulminant liver failure.
b. Patients with MELD < 15 but with complications of liver disease that are uncorrectable and not reflected in the MELD score may be considered for living donor liver transplantation on a case by case basis after consultation with a hepatologist.
c. Recipients with hepatocellular carcinoma (HCC) should meet the same guidelines as listed for cadaveric donor patient referral guidelines.
d. Living donor liver transplant is not contraindicated for pediatric patients with acute liver failure if patient is a candidate for liver transplant.

7. ADDITIONAL INFORMATION ON LIVER TRANSPLANTATION

For additional information about UNOS policies on organ allocation and candidate criteria, please visit **https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf#nameddest=Policy_09**

APPENDIX I:

Reduced Duration Alcohol Sobriety Pathway to Liver Transplant Listing - Kaiser Permanente Protocol

(For Northern California, please consult the "**Reduced Duration Alcohol Sobriety Pathway to Liver Transplant Listing Kaiser Permanente Northern California Protocol**", available on the Clinical Library under Northern California)

BACKGROUND / PURPOSE:

- There is data suggesting that the currently utilized 6-month alcohol sobriety rule needed for liver transplant listing may not be the best predictor of relapse on a liver transplant list or post-transplant
- Some liver transplant programs in the United States and Europe accept a reduced duration alcohol sobriety pathway to liver transplant listing
- This protocol is designed to evaluate and qualify Kaiser Permanente patients for liver transplant listing who have not reached 6-months of alcohol sobriety

WHO THIS PATHWAY APPLIES TO:

- This protocol applies to patients with a first alcohol-related / liver decompensating event (as defined below) and whose severity of liver disease suggests they are unlikely to survive to reach 6 months alcohol abstinence (see suggested scenarios below)
- Patient must be without incapacitating hepatic encephalopathy and/or cannot be intubated when evaluated by addiction medicine and supporting gastroenterology and hepatology physician
  - Family/family friends or significant others will not be used as sole historians in the event the candidate is incapacitated with hepatic encephalopathy and/or intubated
- This protocol does not apply to patients who are not presenting with a first liver-decompensating event or who have already reached 6 months alcohol abstinence. Standard criteria for liver transplant listing should be applied to those patients.

Protocol Flow Diagram:

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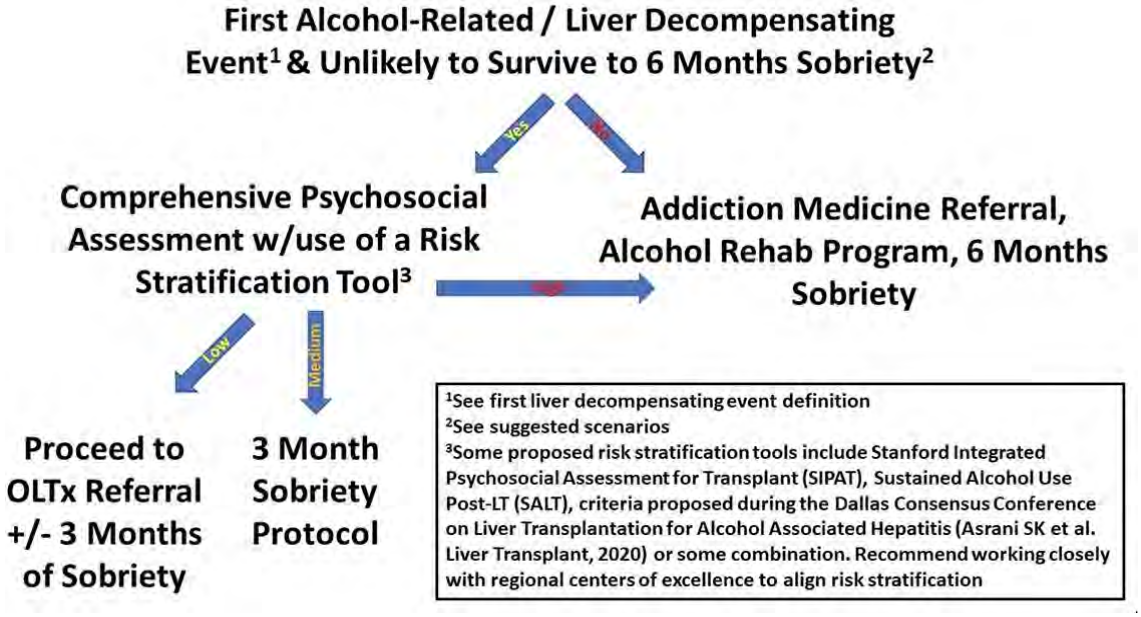

DEFINITION OF FIRST ALCOHOL-RELATED / LIVER DECOMPENSATION

To help define a potential first alcohol-related / liver decompensating event, try to answer this question: When faced with the knowledge that their alcohol use was linked to a negative effect on their legal status or medical health, did the candidate stop drinking? If no, then the candidate's presentation with severe alcoholic hepatitis or acute on chronic liver failure is not considered their first decompensating event, as it demonstrated poor insight and decision-making. These criteria represent relatively easy to find information within the medical chart that represent exclusion criteria.

- Exclusion of patients with history of hospital admission due to the following complication of alcohol abuse within *the last 2 years*:
  - Alcohol-related hepatitis
  - Alcohol-related pancreatitis
  - Alcohol-related cardiomyopathy
  - Alcohol withdrawal (including delirium tremens and/or seizures)
  - Alcohol psychosis
- Exclusion of patients with history of an emergency room visit due to the following complication of alcohol abuse within *the last 2 years:*
  - Alcohol-related hepatitis
  - Alcohol-related pancreatitis
  - Alcohol-related cardiomyopathy
  - Alcohol withdrawal (including delirium tremens and/or seizures)
  - Alcohol psychosis
  - Alcohol intoxication with or without a complication (like fall or altercation)
- Exclusion of patients with *more than one* failed alcohol rehabilitation attempt within *the last 2 years*
- Exclusion of patients with any previous diagnosis in problem list of the following complications of alcohol abuse within *the last 2 years*:

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- Alcohol-related hepatitis
- Alcohol-related pancreatitis
- Alcohol-related cardiomyopathy
- Severe alcohol use disorder

➢ Exclusion of patients with any previous diagnosis in problem list of alcohol-related cirrhosis at *any time*.
➢ Exclusion of patients with active polysubstance abuse (any co-substance except for marijuana and/or nicotine) within *the last 2 years*.

UNLIKELY TO SURVIVE TO REACH 6 MONTHS ALCOHOL ABSTINENCE

No comprehensive definition of patients with severe acute alcohol related hepatitis or alcohol related acute on chronic liver failure can be provided. Ultimately, this assessment is left to patient's treating hepatologist and larger treatment team. Some suggested scenarios include:

- Patient with severe acute alcoholic hepatitis (Maddrey's Discriminant Function >32) who is not a candidate for or has failed medical management (including use of prednisolone with or without N-acetylcysteine infusion with resultant 7-day Lille Score > 0.45)
- Inpatient with persistent MELD score > 30 (see 3-month predicted survival based on MELD score below) Inpatient with dialysis dependent hepatorenal syndrome type 1

3-Month Mortality Based on MELD Scores

The estimated 3-month mortality is based on the MELD score highlighted in yellow above.

MELD Score	Mortality Probability
40	71.3% mortality
30-39	52.6% mortality
20-29	19.6% mortality
10-19	6.0% mortality
9 or less	1.9% mortality

Footnotes

1. Liver Transplantation 2006, .12:813-820. Alcohol consumption patterns and predictors of use following liver transplantation for alcoholic liver disease.
2. Liver Transplant Surg. 1997, Vol 3, 304 – 310. The natural history of alcoholism and its relationship to liver transplantation.
3. Alcohol abstinence prior to liver transplantation for Alcoholic Liver Disease (G110807), TPMG New Medical Technology
4. American Journal of Transplantation 5 (2) 203-205, February 2005.
5. Hepatoblastoma (HB) is the most common type of liver cancer in children. The gold standard treatment of HB is perioperative chemotherapy followed by complete resection of tumor. Liver transplantation (LT) for children with HB should be considered (even if beyond Milan criteria) if the tumors are nonresectable or show chemotherapy resistance. LT for children with HB should be considered even with very high AFP levels. LT may be considered even if there is a history of pulmonary metastasis (after thoracotomy and resection +/- chemotherapy). Contraindications to LT for HB: Vascular invasion (including tumor clot).
6. The Milan Criteria for liver patients with HCC is 1 tumor: 5 cm or 2 – 3 lesions, none >3 cm and no vascular invasion. Source: NEJM 1996, 334; 693-699.
7. The UCSF/Region 5 Criteria for liver patients with HCC is 1 tumor: 6.5 cm, or 2 – 3 lesions, none >4.5 cm and total tumor diameter ::8 cm, and no vascular invasion. Hepatology, 2001, 33; 1394-1403.

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8. Transplantation for Hilar Cholangiocarcinoma. Liver Transplantation, Vol. 10, (10); Supplement II (October) 2004:pp 565-568
9. Goldberg, et. Al. (2014), Hepatology, 60 (5), 1717-1726.

If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Liver transplantation or hepatic transplantation is the replacement of a diseased liver with a healthy liver from another person (allograft). Liver transplantation is a viable treatment option for end-stage liver disease and acute liver failure.

Medical Technology and Assessment Committee (MTAC)

Living-Donor Liver Transplant – Adult-to-Adult

BACKGROUND

Living donor liver transplantation (LDLT) was developed as an alternative to cadaveric liver transplantations due to the dramatic shortage of available livers. LDLT to pediatric recipients was introduced into clinical practice in 1989 and the procedures are now performed worldwide. Adult-to-adult LDLT was initiated in the United States in the late 1990s. In 1997, one adult-to-adult LDLT was performed at one center in the U.S. and this grew to 266 procedures at 38 centers in 2000 (Brown et at, 2003). Left lateral segmentectomy, which uses approximately 20% of the hepatic mass, is generally used for LDLT to pediatric donors. However, these grafts provide insufficient liver mass for an average sized adult recipient. With adult recipients, a larger portion of the donor's liver must be taken which poses increased risks to the donor. Adult-to-adult liver transplantation involves either a full left or right hepatic lobe. Initially, all adult LDLT used the smaller left hepatic lobe. The hepatic mass was sufficient for some Asian recipients, but not for the average U.S. patient. Currently, adult-to-adult LDLTs in the U.S. use donation of the right hepatic lobe, which represents about 60% of the hepatic mass. Risks to the donor in adult-to-adult LDLT include the possibility that the donor will not be left with sufficient hepatic function, the possibility of biliary complications, risks associated with blood transfusion, risks associated with surgery and unknown, long-term risks associated with major hepatic resection. (American Society of Transplant Surgeons: Ethics Committee, 2000; Renz and Roberts, 2000; Hayashi & Trotter, 2002).There is an ethical debate on adult-to-adult LDLT centering on the question of whether or not it is acceptable for a consenting healthy individual to undergo this surgery and take the risk of complication or death in order to potentially save the life of a loved one. LDLT programs conduct extensive physical and psychological examinations of donors. Related ethical issues are how to select adult recipients of LDLT (i.e. to what extent are they at risk of dying), how successful LDLT is in adult recipients (i.e. increased life expectancy in recipient vs. risk to donor) and how to allocate cadaveric livers.

04/12/2000: MTAC REVIEW

Living-Donor Liver Transplant – Adult-to-Adult

Evidence Conclusion: The limited amount of evidence available is not sufficient to determine the safety and efficacy of LRLT. Case series reports were the best available evidence. The published case studies have small sample sizes and were not rigorously performed (i.e. did not specify inclusion/exclusion criteria or outcome measurement, had variable and relatively short length of follow-up). In addition, the published studies report on different clinical techniques for performing LRLT and these individual techniques have not been systematically evaluated.

Articles: There were no randomized control trials, meta-analyses or cohort studies. Case series for adult-to-adult transplants all had small sample sizes (<50). Several larger case series included both adults and children as recipients and did not present results separately. Evidence tables were created for those with the largest sample sizes: (n=33) Hashikura, Y, Kawasaki, S, Miyagawa, S, Terada, M, Ikegami, T, Miwa, S, Kubota, T, Mita, A. Living-related donor liver transplantation in adults: Experience at Shinshu University Hospital. Transplantation Proceedings 1999; 31: 1953-4; (N=25) Marcos, A, Fisher, RA, Ham, JA, Shiffman, ML, Sanyal, AJ, Luketic, VAC, Sterling, RK, Posner, MP. Right lobe living donor liver transplantation. Transplantation 1999; 68: 798-803. Hashikura, Y, Kawasaki, S, Miyagawa, S, Terada, M, Ikegami, T, Miwa, S, Kubota, T, Mita, A. Living-related donor liver transplantation in adults: Experience at Shinshu University Hospital. Transplantation Proceedings 1999; 31: 1953-4. See Evidence Table. Marcos, A, Fisher, RA, Ham, JA, Shiffman, ML, Sanyal, AJ, Luketic, VAC, Sterling, RK, Posner, MP. Right lobe living donor liver transplantation. Transplantation 1999; 68: 798-803. See Evidence Table.

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The use of Adult to Adult Living Related Donor Liver Transplant treatment of Liver Failure does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

06/11/2003: MTAC REVIEW
Living-Donor Liver Transplant – Adult-to-Adult

Evidence Conclusion: There is a lack of evidence on the effectiveness of adult-to-adult living-donor liver transplantation compared to cadaveric whole or split-liver transplantation and one small study (Liu) that addresses the effectiveness of LDLT compared to remaining on a wait list for cadaveric transplantation. Liu found a higher survival rate with right lobe LDLT than no transplantation among patients with acute liver failure; however, findings do not necessarily generalize to patients with other indications for transplantation.
The remaining studies are case series. One-year recipient survival rates were 72% in the case series of 308 adults from Japan (Todo) in which 71% of the operations were left-lobe transplantations and 85% for 50 right-lobe operations in the U.S. (Miller). No peri-operative donor mortality was reported in the recent case series articles. Brown identified one donor death among 449 right-lobe adult-to-adult living-donor transplantations performed in the U.S. between 1997 and 2000. Brown's survey found a 14.5% donor complication rate including 6% experiencing biliary leakage and 4.5% needing re-operation. A limitation of the case series data and the Brown survey data is variability in the eligibility criteria and interventions across centers and within centers over time. There are no quality long-term data on outcomes among recipients or donors.
Articles: The search yielded 206 articles, many of which were reviews, opinion pieces or dealt with technical aspects of the procedure. There were no randomized controlled trials. The next preference was given to non-randomized comparative trials. There was one study that compared patients with acute liver failure who did and did not opt for LDLT; this study was reviewed. The remaining studies were case series. Other articles selected were the largest case series (conducted in Japan), the largest case series in the United States and a survey of transplantation programs focusing on donor outcomes. The following four articles were critically appraised:
Liu CL, Fan ST, Lo CM et al. Right-lobe live donor liver transplantation improves survival of patients with acute liver failure. *Br J Surg* 2002; 89: 317-322. See Evidence Table. Todo S, Furukawa H, BonJin M et al. Living donor liver transplantation in adults: Outcome in Japan. *Liver Transplantation* 2000; 6 (Suppl 2): S66-S72. See Evidence Table. Miller CM, Gondolesi CE, Florman S. et al. One hundred nine living donor liver transplants in adults and children: A single-center experience. *Ann Surg* 2001; 234: 301-012. Brown RS, Russo MW, Lai M. et al. A survey of liver transplantation from living adult donors in the United States. *N Engl J Med* 2003; 348: 818-825. See Evidence Table.

The use of Adult to Adult Living Related Donor Liver Transplant treatment of Liver Failure does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Kidney Transplantation in the treatment of HIV+

BACKGROUND
HIV infected patients are at risk for end-stage renal disease caused by HIV-related disease such as HIV-associated nephropathy and hepatitis C infection. HIV-positive patients co-infected with hepatitis B or hepatitis C are also at risk of progression of liver disease (Roland & Stock; Fishman). Until recently, HIV-positive patients have been excluded from organ transplantation programs. A primary reason for this exclusion has been the belief that patients in an immuno-compromised state would be adversely affected by the immunosuppression required for transplantation. Several changes have occurred that have caused some transplant centers to question the exclusion based on HIV infection. Highly active anti-retroviral therapy (HAART) became available in the mid to late 1990s. HAART can prolong survival in HIV-positive patients, thereby increasing the number of patients with stable HIV infection who progress to end-stage organ failure. In addition, there have been improvements in immunosuppressive drug regimens and surgical techniques associated with transplantation. This review will evaluate the evidence published to date on the safety and efficacy of organ transplantation among HIV-positive patients in the HAART era. Kidney transplantation in HIV positive patients was previously reviewed by MTAC in December 2001. At that time, the evidence consisted of several case series with five or fewer HIV-positive patients and the item failed MTAC evaluation criteria. Other types of organ transplantation (liver, lung, heart) have not been reviewed by MTAC.

12/12/2001: MTAC REVIEW
Kidney Transplantation in the treatment of HIV+

Evidence Conclusion: There is insufficient published evidence on which to base a conclusion about the effect of kidney transplant in HIV-positive patients on health outcomes. Although recent changes in the prognosis of HIV-positive individuals suggest that some may benefit from kidney transplant, there are no direct empirical data to support this claim.

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Articles: The search yielded 64 articles, many of which dealt with other related procedures or populations or were review articles or opinion pieces. No articles with empirical data were included in the search. Three older case series were identified in the reference list of the Gow review article. Each of these case series included 5 or fewer HIV-positive patients receiving kidney transplants. None of the articles was suitable for critical appraisal.

The use of Kidney Transplantation in the treatment of HIV+ patients with renal failure does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

08/11/2004: MTAC REVIEW
Heart, Lung, Kidney, & Liver Transplantation in the treatment of HIV+
Evidence Conclusion: There were two primary issues addressed in this review: 1) evidence on the safety and effectiveness of organ transplantation for HIV-positive individuals and; 2) evidence on whether survival among HIV-positive individuals who receive organ transplants is lower than among HIV-negative individuals. There is no published evidence on the safety and effectiveness of lung transplantation in HIV-positive individuals and only two case reports of heart transplants. There were no articles comparing transplantation to another intervention in HIV-positive patients with end-stage liver or kidney disease. The best published evidence on kidney and liver transplants in HIV-positive individuals is from cohort studies conducted in the HAART era. Abbott did a retrospective study comparing outcomes in HIV-positive and HIV-negative individuals, all of whom were identified in a national database of kidney transplants. Ragni compared survival in a prospective series of HIV-positive patients and a retrospective analysis of selected HIV-negative patients from the UNOS Scientific Registry for Liver Transplantation. In both studies, three-year survival rates did not differ significantly in the HIV-positive and HIV-negative groups. Limitations of both studies include: The relatively small sample sizes of HIV-positive patients, 24 in the Ragni study and 47 in the Abbott study. The HIV-positive and HIV-negative groups may have differed in ways that affected outcomes (despite statistical adjustment for confounding in the Abbott study). The authors commented that clinicians may have selected the healthiest HIV-positive patients for transplantation which might increase the likelihood of a successful outcome compared with the HIV-negative patients. The Abbott study was retrospective and the Ragni study included a prospective group of HIV-positive patients but did a retrospective analysis of the HIV-negative control group. Prospective designs are preferred. A prospective, multi-center uncontrolled study to evaluate the safety and efficacy of kidney and liver transplants performed in HIV-positive patients is currently in its early phases. The study is being coordinated by UCSF. The investigators anticipate enrolling up to 275 transplant recipients and following them for 2-5 years.
Articles: The search yielded 217 articles. Most were opinion pieces, on technical aspects of transplantation in HIV-positive patients and articles on related clinical topics. Empirical studies on specific types of organ transplantation were as follows: Lung There were no studies with empirical data. Heart There were two case reports, each reporting on a single case. The articles were ineligible for critical appraisal. Kidney and Liver There was one study on kidney transplants (Abbott et al., 2004) and one study on liver transplants (Ragni et al., 2003) that compared outcomes in HIV-positive patients to outcomes in HIV-negative patients. Data from HIV-negative patients were taken from national transplantation databases in both studies. These two studies were critically appraised. The largest published series from UCSF included 14 patients, 10 received kidney transplants and 3 received liver transplants (Stock et al. 2003). Newer reports with additional patients have been presented at conferences and discussed in review articles, but the data have not been published in empirical articles. The case series was not critically appraised due to the small sample and availability of comparative studies. There was also a retrospective cohort study evaluating data on kidney transplants from 1987-1997; this study was not critically appraised because it primarily included cases from the pre-HAART era.
The studies reviewed were Abbott KC, Swanson SJ, Agodoa LYC et al. Human immunodeficiency virus infection and kidney transplantation in the era of highly active antiretroviral therapy and modern immunosuppression. *J Am Soc Nephrol* 2004; 15: 1633-1639. See Evidence Table. Ragni MV, Belle SH, Im K et al. Survival of human immunodeficiency virus-infected liver transplant recipients. *J of Infect Dis* 2003; 188: 1412-1420. See Evidence Table.

The use of Heart Transplantation in the treatment of HIV+ patients with heart failure does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

The use of Lung Transplantation in the treatment of HIV+ patients with lung failure does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

The use of Kidney Transplantation in the treatment of HIV+ patients with renal failure evidence is not sufficient to determine whether HIV infection should or should not be an exclusion for kidney transplantation.

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The use of Liver Transplantation in the treatment of HIV+ patients with renal failure the evidence is not sufficient to determine whether HIV infection should or should not be an exclusion for liver transplantation.

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
47135	Liver allotransplantation, orthotopic, partial or whole, from cadaver or living donor, any age
47140	Donor hepatectomy (including cold preservation), from living donor; left lateral segment only (segments II and III)
47141	Donor hepatectomy (including cold preservation), from living donor; total left lobectomy (segments II, III and IV)
47142	Donor hepatectomy (including cold preservation), from living donor; total right lobectomy (segments V, VI, VII and VIII)
47146	Backbench reconstruction of cadaver or living donor liver graft prior to allotransplantation; venous anastomosis, each
47147	Backbench reconstruction of cadaver or living donor liver graft prior to allotransplantation; arterial anastomosis, each

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Date Created	Date Reviewed	Date Last Revised
05/1996	07/06/2010[MDCRPC], 05/03/2011[MDCRPC], 08/02/2011[MDCRPC], 03/06/2012[MDCRPC], 01/08/2013[MDCRPC],11/05/2013[MPC], 02/04/2014[MPC], 09/02/2014[MPC], 10/07/2014[MPC], 07/07/2015[MPC], 05/03/2016[MPC], 03/07/2017[MPC], 01/09/2018[MPC], 12/04/2018[MPC], 12/03/2019[MPC], 12/01/2020[MPC],12/07/2021[MPC],12/06/2022[MPC], 12/09/2023[MPC]	01/10/2022

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
10/06/2015	Merged Living Donor Related criteria to Liver Transplant criteria
11/03/2015	Merged Organ Transplantation for HIV+ Patients for Liver and Kidney
03/05/2019	MPC approved to adopt KP National Criteria for Liver Transplant
09/03/2019	MPC approved to change General Principles 1.3 to *Uncontrollable infection is a contraindication to transplant* as recommended by KP National Transplant Services.
03/03/2020	MPC approved proposed changes from KP National Transplant Services
04/06/2021	MPC approved proposed changes from KP National Transplant Services. Requires 60-day notice, effective date September 1, 2021.
01/10/2022	MPC approved proposed changes from KP National Transplant Services. 60-day notice is not required.

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Clinical Review Criteria
Localization System for External Beam Radiation

- Calypso 4D Localization
- Electromagnetic Localization System
- GPS for the Body
- Tracking with Beacon Transponders during External Beam Radiation Therapy (Calypso Medical)

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article	None
Kaiser Permanente Medical Policy	Due to the absence of an active NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Clinical Review Criteria, **"**Localization System for External Beam Radiation**"** for medical necessity determinations. Use the Non-Medicare criteria below.

For Non-Medicare Members

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

If requesting review for this service, please send the following documentation:

- Last 6 months of clinical notes from requesting provider &/or specialist

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Prostate cancer is the most commonly diagnosed cancer and second leading cause of death in men in the United States. The treatment options for early-stage prostate cancer include radical prostatectomy, high dose brachytherapy, and high dose external beam radiation therapy (EBRT). Several studies showed improvement in biochemical progression free survival with radiation dose escalation. However, this comes at the cost of higher bladder and bowel toxicity. Investigators found that toxicity due to radiation therapy can be reduced by the use of intensity modulated radiotherapy (IMRT) techniques that focus a high dose radiation to the prostate while decreasing the dose to the bladder and rectum. With the higher doses being delivered with increased conformity,

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it is critical that the isocenter of the prostate treatment volume be placed with precision (Kuban 2008, Quigley 2009, Rajendran 2010).

The prostate gland is known to have some movement during the day as the bladder and rectum are filled at different volumes. Two types of motion have been described and may be an issue for treatment planning: 1. Interfraction motion from day-to-day, and 2. Intrafraction movement that is motion occurring while the patient is on the treatment table during radiation delivery. This is thought to be caused by breathing or other biological factors as contraction/relaxation of the pelvic floor and by rectal gas. Target localization during radiation therapy for prostate cancer has two aspects: the initial setup before delivering the radiation, and the subsequent real-time target position monitoring during the actual delivery of radiation. The interfraction position has been addressed by various techniques including ultrasound, infrared cameras, diagnostic CT imaging, and x-ray imaging. The use of implanted markers as gold is accepted as an accurate, reliable, and reproducible method to establish the position of the prostate gland during EBRT treatment. Other techniques used to estimate the motion of prostate during delivery of radiation include transabdominal ultrasound, X-rays, MRI, CT, and fluoroscopy. The use of these technologies may be limited as they may not be available in the treatment room or usable during radiation delivery, provide only a snapshot of the prostate position, result into additional radiation dose, are labor intensive and /or require user skill for image acquisition or interpretation (Kupelian 2006, Rajendran 2010).

In the last few years, the use of an implantable radiofrequency emitting device has been proposed as an alternative to radiopaque fiducial markers and radiographic localization to provide an objective, accurate real-time method of localizing and monitoring prostate position. The Calypso 4D Localization System is based on electromagnetic detection of implanted Beacon transponders that allows the three-dimensional position of the implanted transponders and target isocenter to be tracked at a frequency of 10Hz. This provides continuous real-time localization and monitoring of the prostate. The Calypso System (Calypso Medical, Seattle, WA) consists of three implantable wireless Beacon transponders approximately 8 mm in length and 2mm in diameter, an electromagnetic array, an infrared camera system, and a tracking station. Typically, three transponders are implanted in the right and left base and the apex of the prostate gland under transrectal ultrasound guidance in a manner similar to needle biopsy. The coordinates of the Beacons and the isocenter are identified on the treatment planning CT and entered into the calypso tracking station. Similar to ultrasound localization, the initial localization with the Calypso System is performed using skin marks to align with room lasers. Calypso is used to localize the prostate and the system calculates the initial offset. The couch is shifted until the three offsets are zero. During treatment Calypso monitors and reports the offset between the actual and planned isocenter position (Santanam 2009, Foster 2010, Rajendran 2010).

Potential benefits of the Calypso system include its ability to continuously monitor target position during treatment, with no exposure to ionizing radiation to perform the localization, and without using complicated procedures of acquiring X-ray images. Potential disadvantaged on the other hand, are the need for implantation, transponders stability within the implanted tissues, and the absence of any associated image of the targeted areas.
The Calypso System has received 510 (K) clearance from the FDA in 2006.

Medical Technology Assessment Committee (MTAC)

Calypso 4D Localization System

12/20/2010: MTAC REVIEW

Evidence Conclusion: The published literature on the Calypso system is very limited and do not provide sufficient evidence to determine the safety of the technology or its effect on patients with localized prostate cancer treated with radiation therapy. The published studies were small case series the majority of which were conducted by the same group of authors many of whom had financial interest with the manufacturer of the technology. The safety of the Calypso system and its effect on improving health outcomes were not examined in randomized controlled trials. Assessing the Impact of Margin Reduction (AIM) study was the largest case series on the Calypso System published to date, and the first with clinical outcomes. However, it was not randomized and used a historical comparison group. It had several other limitations including the significant baseline differences between study participants and the comparison groups, difference in the time of treatment, and variations in the radiation therapy received by the two groups, as well as the absence of long-term follow-up to determine the effect of the technology on the incidence of late complications. Moreover only 83% of the participants were included in the analysis, and the study was funded by the manufacturer.
Articles: The published literature on the Calypso 4D localization system for the prostate is very limited. There are no published randomized controlled trials that compared the effect of the Calypso system versus other localization technologies on reducing radiation toxicity or improving quality of life (QoL) in patients with prostate cancer. The

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literature search identified the 'Assessing the Impact of Margin Reduction (AIM)' study that assessed the effect of reducing the planning target volume margins while using real-time tumor tracking on the quality of life of patients with prostate cancer treated with radiation therapy. It did not include a comparison or control group. No trials on the safety of the technology were identified.
The AIM study was selected for critical appraisal: Sandler M, Liu P-Y, Dunn RL, et al. Reduction in patient-reported acute morbidity in prostate cancer patients treated with 81-Gy Intensity-modulated radiotherapy using reduced planning target volume margins and electromagnetic tracking: assessing the impact of margin reduction study. *Urology.* 2010 May;75(5):1004-8. Epub 2010 Feb 13. See Evidence Table

The use of Calypso 4D localization system (Calypso 4D localization and Tracking with Beacon transponders during external beam radiation therapy [Calypso Medical], GPS for the Body, electromagnetic localization system) does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Considered Not Medically Necessary:

CPT® / HCPC Codes	Description
77387	Guidance for localization of target volume for delivery of radiation treatment, includes intrafraction tracking, when performed
G6017	Intra-fraction localization and tracking of target or patient motion during delivery of radiation therapy (e.g., 3D positional tracking, gating, 3D surface tracking), each fraction of treatment

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Creation Date	Review Dates	Date Last Revised
12/20/2010	02/10/2011[MDCRPC], 12/06/2011[MDCRPC], 10/02/2012[MDCRPC], 08/06/2013[MPC], 06/03/2014[MPC], 04/07/2015[MPC], 02/02/2016[MPC], 12/06/2016[MPC], 10/03/2017[MPC], 09/04/2018[MPC], 09/03/2019[MPC], 09/01/2020[MPC], 09/07/2021[MPC], 09/06/2022[MPC], 09/05/2023[MPC]	09/16/2020

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
09/01/2020	Added KPWA Medical Policy statement under Medicare section
09/16/2020	Added HCPC code G6017

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KAISER PERMANENTE®

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Clinical Review Criteria
Low-Dose CT Screening for Lung Cancer

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Lung Cancer Screening with Low Dose Computed Tomography (LDCT) (210.14)
Local Coverage Determinations (LCD)	None
Local Coverage Article	Medicare Coverage of Screening for Lung Cancer with Low Dose Computed Tomography (LDCT)

For Non-Medicare Members

Low-dose CT screening for lung cancer will be covered when the patient meets the following criteria:

Ages 50 through 79: Annual screening for lung cancer with low dose computed tomography is recommended for patients who:

- Have at least a 20 pack-year smoking history,
- Currently smoke or quit less than 15 years ago, and
- Have no significant comorbidities that would preclude surgical treatment or limit life expectancy.

Ages 80 and over: Annual lung cancer screening with LDCT is not recommended.

Discontinuation

Discontinuation of lung cancer screening is recommended at 15 years following the patient's quit date, or as appropriate for health status.

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Background

Lung cancer is the third most common cancer and the leading cause of cancer death in the United States. According to the U.S. Preventive Services Task Force (USPSTF), nearly 90% of individuals with lung cancer die of the disease. However, when detected at an early stage, non–small cell lung cancer (NSCLC) has a better prognosis and can be treated with surgical resection. (The majority of lung cancer cases are NSCLC.)

The most important risk factor for lung cancer is smoking, which results in approximately 85% of all U.S. lung cancer cases. The incidence of lung cancer increases with age, occurring most commonly in individuals aged 55 years or older. Increasing age and cumulative exposure to tobacco smoke are the two factors most strongly associated with the occurrence of lung cancer.

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The USPSTF found adequate evidence that annual screening with low-dose computed tomography (LDCT) in current and former smokers aged 55 to 79 years who have significant cumulative tobacco smoke exposure can prevent a substantial number of lung cancer deaths. LDCT has greater sensitivity for detecting early-stage cancer than chest X-ray and sputum cytology; however, it also has a very high rate of false positives (about 95%). For the benefits to outweigh the harms, screening needs to be limited those who are at the highest risk for lung cancer.

Medical Technology Assessment Committee (MTAC)

Low-Dose CT Screening for Lung Cancer

12/12/2001: MTAC REVIEW

Evidence Conclusion: There is no evidence on the diagnostic accuracy of the low-dose CT test for lung cancer screening. That is, an independent, blind, comparison of the low-dose CT tests with a gold standard (e.g. high-dose CT) for an appropriate group of patients. In the Henschke study, only patients with certain findings on low-dose CT were recommended to have high-dose CT. There are also no studies comparing the diagnostic accuracy of low-dose CT screening to the current standard, chest radiography. The only available evidence on low-dose CT screening for lung cancer is prospective reports of screening programs. Henschke set up a protocol to screen individuals at increased risk of lung cancer. They found that more non-calcified nodules, malignant nodules and stage I malignant disease was found using low-dose CT than could be detected by chest radiography. These data suggest that low-dose CT may be useful for lung cancer screening. The data presented in the Henschke study are insufficient for evaluating the question of whether screening with low-dose CT reduces disease-specific mortality. Even though more nodules and more stage I nodules were identified than with chest radiography, it is not known whether this early identification will lead to decreased mortality from lung cancer. (Previous randomized controlled trials evaluating the effectiveness of chest radiography for lung cancer screening did not find a difference in mortality in the screened and unscreened groups). Alternatively, CT screening may not increase disease-specific survival due to lead-time bias and over diagnosis bias. Randomized controlled trials comparing CT screening to no screening would provide more rigorous information about its effectiveness as a screening strategy.

Articles: The search yielded 54 articles, many of which were review articles, opinion pieces or dealt with technical aspects of the procedure. There were no randomized controlled trials or meta-analyses. Five case series with relevant clinical outcomes were identified. Four were studies conducted in Japan and one was a study conducted at Cornell University. Of the four Japanese studies, there were two studies by Sone al. and two studies by Kaneko et al. The Sone articles were an earlier and later report on the same project, as were the Kaneko articles. Neither of the Japanese screening projects had specific clinical inclusion and exclusion criteria. The Sone study screened the general population and the Kaneko study screened people who were members of a non-profit organization, the Anti-Lung Cancer Association (ACLA). In addition, neither Japanese screening project appeared to have a consistent protocol that was followed. The Cornell University study by Henschke et al. screened only individuals at high-risk of lung cancer and had clear eligibility criteria as well as screening and follow-up protocols. None of the articles were designed to evaluate the diagnostic characteristics of the low-dose CT test (e.g. sensitivity, specificity). *An evidence table was created for the Henschke study:* Henschke CI, McCauley DI, Yankelevitz DF, Naidich DP, McGuinness G, Miettingen OS, Libby DM, Pasmantier MW et al. Early Lung Cancer Action Project: Overall design and findings from baseline screening. Lancet 1999; 354: 99-105. See Evidence Table

The use of CT Scanning in the screening of lung cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria* 2 for effectiveness of diagnostic test.

Low-Dose CT Screening for Lung Cancer

8/15/2011: MTAC REVIEW

Evidence Conclusion: The National Lung Screening Trial (NLST), a large RCT that included 53,454 participants, examined whether screening high-risk individuals for lung cancer annually for three years with either LDCT or chest x-ray would reduce lung cancer mortality. Results from the NLST suggest that in high-risk patient's annual lung cancer screening for three years using LDCT reduced lung-cancer mortality with a number needed to screen to prevent one cancer death of 320. However, before recommending a screening test there are other factors to consider such as overdiagnosis, cost-effectiveness, false positive results, and other potential harms such as radiation-induced cancer. The effect of overdiagnosis and radiation-induced cancer could not be directly measured in this trial and cost-effectiveness analyses are currently underway. With regard to false positive results, across the three rounds of screening, 96.4% of the positive results in the LDCT and 94.5% in the x-ray group were false positive results. Additionally, 39.1% of subjects in the LDCT group and 16.0% in the x-ray group had at least one positive screening test during the screening phase of the trial (NSLT 2011). A recent interim analysis from a RCT that included 2,472 men who were at high-risk for lung cancer examined whether yearly lung

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cancer screening using LDCT in combination with a medical interview and physical exam would reduce lung cancer mortality compared to yearly medical interview and physical exam alone. After approximately 3 years of follow-up, significantly more men in the intervention group were diagnosed with lung cancer [intervention 60 (4.7%) vs. control 34 (2.8%), P=0.02]. However, there was no significant difference in lung cancer mortality between the two groups [intervention 20 (1.6%) vs. control 20 (1.7%), P=0.84]. Conclusion: Results from the NLST suggest that screening high-risk patients with LDCT annually for three years may reduce lung-cancer mortality; however, despite these positive results there are many other questions that still need to be answered such as screening frequency and duration. In 2007, the California Technology Assessment Forum evaluated the use of low-dose spiral computed tomography (LDCT) screening for lung cancer. They concluded that while the use of LDCT to screen for lung cancer in high-risk populations appeared promising, there was insufficient published evidence to recommend the use of LDCT outside of the investigational setting. Since the 2007 technology assessment, two randomized controlled trials (RCTs) were selected for review that examined the effectiveness of screening high-risk individuals for lung cancer using LDCT compared to chest x-ray.
Articles: The following studies were critically appraised: National Lung Screening Tral (NLST). Reduced lung-cancer mortality with computed tomographic screening. *N Engl J Med 2011.* [Epub ahead of print] See Evidence Table Infante M, Cavuto S, Lutman FR, et al. A randomized study of lung cancer screening with spiral computed tomography: three-year results from the DANTE trial. *Am J Respir Crit Care Med 2009;* 180:445. See Evidence Table

The use of CT Scanning in the screening of lung cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria* 2 for effectiveness of diagnostic test.

Low-Dose CT Screening for Lung Cancer

10/15/2012: MTAC REVIEW

Evidence Conclusion: The Danish Lung Cancer Screening (DLCST), a RCT that included 4,104 participants, examined whether screening high-risk individuals yearly with LDCT would reduce lung cancer mortality compared to usual care (no screening). Results from this trial suggest that after 5 years of screening, LDCT did not reduce lung cancer mortality or all-cause mortality compared to usual care. Significantly more lung cancers were diagnosed in the screening group compared to the control group (69 vs. 24, P<0.001), and more were early stage (48 vs. 21, P=0.002). There was no significant difference in the number of late stage lung cancer (21 vs. 16, P=0.51). The diagnostic false positive rate was 7.9% at baseline, 1.7% at year 1, 2.0% at year 2, 1.6% year 3, and 1.9% year 4. One limitation of this trial is that the sample size may be insufficient and the duration of follow-up may not be long enough to detect a reduction in mortality (Saghir 2012) The Multicentric Italian Lung Detection (MILD), a RCT that included 4,099 participants, examined whether screening high-risk individuals yearly or every two years with LDCT would reduce lung cancer mortality compared to usual care (no screening). Results from this trial suggest that after 5 years of follow-up, annual or biennial screening with LDCT did not reduce lung cancer mortality compared to usual care. The incidence of lung cancer was significantly higher in LDCT screening groups compared to the control group (P=0.025), but not in the annual versus the biennial groups (P=0.24). Due to recruitment issues the trial may be underpowered to detect differences in mortality. Additionally, at baseline more subjects in the control group were current smokers (Pastorino 2012). Conclusion: Results from the NLST suggest that screening high-risk patients with LDCT annually for three years may reduce lung-cancer mortality; however, despite these positive results there are many other questions that still need to be answered such as screening frequency and duration, and the effects of cumulative radiation exposure. Results from other RCTs have not shown a mortality benefit; however, these trials may be underpowered.
Articles: Low-dose CT screening for lung cancer was previously reviewed in 2001 and 2011. Since the 2011 review, two randomized controlled trial were identified that assessed the benefits and harms of screening for lung cancer using low-dose CT in high risk patients. The following studies were critically appraised: Saghir Z, Dirksen A, Ashraf H, et al. CT screening for lung cancer brings forward early disease. The randomized Danish Lung Cancer Screening Trial: status after five annual screening rounds with low-dose CT. *Thorax.* 2012; 67:296-301. See Evidence Table Pastorino U, Rossi M, Rosato V, et al. Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial. *Eur J Cancer Prev.* 2012; 21:308-315. See Evidence Table

The use of CT Scanning in the screening of lung cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria* 2 for effectiveness of diagnostic test.

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

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CPT® or HCPC Codes	Description
71271	Computed tomography, thorax, low dose for lung cancer screening, without contrast material(s)
Diagnosis Codes	**Description**
Z87.891	Personal history of nicotine dependence
F17.210	Nicotine dependence, cigarettes, uncomplicated
F17.211	Nicotine dependence, cigarettes, in remission
F17.213	Nicotine dependence, cigarettes, with withdrawal
F17.218	Nicotine dependence, cigarettes, with other nicotine-induced disorders
F17.219	Nicotine dependence, cigarettes, with unspecified nicotine-induced disorders

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Date Created	Date Reviewed	Date Last Revised
12/28/2001	05/03/2011[MDCRPC], 08/02/2011[MDCRPC], 09/06/2011[MDCRPC], 07/03/2012[MDCRPC], 11/06/2012[MDCRPC], 09/03/2013 [MPC], 07/01/2014[MPC], 11/04/2014[MPC], 09/01/2015[MPC], 07/05/2016[MPC], 05/02/2017[MPC], 03/06/2018[MPC], 02/05/2019[MPC], 02/04/2020[MPC] , 02/02/2021[MPC],02/01/2022[MPC],02/07/2023[MPC]	12/07/2021

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
11/04/2014	MPC adopted the USPSTF guidelines for lung cancer screening
05/05/2015	Age limits were changed to align with Medicare: • Ages 75 through 77 • Ages 78 and over
11/17/2015	Changed Medicare link
08/26/2021	Updated link under Medicare Local Coverage Article section
12/07/2021	MPC approved to adopt the modifications to the current Low Dose CT Cancer Screening to align with updated recommendations from the USPSTF. Requires 60-day notice, effective 03/01/2022.

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KAISER PERMANENTE®

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Clinical Review Criteria
Low Level Laser Therapy for Pain

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Laser Procedures (140.5)
Local Coverage Determinations (LCD)	None
Local Coverage Article	None

For Non-Medicare Members

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Low level laser therapy (LLLT) is a non-invasive therapeutic option which uses low intensity light at a wavelength ranging from 540 to 830 nm. LLLT produces photochemical reactions and enhance the metabolism of cells. The photochemical reactions change the permeability of cell membrane, increase accumulation of mRNA and result in cell proliferation. After the light is applied, there is activation of photoacceptors, located in the mitochondria, followed by protein synthesis (through several mechanisms). The process reduces pain, causes anti-inflammatory effects, cell proliferation, neovascularization, and balancing immune system. LLLT uses photons at a non-thermal radiation and does not produce heat. In addition, no destruction of the surrounding tissue is reported. Since the density of LLLT is inferior to 5.0 W/cm2, the technique is also called cold laser. (Rayegani, Raeissadat, Heidari, & Moradi-Joo, 2017).

Low-level light with different wavelengths is applied to a specific site. This is followed by absorption of the light by the tissue. The red or infrared light causes the photochemical response and regeneration described above. The wavelengths vary between 600 to 700 nm for small penetration and 780 to 950 nm for more profound penetration. The procedure is short, and no pain, sound, vibration or heat is generated. (https://www.healthline.com/health/cold-laser-therapy#procedure).

The clinical application of low-level laser therapy is broad, but it's mainly used for pain reduction. The current review will focus on knee pain (osteoarthritis/musculoskeletal disorders), painful diabetic neuropathy, and carpal tunnel syndrome.

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The incidence and prevalence of osteoarthritis vary and depend on its definition. In the United States, its incidence is lower in African Americans than Caucasians (Nelson, 2018). Based on United States data ranging from 2007 to 2008, 7% of adults over age 25 had symptomatic knee osteoarthritis (Nelson, 2018). Knee osteoarthritis (KOA) is a degenerative disease characterized by gradual loss of cartilage.
Symptoms of KOA include pain, limited range of motion, bony swelling, deformity, instability, disability, and reduced quality of life. The diagnosis is clinical; imaging can be performed if the diagnosis is not clear. Conservative therapy includes exercise therapy, non-steroidal anti-inflammatory drugs (NSAIDs), and low-level laser therapy (LLLT) (Stausholm et al., 2019).

Carpal tunnel syndrome is characterized by tingling, pain, even numbness in the wrist/hand. It is the result of compression of the median nerve.

Medical Technology Assessment Committee (MTAC)

12/20/2010: MTAC Review
Lower Level Laser Therapy for Pain
Evidence Conclusion: *Back pain* **-** A meta-analysis of 7 RCTs that included 384 participants assessed the effects of LLLT in patients with non-specific low-back. Because the studies included in the meta-analysis were heterogeneous with respect to population, intervention, and comparison group, it is difficult to draw conclusions on the clinical effect of LLLT for low back pain (Yousefi-Nooraie 2008). A double-blind RCT that included 80 participants was conducted after the meta-analysis and compared the effectiveness of LLLT on pain and functional capacity in patients with acute and chronic low back pain caused by lumbar disc herniation (LDH). Patients were randomized to one of four treatment groups: LLLT + hot pack (acute back pain), placebo LLLT + hot pack (acute back pain), LLLT + hot pack (chronic back pain), and placebo LLLT + hot pack (chronic back pain). After treatment, there were statistically significant improvements in pain, range of motion, and disability in all groups with respect to all outcome parameters. However, there was no statistically significant difference between the four treatment groups for any of the treatment parameters. This study had several limitations. The sample size may have been too small to detect between group differences and the follow-up duration was only 3 weeks (Ay 2010). *Neck pain* - A recent meta-analysis of 16 RCTs that included 820 participants assessed the safety and efficacy of LLLT in treating acute and chronic neck pain. Subjects with acute neck pain who were treated with LLLT were significantly more likely to experience an improvement in pain compared to subjects treated with placebo (RR 1.69, 95% CI 1.22 to 2.33). Patients with chronic neck pain treated with LLLT also experienced greater reductions in pain compared to patients receiving placebo (WMD 19.86, 95% CI 10.04 to 29.68). Results from this analysis also suggest that the effects of treatment may last as long as 22 weeks. Side-effects included tiredness, nausea, headache, and increased pain. Side-effects were generally mild and did not differ from those in the placebo group. Trials included in the meta-analysis were small RCTs that were heterogeneous with respect to laser parameters, application technique, and intended rationale for treatment (Chow 2009).A small double-blind RCT that included 60 participants investigated the clinical effects of LLLT in patients with acute neck pain with radiculopathy. Results from this study suggest that compared to placebo, patients treated with LLLT experienced significantly greater improvements in arm pain, disability, and neck mobility. There was no significant difference in neck pain between the two groups. All adverse events occurred in the LLLT group and included: transitional worsening of pain (6/30), persistent nausea (1/30), and increased blood pressure (1/30). Results from this study are generalizable to patients with acute neck pain with radiculopathy with severe levels of pain and moderate to severe levels of disability (Konstantinovic 2010). *Carpal tunnel syndrome* **- LLLT vs. placebo** A double-blind RCT that included 36 patients with mild to moderate carpal tunnel syndrome (CTS) evaluated the therapeutic effects of LLLT versus placebo for the treatment of CTS. The primary outcome measures included: pain, grip strength, symptom severity, functional status, and motor and sensory peak latency. After treatment there was no significant differences between LLLT and placebo for any of the outcomes except for pain. Patients who were treated with LLLT experienced a greater reduction in pain compared to patients treated with placebo. However, after 2 weeks of follow-up, patients who received LLLT showed significant improvement in pain, symptom severity, functional status, and grip strength. There was no significant difference in sensory peak latency or motor latency between the groups after treatment or after 2 weeks of follow-up. This was a small trial with a short duration of follow-up (Chang 2008). Another RCT that included 81 patients and compared LLLT to placebo found no significant difference with regard to pain and functional capacity between the two treatment groups after 12 weeks of follow-up (Evcik 2007). **LLLT vs. ultrasound** An RCT that included 50 patients with mild to moderate CTS (90 wrists) compared the efficacy of LLLT and ultrasound for the treatment of CTS. Results from this study suggest that compared to patients treated with LLLT, patients treated with ultrasound showed significant improvements in pain, pinch strength, grip strength, and electroneurographic measurements (Bakhtiary 2004). **Splinting vs. splinting + ultrasound vs. splinting + LLLT** A recent RCT that included 100 wrists of patients with mild to moderate CTS investigated the effectiveness of splinting, ultrasound, and LLLT for the management of CTS. The primary outcome measures were symptom severity, functional status, pain, median

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nerve sensory velocity, and median nerve motor distal latency. For all measurements, the combination of a splint plus ultrasound or LLLT was significantly better than the use of a splint alone. Patients who were treated with a splint plus LLLT experience significantly greater reductions in pain and symptom severity compared to patients treated with a splint plus ultrasound. Results from this study should be interpreted with caution as power was not addressed, it was not stated if an ITT analysis was performed, 4 patients did not finish therapy, 6 patients were lost to follow-up, and splint compliance was not addressed (Dincer 2009). *Conclusion:* There is insufficient evidence to determine the safety and efficacy of LLLT for the treatment of: Low back pain, Neck pain, and Carpal tunnel syndrome

Articles: A meta-analysis of RCT and an RCT published after the meta-analysis were identified that addressed the safety and efficacy of LLLT for the treatment of low back pain. The literature search also revealed a meta-analysis and RCT that looked at LLLT for the treatment of neck pain. Several RCT were identified that addressed the efficacy of LLLT for the treatment of carpal tunnel syndrome. Trials were selected for review if they had more than 25 participants and compared LLLT alone or in combination with another therapy to placebo or another active treatment. The following studies were critically appraised: Ay S, Doğan SK, and Evcik D. Is low-level laser therapy effective in acute or chronic low back pain? *Clin Rheumatol 2010;* 29:905-910. See Evidence Table**.** Bakhtiary AH and Rashidy-Pour A. Ultrasound and laser therapy in the treatment of carpal tunnel syndrome. *Aust J Physiother 2004;* 50:147-151. See Evidence Table**.** Chang WD, Wu JH, Jiang JA, et al. Carpal tunnel syndrome treated with a diode laser: a controlled treatment of the transverse carpal ligament. *Photomed Laser Surg 2008;* 26:551-557. See Evidence Table**.** Chow RT, Johnson MI, Lopes-Martins RAB, et al. Efficacy of low-level laser therapy in the management of neck pain: a systematic review and meta-analysis of randomized placebo controlled, or active-treatment controlled trials. *Lancet 2009;* 374:1894-1908. See Evidence Table**.** Dincer U, Cakar E, Kiralp MZ, et al. The effectiveness of conservative treatments of carpal tunnel syndrome: splinting, ultrasound, and low-level laser therapies. *Photomed Laser Surg 2009;* 27:119-125. See Evidence Table**.** Konstantinovic LM, Cutovic MR, Milovanovic AN, et al. Low-level laser therapy for acute neck pain with radiculopathy: a double-blind placebo-controlled randomized study. *Pain Med 2010;* 11:1169-1178. See Evidence Table**.** Yousefi-Nooraie R, Schonstein E, Heidari K, et al. Low-level laser therapy for nonspecific low-back pain. *Cochrane Database of Systematic Reviews* 2008, Issue 2. Art. No. CD005107.DOI: 10.1002/14651858. CD005107.pub4. See Evidence Table.

The use of low-level laser therapy for pain does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

01/13/2020: MTAC Review
Lower Level Laser Therapy for Pain
Evidence Conclusion:

- Low evidence supports the effectiveness (reduction of pain and disability) of LLLT (with or without exercise therapy) in patients with knee osteoarthritis compared to placebo/sham.
- There is insufficient evidence to assess the safety of LLLT in patients with knee osteoarthritis or musculoskeletal disorders.
- There is also insufficient evidence to compare LLLT versus physical therapy or NSAIDs.
- The evidence is insufficient to assess quality of life.
- There is insufficient evidence to assess the effectiveness and safety of LLLT in patients with painful diabetic neuropathy.
- Low evidence indicates that LLLT may be more effective than placebo on the short-term, but there is insufficient evidence to compare LLLT vs ultrasound or as adjunct to other treatment for patients with carpal tunnel syndrome.

Articles: PubMed was searched through January 3, 2020. Search terms included Low level laser therapy OR LightForce OR Cold laser treatment OR cold laser therapy OR LLLT AND with variations. The search was limited to English language publications and human populations. The reference lists of relevant studies were reviewed to identify additional publications. Filters included meta-analysis and randomized controlled trials. The search yielded several articles. The following articles (under summary) were reviewed. See Evidence Table.

The use of low-level laser therapy for pain does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

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Medicare - Considered Medically Necessary when criteria in the applicable policy statements listed above are met
Non-Medicare - Considered Not Medically Necessary

CPT® or HCPC Codes	Description
S8948	Application of a modality (requiring constant provider attendance) to one or more areas; low-level laser; each 15 minutes
0552T	Low-level laser therapy, dynamic photonic and dynamic thermokinetic energies, provided by a physician or other qualified health care professional

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Date Created	Date Reviewed	Date Last Revised
12/20/2010	02/10/2011[MDCRPC] ,12/06/2011[MDCRPC],10/02/2012[MDCRPC], 08/06/2013[MPC], 06/03/2014[MPC], 04/07/2015[MPC], 02/02/2016[MPC], 12/06/2016[MPC], 10/03/2017[MPC], 09/04/2018[MPC], 09/03/2019[MPC], 09/01/2020[MPC], 09/07/2021[MPC], 09/06/2022[MPC], 09/05/2023[MPC]	09/01/2020

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
06/04/2019	Removed MCG A-0511 for clinical guidelines
03/03/2020	Added January 2020 MTAC review; MPC approved to retain existing non-coverage policy for LLT.
09/01/2020	Added CPT code 0552T

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KAISER PERMANENTE®

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Clinical Review Criteria
Lower Limb Prosthesis

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Prosthetic Shoe 280.1
Local Coverage Determinations (LCD)	Lower Limb Prosthesis (L33787)
Local Coverage Article	Lower Limb Prostheses (A52496)

For Non-Medicare Members

Kaiser Permanente has elected to use the Lower Limb Prosthesis (KP-0487) MCG* for medical necessity determinations. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.

If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist, including the Prosthetics & Orthotics practitioner

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The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

A large number of lower limb prosthetic designs are now available. The choice of the most appropriate prosthetic depends on factors such as amputation level, height, weight, and activity level of the amputee. Prosthetics fall mainly under two broad functional groups: non-microprocessor-controlled prosthetics and microprocessor-controlled prosthetics. The normal gait cycle is comprised of the stance phase, the period when the leg is on the ground, and the swing phase, the period when the leg is off the ground. Non-microprocessor-controlled prosthetics incorporate friction, pneumatic, or hydraulics in the joint to control the swing and stance phases of gait. While they have helped amputees gain mobility these prosthetics have limitations. Prosthetics that utilize friction to control the swing phase can only be adjusted for one walking speed. Pneumatic and hydraulics prosthetics allow amputees to change their walking speed; however, these prosthetics do not incorporate adaptive stance phase control. The lack of adaptive stance phase control requires the amputee to lock the knee mechanism in full extension during stance to avoid buckling. The limitations of the non-microprocessor-controlled prosthetics result in gait asymmetries which may contribute to problems such as increased energy expenditure and secondary disabilities.

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Microprocessor-controlled prosthetics incorporate sensors that measure angles and movement every 20 millisecond and alter the damping of the hydraulic unit for each phase of gait. This technology is intended to normalize the swing and stance phase of gait over a wide range of walking speeds. Potential benefits of this technology include: decreased effort in walking, improved gait symmetry, reduced need for muscular compensation on the contralateral limb, fewer falls, and more stable gait on uneven terrain, ramps, inclines, and stairs (Berry 2009, Segal 2006).

C-leg® is a microprocessor-controlled knee joint system with hydraulic stance and swing phase control. In 1999, C-Leg® (Otto Block Healthcare, Duderstadt, Germany) received FDA approval.

Medical Technology Assessment Committee (MTAC)

Lower Limb Prosthesis

08/11/2004: MTAC REVIEW

Evidence Conclusion: The few studies published in peer-reviewed journals, included a small number of selected active participants, and do not provide sufficient evidence on effectiveness of the microprocessor-controlled lower limb prosthesis.

Articles: The search yielded 32 articles. The majority dealt with the technical aspects and mechanisms of action of the prostheses. The search did not reveal any randomized controlled trials. There was a pilot study (N=10) that compared the cognitive demand of walking using the intelligent prosthesis with the conventional damped knees. Another open crossover study of six amputees that compared the gait symmetry, energy expenditure, and patient impressions of the intelligent prosthesis to the standard pneumatic swing-phase control knee was also identified. The other reports/studies revealed by the search were small descriptive case series with less than 25 participants. None of the articles was selected for critical appraisal.

The use of microprocessor-controlled lower limb prostheses in the treatment of lower limb amputation does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

08/07/2006: MTAC REVIEW

Lower Limb Prosthesis

Evidence Conclusion: The few studies published in peer-reviewed journals, included small numbers of participants, and do not provide sufficient evidence to determine the effectiveness and benefit of the microprocessor-controlled lower limb prosthesis.

Articles: The search yielded 43 articles. The majority dealt with the technical aspects and mechanisms of action of the prostheses. The search identified one recent (Klute 2006) * small randomized controlled that compared the functional mobility and daily activity level of microprocessor-controlled hydraulic knee vs. the non-microprocessor hydraulic knee. Eighteen transfemoral amputees agreed to enroll in the study, but the majority withdrew before randomization. Eight amputees were randomized, and only five completed the trial. The other reports/studies revealed by the search were small comparative non-randomized studies or case series with less than 10 participants each. *None of the articles were selected for critical appraisal.*

The use of microprocessor-controlled lower limb prostheses in the treatment of lower limb amputation does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

10/18/2010: MTAC REVIEW

Lower Limb Prostheses

Evidence Conclusion: *Energy expenditure* - Two studies investigated the use of microprocessor-controlled prosthetics and non-microprocessor-controlled prosthetics with respect to energy expenditure. Both studies used a non-randomized, non-blinded cross-over design. The first study found no significant difference in energy efficiency; however, there was an increase in physical activity related energy expenditure when subjects used the microprocessor-controlled prosthetic (Kaufman 2008). The second study compared energy expenditure at self-selected typical and fast walking paces on a motorized treadmill. There was no significant difference in heart rate at either pace; however, when subjects used the microprocessor-controlled prosthetic there was a small, but statistically significant decrease in energy expenditure (Seymour 2007). *Walking speed and dynamics* - Seymour and colleagues also found that on a standardized walking obstacle course when subjects wore the microprocessor-controlled prosthetic they were significantly faster, took less steps, and had less step-offs than when they used the non-microprocessor-controlled prosthetic (Seymour 2007). Another study found that when subjects wore the microprocessor-controlled prosthetic walking speeds on a variety of surfaces improved and self-reported falls and stumbles decreased (Kahle 2008). Significant improvements in stair decent, hill decent time, hill affected side step length, and falls/stumbles were also found when subjects used a microprocessor-controlled prosthetic compared to when they used a mechanical prosthetic (Hafner 2007). Additionally, after

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receiving the microprocessor-controlled limb, subjects demonstrated significant improvements in gait and balance (Kaufman 2007). *Preference* - In a survey of 368 amputees, the majority of participants reported improvements with the microprocessor-controlled prosthetic compared to the non-microprocessor-controlled prosthetic with regard to comfort, security, maneuverability, cosmetic attributes, adverse events, and safety (Berry 2009). The prosthesis evaluation questionnaire (PEQ) measures subjective prosthesis function and prosthesis-related quality of life. Three studies found improvement in PEQ scores when subjects used the microprocessor-controlled prosthetic (Hafner 2007, Kahle 2008, Kaufman 2008).
Conclusion: As the majority of the published studies to date are small and non-randomized it is hard to draw firm conclusions regarding the superiority of microprocessor-controlled prosthetics compared to non-microprocessor-controlled prosthetics; however, results from the above studies suggest that the microprocessor-controlled prosthetics decreased energy expenditure, improved walking speed and dynamics, and improved PEQ scores.
Articles: The literature search revealed several studies that compared non-microprocessor-controlled prosthetics and microprocessor-controlled prosthetics. The majority of the studies were small comparative non-randomized studies or case series with less than 20 participants. Studies with more than 10 participants were reviewed. One randomized trial was identified; however, it was not selected for review as it included only 8 participants.
The following studies were critically appraised: Berry D, Olson MD, and Larntz K. Perceived stability, function, and satisfaction among transfemoral amputees using microprocessor and non-microprocessor-controlled knees: a multicenter survey. *J Prosthet Orthot 2009;* 21:32-42. See Evidence Table. Hafner BJ, Willingham LL, Buell NC, et al. Evaluation of function, performance, and preference as transfemoral amputees' transition from mechanical to microprocessor control of the prosthetic knee. *Arch Phys Med Rehabil 2007;* 88:207-217. See Evidence Table. Kahle JT, Highsmith MJ, and Hubbard SL. Comparison of non-microprocessor knee mechanism versus C-Leg® on prosthesis evaluation questionnaire, stumbles, falls, walking tests, stair descent, and knee performance. *J Rehabil Res Dev 2008;* 45:1-14. See Evidence Table. Kaufman KR, Levine JA, Brey RH, et al. Gait and balance of transfemoral amputees using passive mechanical and microprocessor-controlled prosthetic knees. *Gait Posture 2007;* 26:489-493. See Evidence Table. Kaufman KR, Levine JA, Brey RH, et al. Energy expenditure and activity of transfemoral amputees using mechanical and microprocessor-controlled prosthetic knees. *Arch Phys Med Rehabil 2008;* 89:1380-1385. See Evidence Table. Seymour R, Engbreston B, Kott K, et al. Comparison between C-Leg® microprocessor-controlled prosthetic knee and non-microprocessor controlled prosthetic knees: a preliminary study of energy expenditure, obstacle course performance, and quality of life survey. *Prosthet Orthot Int 2007;* 31:51-61. See Evidence Table.

The use of microprocessor-controlled lower limb prostheses in the treatment of lower limb amputation does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPC Codes	Description
L5010	Partial foot, molded socket, ankle height, with toe filler
L5020	Partial foot, molded socket, tibial tubercle height, with toe filler
L5050	Ankle, Symes, molded socket, SACH foot
L5060	Ankle, Symes, metal frame, molded leather socket, articulated ankle/foot
L5100	Below knee (BK), molded socket, shin, SACH foot
L5105	Below knee (BK), plastic socket, joints and thigh lacer, SACH foot
L5150	Knee disarticulation (or through knee), molded socket, external knee joints, shin, SACH foot
L5160	Knee disarticulation (or through knee), molded socket, bent knee configuration, external knee joints, shin, SACH foot
L5200	Above knee (AK), molded socket, single axis constant friction knee, shin, SACH foot
L5210	Above knee (AK), short prosthesis, no knee joint (stubbies), with foot blocks, no ankle joints, each
L5220	Above knee (AK), short prosthesis, no knee joint (stubbies), with articulated ankle/foot, dynamically aligned, each
L5230	Above knee (AK), for proximal femoral focal deficiency, constant friction knee, shin, SACH foot
L5250	Hip disarticulation, Canadian type; molded socket, hip joint, single axis constant friction knee, shin, SACH foot
L5270	Hip disarticulation, tilt table type; molded socket, locking hip joint, single axis constant friction knee, shin, SACH foot
L5280	Hemipelvectomy, Canadian type; molded socket, hip joint, single axis constant friction knee, shin,

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	SACH foot
L5301	Below knee (BK), molded socket, shin, SACH foot, endoskeletal system
L5312	Knee disarticulation (or through knee), molded socket, single axis knee, pylon, SACH foot, endoskeletal system
L5321	Above knee (AK), molded socket, open end, SACH foot, endoskeletal system, single axis knee
L5331	Hip disarticulation, Canadian type, molded socket, endoskeletal system, hip joint, single axis knee, SACH foot
L5341	Hemipelvectomy, Canadian type, molded socket, endoskeletal system, hip joint, single axis knee, SACH foot
L5400	Immediate postsurgical or early fitting, application of initial rigid dressing, including fitting, alignment, suspension, and one cast change, below knee (BK)
L5410	Immediate postsurgical or early fitting, application of initial rigid dressing, including fitting, alignment and suspension, below knee (BK), each additional cast change and realignment
L5420	Immediate postsurgical or early fitting, application of initial rigid dressing, including fitting, alignment and suspension and one cast change above knee (AK) or knee disarticulation
L5430	Immediate postsurgical or early fitting, application of initial rigid dressing, including fitting, alignment and suspension, above knee (AK) or knee disarticulation, each additional cast change and realignment
L5500	Initial, below knee (BK) PTB type socket, nonalignable system, pylon, no cover, SACH foot, plaster socket, direct formed
L5505	Initial, above knee (AK), knee disarticulation, ischial level socket, nonalignable system, pylon, no cover, SACH foot, plaster socket, direct formed
L5510	Preparatory, below knee (BK) PTB type socket, nonalignable system, pylon, no cover, SACH foot, plaster socket, molded to model
L5520	Preparatory, below knee (BK) PTB type socket, nonalignable system, pylon, no cover, SACH foot, thermoplastic or equal, direct formed
L5530	Preparatory, below knee (BK) PTB type socket, nonalignable system, pylon, no cover, SACH foot, thermoplastic or equal, molded to model
L5535	Preparatory, below knee (BK) PTB type socket, nonalignable system, no cover, SACH foot, prefabricated, adjustable open end socket
L5540	Preparatory, below knee (BK) PTB type socket, nonalignable system, pylon, no cover, SACH foot, laminated socket, molded to model
L5560	Preparatory, above knee (AK), knee disarticulation, ischial level socket, nonalignable system, pylon, no cover, SACH foot, plaster socket, molded to model
L5570	Preparatory, above knee (AK), knee disarticulation, ischial level socket, nonalignable system, pylon, no cover, SACH foot, thermoplastic or equal, direct formed
L5580	Preparatory, above knee (AK), knee disarticulation, ischial level socket, nonalignable system, pylon, no cover, SACH foot, thermoplastic or equal, molded to model
L5585	Preparatory, above knee (AK), knee disarticulation, ischial level socket, nonalignable system, pylon, no cover, SACH foot, prefabricated adjustable open end socket
L5590	Preparatory, above knee (AK), knee disarticulation, ischial level socket, nonalignable system, pylon, no cover, SACH foot, laminated socket, molded to model
L5595	Preparatory, hip disarticulation/hemipelvectomy, pylon, no cover, SACH foot, thermoplastic or equal, molded to patient model
L5600	Preparatory, hip disarticulation/hemipelvectomy, pylon, no cover, SACH foot, laminated socket, molded to patient model
L5610	Addition to lower extremity, endoskeletal system, above knee (AK), hydracadence system
L5611	Addition to lower extremity, endoskeletal system, above knee (AK), knee disarticulation, four-bar linkage, with friction swing phase control
L5613	Addition to lower extremity, endoskeletal system, above knee (AK), knee disarticulation, four-bar linkage, with hydraulic swing phase control
L5614	Addition to lower extremity, exoskeletal system, above knee (AK), knee disarticulation, four-bar linkage, with pneumatic swing phase control
L5616	Addition to lower extremity, endoskeletal system, above knee (AK), universal multiplex system, friction swing phase control
L5617	Addition to lower extremity, quick change self-aligning unit, above knee (AK) or below knee (BK), each
L5618	Addition to lower extremity, test socket, Symes
L5620	Addition to lower extremity, test socket, below knee (BK)

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L5622	Addition to lower extremity, test socket, knee disarticulation
L5624	Addition to lower extremity, test socket, above knee (AK)
L5626	Addition to lower extremity, test socket, hip disarticulation
L5628	Addition to lower extremity, test socket, hemipelvectomy
L5629	Addition to lower extremity, below knee, acrylic socket
L5630	Addition to lower extremity, Symes type, expandable wall socket
L5631	Addition to lower extremity, above knee (AK) or knee disarticulation, acrylic socket
L5632	Addition to lower extremity, Symes type, PTB brim design socket
L5634	Addition to lower extremity, Symes type, posterior opening (Canadian) socket
L5636	Addition to lower extremity, Symes type, medial opening socket
L5637	Addition to lower extremity, below knee (BK), total contact
L5638	Addition to lower extremity, below knee (BK), leather socket
L5639	Addition to lower extremity, below knee (BK), wood socket
L5640	Addition to lower extremity, knee disarticulation, leather socket
L5642	Addition to lower extremity, above knee (AK), leather socket
L5643	Addition to lower extremity, hip disarticulation, flexible inner socket, external frame
L5644	Addition to lower extremity, above knee (AK), wood socket
L5645	Addition to lower extremity, below knee (BK), flexible inner socket, external frame
L5646	Addition to lower extremity, below knee (BK), air, fluid, gel or equal, cushion socket
L5647	Addition to lower extremity, below knee (BK), suction socket
L5648	Addition to lower extremity, above knee (AK), air, fluid, gel or equal, cushion socket
L5649	Addition to lower extremity, ischial containment/narrow M-L socket
L5650	Additions to lower extremity, total contact, above knee (AK) or knee disarticulation socket
L5651	Addition to lower extremity, above knee (AK), flexible inner socket, external frame
L5652	Addition to lower extremity, suction suspension, above knee (AK) or knee disarticulation socket
L5653	Addition to lower extremity, knee disarticulation, expandable wall socket
L5654	Addition to lower extremity, socket insert, Symes, (Kemblo, Pelite, Aliplast, Plastazote or equal)
L5655	Addition to lower extremity, socket insert, below knee (BK) (Kemblo, Pelite, Aliplast, Plastazote or equal)
L5656	Addition to lower extremity, socket insert, knee disarticulation (Kemblo, Pelite, Aliplast, Plastazote or equal)
L5658	Addition to lower extremity, socket insert, above knee (AK) (Kemblo, Pelite, Aliplast, Plastazote or equal)
L5661	Addition to lower extremity, socket insert, multidurometer Symes
L5665	Addition to lower extremity, socket insert, multidurometer, below knee (BK)
L5666	Addition to lower extremity, below knee (BK), cuff suspension
L5668	Addition to lower extremity, below knee (BK), molded distal cushion
L5670	Addition to lower extremity, below knee (BK), molded supracondylar suspension (PTS or similar)
L5671	Addition to lower extremity, below knee (BK)/above knee (AK) suspension locking mechanism (shuttle, lanyard, or equal), excludes socket insert
L5672	Addition to lower extremity, below knee (BK), removable medial brim suspension
L5673	Addition to lower extremity, below knee (BK)/above knee (AK), custom fabricated from existing mold or prefabricated, socket insert, silicone gel, elastomeric or equal, for use with locking mechanism
L5676	Additions to lower extremity, below knee (BK), knee joints, single axis, pair
L5677	Additions to lower extremity, below knee (BK), knee joints, polycentric, pair
L5678	Additions to lower extremity, below knee (BK), joint covers, pair
L5679	Addition to lower extremity, below knee (BK)/above knee (AK), custom fabricated from existing mold or prefabricated, socket insert, silicone gel, elastomeric or equal, not for use with locking mechanism
L5680	Addition to lower extremity, below knee (BK), thigh lacer, nonmolded
L5681	Addition to lower extremity, below knee (BK)/above knee (AK), custom fabricated socket insert for congenital or atypical traumatic amputee, silicone gel, elastomeric or equal, for use with or without locking mechanism, initial only (for other than initial, use code L5673 or L5679)
L5682	Addition to lower extremity, below knee (BK), thigh lacer, gluteal/ischial, molded
L5683	Addition to lower extremity, below knee (BK)/above knee (AK), custom fabricated socket insert for other than congenital or atypical traumatic amputee, silicone gel, elastomeric or equal, for use with or without locking mechanism, initial only (for other than initial, use code L5673 or L5679)

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L5684	Addition to lower extremity, below knee, fork strap
L5686	Addition to lower extremity, below knee (BK), back check (extension control)
L5688	Addition to lower extremity, below knee (BK), waist belt, webbing
L5690	Addition to lower extremity, below knee (BK), waist belt, padded and lined
L5692	Addition to lower extremity, above knee (AK), pelvic control belt, light
L5694	Addition to lower extremity, above knee (AK), pelvic control belt, padded and lined
L5695	Addition to lower extremity, above knee (AK), pelvic control, sleeve suspension, neoprene or equal, each
L5696	Addition to lower extremity, above knee (AK) or knee disarticulation, pelvic joint
L5697	Addition to lower extremity, above knee (AK) or knee disarticulation, pelvic band
L5698	Addition to lower extremity, above knee (AK) or knee disarticulation, Silesian bandage
L5699	All lower extremity prostheses, shoulder harness
L5700	Replacement, socket, below knee (BK), molded to patient model
L5701	Replacement, socket, above knee (AK)/knee disarticulation, including attachment plate, molded to patient model
L5702	Replacement, socket, hip disarticulation, including hip joint, molded to patient model
L5703	Ankle, Symes, molded to patient model, socket without solid ankle cushion heel (SACH) foot, replacement only
L5704	Custom shaped protective cover, below knee (BK)
L5705	Custom shaped protective cover, above knee (AK)
L5706	Custom shaped protective cover, knee disarticulation
L5707	Custom shaped protective cover, hip disarticulation
L5710	Addition, exoskeletal knee-shin system, single axis, manual lock
L5711	Additions exoskeletal knee-shin system, single axis, manual lock, ultra-light material
L5712	Addition, exoskeletal knee-shin system, single axis, friction swing and stance phase control (safety knee)
L5714	Addition, exoskeletal knee-shin system, single axis, variable friction swing phase control
L5716	Addition, exoskeletal knee-shin system, polycentric, mechanical stance phase lock
L5718	Addition, exoskeletal knee-shin system, polycentric, friction swing and stance phase control
L5722	Addition, exoskeletal knee-shin system, single axis, pneumatic swing, friction stance phase control
L5724	Addition, exoskeletal knee-shin system, single axis, fluid swing phase control
L5726	Addition, exoskeletal knee-shin system, single axis, external joints, fluid swing phase control
L5728	Addition, exoskeletal knee-shin system, single axis, fluid swing and stance phase control
L5780	Addition, exoskeletal knee-shin system, single axis, pneumatic/hydra pneumatic swing phase control
L5781	Addition to lower limb prosthesis, vacuum pump, residual limb volume management and moisture evacuation system
L5782	Addition to lower limb prosthesis, vacuum pump, residual limb volume management and moisture evacuation system, heavy-duty
L5785	Addition, exoskeletal system, below knee (BK), ultra-light material (titanium, carbon fiber or equal)
L5790	Addition, exoskeletal system, above knee (AK), ultra-light material (titanium, carbon fiber or equal)
L5795	Addition, exoskeletal system, hip disarticulation, ultra-light material (titanium, carbon fiber or equal)
L5810	Addition, endoskeletal knee-shin system, single axis, manual lock
L5811	Addition, endoskeletal knee-shin system, single axis, manual lock, ultra-light material
L5812	Addition, endoskeletal knee-shin system, single axis, friction swing and stance phase control (safety knee)
L5814	Addition, endoskeletal knee-shin system, polycentric, hydraulic swing phase control, mechanical stance phase lock
L5816	Addition, endoskeletal knee-shin system, polycentric, mechanical stance phase lock
L5818	Addition, endoskeletal knee-shin system, polycentric, friction swing and stance phase control
L5822	Addition, endoskeletal knee-shin system, single axis, pneumatic swing, friction stance phase control
L5824	Addition, endoskeletal knee-shin system, single axis, fluid swing phase control
L5826	Addition, endoskeletal knee-shin system, single axis, hydraulic swing phase control, with miniature high activity frame
L5828	Addition, endoskeletal knee-shin system, single axis, fluid swing and stance phase control
L5830	Addition, endoskeletal knee-shin system, single axis, pneumatic/swing phase control

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L5840	Addition, endoskeletal knee-shin system, four-bar linkage or multiaxial, pneumatic swing phase control
L5845	Addition, endoskeletal knee-shin system, stance flexion feature, adjustable
L5848	Addition to endoskeletal knee-shin system, fluid stance extension, dampening feature, with or without adjustability
L5850	Addition, endoskeletal system, above knee (AK) or hip disarticulation, knee extension assist
L5855	Addition, endoskeletal system, hip disarticulation, mechanical hip extension assist
L5856	Addition to lower extremity prosthesis, endoskeletal knee-shin system, microprocessor control feature, swing and stance phase, includes electronic sensor(s), any type
L5857	Addition to lower extremity prosthesis, endoskeletal knee-shin system, microprocessor control feature, swing phase only, includes electronic sensor(s), any type
L5858	Addition to lower extremity prosthesis, endoskeletal knee-shin system, microprocessor control feature, stance phase only, includes electronic sensor(s), any type
L5859	Addition to lower extremity prosthesis, endoskeletal knee-shin system, powered and programmable flexion/extension assist control, includes any type motor(s)
L5910	Addition, endoskeletal system, below knee (BK), alignable system
L5920	Addition, endoskeletal system, above knee (AK) or hip disarticulation, alignable system
L5925	Addition, endoskeletal system, above knee (AK), knee disarticulation or hip disarticulation, manual lock
L5930	Addition, endoskeletal system, high activity knee control frame
L5940	Addition, endoskeletal system, below knee (BK), ultra-light material (titanium, carbon fiber or equal)
L5950	Addition, endoskeletal system, above knee (AK), ultra-light material (titanium, carbon fiber or equal)
L5960	Addition, endoskeletal system, hip disarticulation, ultra-light material (titanium, carbon fiber or equal)
L5961	Addition, endoskeletal system, polycentric hip joint, pneumatic or hydraulic control, rotation control, with or without flexion and/or extension control
L5962	Addition, endoskeletal system, below knee (BK), flexible protective outer surface covering system
L5964	Addition, endoskeletal system, above knee (AK), flexible protective outer surface covering system
L5966	Addition, endoskeletal system, hip disarticulation, flexible protective outer surface covering system
L5968	Addition to lower limb prosthesis, multiaxial ankle with swing phase active dorsiflexion feature
L5969	Addition, endoskeletal ankle-foot or ankle system, power assist, includes any type motor(s)
L5970	All lower extremity prostheses, foot, external keel, SACH foot
L5971	All lower extremity prostheses, solid ankle cushion heel (SACH) foot, replacement only
L5972	All lower extremity prostheses, foot, flexible keel
L5973	Endoskeletal ankle foot system, microprocessor controlled feature, dorsiflexion and/or plantar flexion control, includes power source
L5974	All lower extremity prostheses, foot, single axis ankle/foot
L5975	All lower extremity prostheses, combination single axis ankle and flexible keel foot
L5976	All lower extremity prostheses, energy storing foot (Seattle Carbon Copy II or equal)
L5978	All lower extremity prostheses, foot, multiaxial ankle/foot
L5979	All lower extremity prostheses, multiaxial ankle, dynamic response foot, one-piece system
L5980	All lower extremity prostheses, flex-foot system
L5981	All lower extremity prostheses, flex-walk system or equal
L5982	All exoskeletal lower extremity prostheses, axial rotation unit
L5984	All endoskeletal lower extremity prostheses, axial rotation unit, with or without adjustability
L5985	All endoskeletal lower extremity prostheses, dynamic prosthetic pylon
L5986	All endoskeletal lower extremity prostheses, dynamic prosthetic pylon
L5987	All lower extremity prostheses, shank foot system with vertical loading pylon
L5988	Addition to lower limb prosthesis, vertical shock reducing pylon feature
L5990	Addition to lower extremity prosthesis, user adjustable heel height
L5999	Lower extremity prosthesis, not otherwise specified

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***Note**: Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

**To verify authorization requirements for a specific code by plan type, please use the Pre-authorization Code Check.

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Date Created	Date Reviewed	Date Last Revised
2004	10/05/2010 MDCRPC, 12/07/2010 MDCRPC, 10/04/2011 MDCRPC, 08/07/2012 MDCRPC, 02/05/2013 MDCRPC, 12/03/2013 MPC, 10/07/2014 MPC, 01/06/2015 MPC, 11/03/2015 MPC, 09/06/2016 MPC, 07/11/2017 MPC, 05/01/2018 MPC, 05/07/2019 MPC, 05/05/2020 MPC, 05/04/2021 MPC, 05/03/2022 MPC, 05/02/2023 MPC, 01/09/2024 MPC	12/21/2023

MDCRPC Medical Director Clinical Review and Policy Committee
MPC Medical Policy Committee

Ad	Description
05/04/2021	Updated applicable coding.
12/21/2023	Added NCD Prosthetic Shoe 280.1

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KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Low Vision Aides and Devices

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	Refractive Lenses (L33793)
Local Coverage Article	Refractive Lenses – Policy Article (A52499) **Low vision aids (V2600, V2610, V2615) will be denied as noncovered because coverage under the Medicare prosthetic benefit is limited to persons with congenital absence or surgical removal of the lens of the eye.*

For Non-Medicare Members

A. To qualify for low vision aides or devices a member must have best corrected vision of 20/70 or worse in the better eye with glasses or contacts on.
   1. The following codes are identified and coverable per contract for low vison aides and devices:
      - **V2600** – Handheld low vision aids and other non-specific mounted aids.
      - **V2610** – Single Lens Spectacles mounted low vision aids
      - **V2615** – Telescope and other compound lens system, including distance vision telescopic, near vision telescopic and compound microscopic lens system.
      - **92354** – Fitting of spectacle mounted low vision aid: single element system
      - **92355** – Fitting of spectacle mounted low vision aid: Telescopic or compound lens system

If requesting one or more of these items, please send the following documentation to support medical necessity:

- Clinical notes from requesting provider &/or specialist indicating corrected visual acuity

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

A wide variety of rehabilitation options are available to help people with low vision live and/or work more effectively, efficiently, and safely. Most people can be helped with one or more low vision treatment options. The more commonly prescribed devices are: Handheld low vision aids and other non-spectacle mounted aids, Single lens spectacle mounted low vision aids, Telescopic and other compound lens system, including distance vision telescopic, near vision telescopes and compound microscopic lens system.

Applicable Codes

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Medicare – Considered not medically necessary
Non-Medicare - Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
V2600	Handheld low vision aids and other nonspectacle mounted aids
V2610	Single lens spectacle mounted low vision aids
V2615	Telescopic and other compound lens system, including distance vision telescopic, near vision telescopes and compound microscopic lens system

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
92354	Fitting of spectacle mounted low vision aid; single element system
92355	Fitting of spectacle mounted low vision aid; telescopic or other compound lens system

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
12/03/2013	12/03/2013[MPC], 09/16/2014[MPC], 08/04/2015[MPC], 06/07/2016[MPC], 04/04/2017[MPC], 02/06/2018[MPC], 01/08/2019[MPC], 01/07/2020[MPC], 01/05/2021[MPC], 01/04/2022[MPC], 01/10/2023[MPC], 01/09/2024[MPC]	09/10/2018

[MPC] Medical Policy Committee

Revision History	Description
08/04/2015	Editorial changes were made to criteria
09/10/2018	Added coverage article A52499

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Clinical Review Criteria
Laparoscopic Uterine Nerve Ablation (LUNA) for Dysmenorrhea

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article	None
Kaiser Permanente Medical Policy	Due to the absence of an active NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Clinical Review Criteria, "***Laparoscopic Uterine Nerve Ablation (LUNA) for Dysmenorrhea***," for medical necessity determinations. Refer to the Non-Medicare criteria below.

For Non-Medicare Members

Kaiser Permanente has elected to use the Laparoscopic Uterosacral Nerve Ablation (LUNA) (A-0284) MCG* for medical necessity determinations. This procedure is not covered per MCG guidelines. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.

***MCG are proprietary and cannot be published and/or distributed**. However, on an individual member basis, Kaiser Permanente can share a copy of the specific criteria document used to make a utilization management decision. If one of your patients is being reviewed using these criteria, you may request a copy of the criteria by calling the Kaiser Permanente Clinical Review staff at 1-800-289-1363 or access the MCG Guideline Index using the link provided above.

If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Dysmenorrhea refers to painful cramping in the lower abdomen that occurs during or just before the menses. The cramping sensation is often accompanied by other symptoms, including sweating, headaches, nausea and vomiting. Dysmenorrhea is sometimes divided into two sub-categories. Primary dysmenorrhea is menstrual pain without any identifiable organic pathology and generally first occurs in women younger than 20. Secondary dysmenorrhea is menstrual pain associated with an identifiable pathological condition, such as endometriosis, cervical stenosis or pelvic adhesions, and is most often seen in women over 20 (Stenchever, 2001).

Non-steroidal anti-inflammatory drugs (NSAIDS) are the standard therapy for primary dysmenorrhea. These act by suppressing prostaglandin levels. Although the pathogenesis of primary dysmenorrhea is still not known, there

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is a close association between dysmenorrhea symptoms and an elevated level of prostaglandin F2a. Oral contraceptive pills (OCPs) are also a commonly prescribed medication treatment for primary dysmenorrhea. OCPs may relieve dysmenorrhea because of a modulating effect on the hypothalamus or a direct reduction in the amount of endometrium present (Stenchever, 2001). Treatment of secondary dysmenorrhea generally involves treating the underlying condition.

Pelvic nerve surgery can be used to treat primary dysmenorrhea that fails to respond to medical therapy and can be used in conjunction with other surgical procedures for secondary dysmenorrhea, such as operative laparoscopy for endometriosis. Laparoscopic uterine nerve ablation (LUNA) involves the use of laser or cauterization to destroy nerves in the uterosacral ligaments, at the point where they insert into the cervix. Doyle first reported that vaginal transection of the uterosacral nerves could be effective for dysmenorrhea in 1955. LUNA is generally associated with few side effects. Potential rare complications include uterine prolapse and bladder dysfunction. There is also a second type of pelvic nerve surgery, laparoscopic presacral neurectomy (LPN). This involves the total removal of the presacral nerves that lie within the boundary of the interiliac triangle and is generally believed to have more side effects than LUNA. More radical surgery, such as hysterectomy, is the treatment of last resort for patients with persistent dysmenorrhea (Proctor et al., 2006; Johnson et al., 2004).

LUNA for dysmenorrhea has not been previously reviewed for MTAC.

Medical Technology Assessment Committee (MTAC)

Laparoscopic Uterine Nerve Ablation

04/03/2006: MTAC REVIEW

Evidence Conclusion: Evidence from the two largest and highest quality RCTs (Johnson et al., 2004; Vercellini et al., 2003) suggests that laparoscopic uterine nerve ablation (LUNA) is not an effective treatment for secondary dysmenorrhea (dysmenorrhea among women with symptoms of endometriosis). The Vercellini study was limited by lack of an intention to treat analysis on pain outcomes. There is insufficient evidence to draw conclusions about laparoscopic uterine nerve ablation (LUNA) as a treatment for primary dysmenorrhea. There is evidence from only one well-done RCT comparing LUNA to a control group (Johnson et al., 2004). However, this study was designed to evaluate LUNA for pelvic pain, not specifically dysmenorrhea. The study included some women who did not present with dysmenorrhea and results were not stratified according to baseline dysmenorrhea status. There were four main pain outcomes. In addition to dysmenorrhea, these were non-menstrual pelvic pain, deep dyspareunia and dyschezia. In the intention to treat analysis, the Johnson study found one statistically significant outcome at $p<0.05$. This was reduction in dysmenorrhea, favoring the LUNA group ($p=0.045$). If the investigators had adjusted for multiple comparisons (i.e. the four primary pain outcomes), the difference in treatment success between the LUNA and control groups would not have been statistically significant.

Articles: There was a Cochrane Collaboration systematic review on surgical interruption of pelvic nerve pathways for dysmenorrhea. The Cochrane literature search identified two high-quality RCTs on LUNA for dysmenorrhea. These two RCTs, which were also identified in the Medline search, were critically appraised. The remainder of the RCTs identified by Cochrane were small and had methodological flaws. The Cochrane Collaboration investigators searched the literature through June 2004. No RCTs on LUNA for dysmenorrhea were identified that were published after the Cochrane search data. *The RCTs reviewed were* Johnson NP, Farquhar CM, Crossley S et al. A double-blind randomized controlled trial of laparoscopic uterine nerve ablation for women with chronic pelvic pain. BJOG 2004; 111: 950-959. See Evidence Table.

The use of laparoscopic uterine nerve ablation in the evaluation of dysmenorrheal does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Considered Not Medically Necessary:

CPT® or HCPCS Codes	Description
No specific codes	

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Date Created	Date Reviewed	Date Last Revised
04/27/2006	04/03/2006[MPC], 07/07/2015[MPC], 05/03/2016[MPC], 02/07/2017[MPC], 11/07/2017[MPC], 10/02/2018[MPC], 10/01/2019[MPC], 10/06/2020[MPC], 10/05/2021[MPC], 10/04/2022[MPC], 10/03/2023[MPC]	05/03/2016

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
05/03/2016	Adopted MCG guideline

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KAISER PERMANENTE®

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PATIENT REFERRAL GUIDELINES
Lung Transplant [i], [ii], [iii]

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Criteria

For Medicare Members

Transplantation may be considered for patients with end-stage or life-threatening disease who have no prospect for prolonged survival, or whose quality of life is severely impaired. The following are current, generally accepted, guidelines for lung & heart/lung transplantation. These guidelines for referral for transplant evaluation are not intended as an automatic inclusion or exclusion of a candidate for referral, rather should be applied together with careful clinical judgment.

For Non-Medicare Members

Transplantation may be considered for patients with end-stage or life-threatening disease who have no prospect for prolonged survival, or whose quality of life is severely impaired. The following are current, generally accepted, guidelines for lung & heart/lung transplantation. These guidelines for referral for transplant evaluation are not intended as an automatic inclusion or exclusion of a candidate for referral, rather should be applied together with careful clinical judgment.

1. GENERAL PRINCIPLES

a. If clinical parameters of end-stage or life-threatening disease indicate the need for transplantation, early referral should be made.
b. Patients with a history of malignancy with moderate to high risk of recurrence (as determined after consultation with oncologist considering tumor type, response to therapy, and presence or absence of metastatic disease) may be unsuitable candidates for transplantation. Patients with low risk of recurrence may be considered.
c. Uncontrollable active infection is a contraindication to transplant.
d. Candidates with a history of substance abuse must be free from alcohol and other substance abuse for six (6) months and have been evaluated by a substance abuse program. The risk of recidivism, which has been documented to negatively impact transplant outcomes, must be addressed and considered to be low. [4, 5, 6] Exceptions may be made on a case-by-case basis.
e. Candidates for thoracic organ (heart, lung and heart/lung) transplants must be free from tobacco use for the previous six (6) months. Routine monitoring may be required. Specific programs for abdominal organs (liver, intestines, and kidney) may require abstinence from tobacco products in order to be actively listed.
f. Candidates must have adequate social support systems and display a proven record of adherence to medical treatment.
    i. Patients must have a care giver or care givers who are physically and cognitively able to assist the patient with self- care activities and are available to travel within short notice to the KP approved transplant Center of Excellence.
    ii. Evidence of non-adherence may be failure to keep appointments, failure to make steady progress in completing pre- transplant evaluation requirements, failure to accurately follow medication regimens or failure to accomplish the activities required for maintenance on the waiting list.

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g. Patients must be willing and able to travel within short notice to the KP approved transplant Center of Excellence and, if necessary, return for treatment of complications.
h. The presence of significant irreversible neurologic dysfunction, active psychological and/or psychiatric conditions, and/or other social behaviors that prevent adherence with a complex medical regimen, are considered contraindications for referral for transplant.
    i. Evidence of such non-adherence may be failure to keep appointments, failure to make steady progress in completing pre-transplant evaluation requirements, failure to accurately follow medication regimens or failure to accomplish the activities required for maintenance on the waiting list.
i. Whenever transplant is considered as an option and discussed with the patient and/or family, consultation with Advanced Life Care Planning/Palliative Care resources is strongly recommended.

2. INDICATIONS FOR LUNG TRANSPLANT

a. Must meet all prerequisites listed in the General Principles section
b. Any disease state in which transplantation has become an accepted mode of treatment worldwide including
    i. Chronic obstructive pulmonary disease (COPD), which may include asthma, chronic bronchitis, emphysema and/or Alpha 1 antitrypsin deficiency
    ii. Idiopathic pulmonary fibrosis
    iii. Sarcoidosis
    iv. Connective tissue disease-related pulmonary fibrosis
    v. Eosinophilic granulomatosis
    vi. Bronchiectasis
    vii. Cystic fibrosis (CF)
    viii. Pulmonary hypertension (both primary and secondary)
    ix. Lymphangiomyomatosis (LAM)
    x. Interstitial lung disease not otherwise defined.
c. Patients should be referred for transplant evaluation by a pulmonologist or a cardiologist who has accumulated data defining both the disease as potentially treatable by transplantation and progression is occurring despite maximal medical therapy.
d. Early referral is strongly encouraged for progressive lung disease with a poor prognosis[7]
e. Ideally, the patient should be ambulatory with rehabilitation potential.

3. CONTRAINDICATIONS FOR LUNG TRANSPLANT

a. Must meet all prerequisites listed in the General Principles section
b. Invasive mechanical ventilator support[8].
c. Unresolved infection (except in cystic fibrosis and bronchiectasis).
d. Uncontrolled chronic infection (i.e., HIV with detectable viral load)
e. Other systemic diseases including but not limited to:
    i. Diabetes with end organ effects; i.e., renal, cardiac or uncorrectable peripheral vascular disease. Insulin use itself is not a contraindication.
    ii. Uncontrolled hypertension.
    iii. Significant neurologic disease impairing cognitive function.
    iv. Malnutrition [9]
    v. Obesity >140% ideal body weight or BMI >32 kg/m2 [10, 11](with an understanding that a BMI <30 may be necessary for transplantation).
        1. May wish to consider initiating transplant workup if patient has pulmonary fibrosis and BMI >32 (but <34) if showing willingness to lose weight.
    vi. Advanced hepatic dysfunction.
    vii. Advanced renal dysfunction (creatinine clearance < 50 ml/min. after maximum therapy). However, patients with underlying cardiopulmonary causes of low creatinine clearance can be considered for transplant on a case-by-case basis.
    viii. Evidence of clinically significant obstructive coronary artery disease and/or LVEF <40%. [12]
    ix. Active or unresolved peptic ulcer disease.
    x. Chronic opiate use: Patients should be seen by a pain management specialist for alternative forms of therapy.
    xi. Uncorrectable bleeding diathesis or clotting disorder

RELATIVE CONTRAINDICATIONS

a. Patients with previous thoracotomy and/or sclerosing procedures should be considered on a case by case basis.

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b. Systemic corticosteroid therapy >10 mgs prednisone daily.
c. Esophageal dysmotility and reflux. Surgical repair may be necessary.[13]
d. Age >70 for lung transplant referral.
e. Symptomatic osteoporosis.
f. Major mechanical chest deformity (such as kyphoscoliosis).
g. Short stature patients (in USA 4'11" for females and 5'4" for males) are significantly disadvantaged and early consideration of multiple listing is encouraged.

PATIENT PROFILE FOR COMMON DIAGNOSES LUNG TRANSPLANT REFERRAL GUIDELINES

Any or all of the listed guidelines for each disease entity should raise consideration for lung transplantation evaluation. Clinical correlation is always of primary importance.

1. GROUP A – Obstructive Lung Disease [14, 15] (See Table 1 Below)
    1. FEV1 < 25 %
    2. DLCO < 40%
    3. Hypoxemia; PO2 < 55
    4. Hypercapnia; PCO2> 51[16]
    5. Bode Index > 5
2. GROUP B – Pulmonary Arterial Hypertension (See Table 1 Below)[17, 18, 19]
    a. Patients with clinically significant PAH should be evaluated by physicians experienced in treating pulmonary hypertension and have received maximum available pharmacological treatment.
    b. Possible indications for referral include:
        i. Pericardial Effusion[20]
        ii. World Health Organization (WHO) (New York Heart Association) class 3 or 4
        iii. Lack of improvement in WHO Class 3 or 4 and/or lack of improvement in 6-minute walk test of < 350 meters, despite maximum pharmacological therapy.
    c. Definite indications, after maximum pharmacologic treatment for referral include: [21]
        i. Mean RA > 15 mmHg
        ii. Cardiac Index < 2L per minute. Untreated, the mean survival for patients with these criteria is 10-11 months.

GROUP C – Cystic Fibrosis [22](See table 1 Below)

a. FEV1 < 40%
b. PO2 < 55
c. Clinical deterioration, especially in young female patients, as characterized by increasing number of hospitalizations, including recurrent pneumothoraxes, rapid fall of FEV1, recurrent major hemoptysis uncontrolled by embolization and/or increasing cachexia should prompt consideration for transplant referral.
d. PCO2 > 51
e. Patients with Burkholderia cepacia have a relative contraindication.

GROUP D – Restrictive Lung Disease) 22, [23](See Table 1 Below)

a. Force Vital Capacity < 80%[22]
b. Decline in Forced Vital Capacity of ≥10% and/or decline in DLCO ≥ 15% during 6 months of follow-up[22]
c. Diffusing Capacity (corrected for alveolar volume) < 60%
d. Evidence of interstitial lung disease on HRCT in conjunction with one or more of the above.

Referral to lung transplant program should be considered when a definitive diagnosis of usual interstitial pneumonitis (UIP) or idiopathic pulmonary fibrosis (IPF) is made and may be considered for the diagnosis of fibrotic nonspecific interstitial pneumonitis (NSIP).

OTHER CONDITIONS

Other conditions for which transplant may be appropriate include the Lung diseases described ~~in~~ Table 1 below.[24]

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Table 1: Lung allocation score (LAS) primary diagnostic groupings for lung transplant candidates

LAS lung disease diagnosis grouping	
Group A (obstructive lung disease)	• Chronic obstructive pulmonary disease (COPD), with or without alpha-1-anti deficiency, due to chronic bronchitis and or emphysema • Lymphangioleiomyomatosis (LAM) • Bronchiectasis, including primary ciliary dyskinesia • Sarcoidosis with a mean pulmonary artery (PA) pressure ≤30 mmHg
Group B (pulmonary vascular disease)	• Idiopathic pulmonary arterial hypertension (iPAH, formerly known as primary hypertension [PPH]) • Eisenmenger's syndrome • Other pulmonary vascular diseases
Group C (cystic fibrosis or immunodeficiency disorders)	• Cystic fibrosis (CF) • Immunodeficiency disorders such as hypogammaglobulinemia
Group D (restrictive lung disease)	• Idiopathic pulmonary fibrosis (IPF) • Pulmonary fibrosis due to other causes • Sarcoidosis with mean PA pressure >30 mmHg • Obliterative bronchiolitis (nonretransplant)

Source: Revision to policy 3.7.6.1.

ADDENDUM

GUIDANCE FOR LUNG TRANSPLANT FOR IRREVERSIBLE PULMONARY FAILURE FROM COVID-19

Background: Transplant has been successful for other conditions, including infections, that lead to irreversible pulmonary failure, so this disease has some familiar aspects within the lung transplant community. Because of the specific conditions surrounding the effects of SARS-C0V-2, and because much of the mechanism underlying the development of lung injury and recovery are still unclear, the following elements are recommended for any consideration for referral of and authorizations for potential candidates for lung transplant. The below represent elements, *IN ADDITION TO THE USUAL CRITERIA PROVIDED IN THE CMS LUNG PATIENT REFERRAL GUIDELINES:*

1. Age under 65 if ECMO has been used as bridge to transplant
2. Disease has progressed in spite of maximal non-invasive ventilatory support
3. No other significant organ dysfunction exists
4. Sufficient time for recovery must be allowed: once on invasive mechanical support or ECMO, referral should not be considered fewer than 4-6 weeks after ventilator-dependent or ECMO-supported pulmonary failure
5. Patients on prolonged 0_2 therapy other than mechanical support or ECMO should be given sufficient time to determine irreversibility of the condition (usually three months) and should be ambulatory with good opportunity for rehabilitation.
6. Evidence of irreversible lung disease (bullae, fibrosis) must be present
7. The ability to gain patient, not surrogate, approval for transplant is an essential ethical concept in light of the relatively poor long-term outcomes from lung transplant
8. Ability to do adequate pulmonary rehabilitation while on support for respiratory failure
9. Have 2 negative SARS-COV-2 PCR tests at least 24 hours apart with one of the samples being a deep respiratory specimen.
10. Transplants should be performed only at lung transplant programs experienced in the highest risk lung transplants including familiarity with transplanting patients with ECMO bridging to transplant. Furthermore, they should have:
    a. Broad donor pool (represented by low time to transplant measures), and
    b. Low wait-list mortality

Reference: Cypel M, Keshavjee S. Comment When to consider lung transplantation for COVID-19. Lancet Respir Med. 2020;8:944–6. https://doi.org/10.1016/S2213-2600(20)30393-3 .

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Footnotes

1. See Addendum 1, New system for lung allocation (enclosed)
2. Orens, JB, et al, 'International Guidelines for the Selection of Lung Transplant Candidates: 2006 Update - A Consensus Report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation', *Journal of Heart and Lung Transplantation*, 25(7), July 2006, 745-755.
3. Weill D, et al. A consensus document for the selection of lung transplant candidates: 2014 An update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2015; 34:1–15
4. *Liver Transplantation* 2006, .12:813-820. Alcohol consumption patterns and predictors of use following liver transplantation for alcoholic liver disease.
5. *Liver Transplant Surg,*. 1997, Vol 3, 304 – 310.The natural history of alcoholism and its relationship to liver transplantation.
6. 6. Alcohol abstinence prior to liver transplantation for Alcoholic Liver Disease (G110807), *TPMG New Medical Technology*
7. J Thorac Dis. 2019 Sep; 11(Suppl 14): S1708–S1720.
8. Under acceptable case-by-case circumstances, a patient who has been listed for a lung transplant and previously ambulatory, and now requires mechanical ventilation, may still be a potential candidate for lung transplantation. Patients who have been listed for lung transplant, and require invasive mechanical ventilation, can remain on the transplant list provided that there remains rehabilitation potential. On a carefully selected case-by-case basis, patients who are on invasive mechanical support, and are ambulatory with a potential for rehabilitation, can be listed for lung transplant. *Chest 2001; 119* (1) 224-227.
9. Any disorder of nutrition causing a lack of necessary or proper food substances in the body or improper absorption and distribution of them (Taber's Cyclopedic Medical Dictionary).
10. *Journal of Heart and Lung Transplantation Vol. 18 (8), August 1999, pg 750-761*
11. *The Journal of Heart and Lung Transplantation 2010*; 29 (9), 1026 – 1033. Impact of Recipient Body Mass Index on Survival after Lung Transplantation.
12. Potential candidate for Heart/Lung transplantation will be evaluated independently.
13. Annals of Surgery, 2006. Vol.244 (4) 491-497.
14. Lung Transplantation in Advanced COPD: Is it Worth it? Semin Respir Crit Care Med. 2010 June; 31(3): 365-372; Selecting lung transplant candidates: where do current guidelines fall short? Expert Rev Respir Med. 2012 February; 6(1): 51-61.
15. Amer *Rev Respir Dis* 140: S92 and S95 1989; Ann Int Med 99: 612: 1983; *New England Journal of Medicine*,1999 340(14), 1081-91
16. Celli BR, Cote CG, Marin JM et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 2004;350:1005-12.
17. Applicable to idiopathic pulmonary arterial hypertension, familial pulmonary arterial hypertension, collagen vascular disease limited to the lungs, pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis, and drug induced pulmonary hypertension. *CHEST, 2004*, Volume 126 (Supplement 1).
18. AJRCCM 201. 184: 159-171 - Thorough review of lung transplantation; J Heart Lung Transplant. 2006. 25(7): 745-55. - Consensus report from ISHLT Pulm Circ. 2011. April-June. 1(2): 182-191 - PH and lung transplant.
19. *Transplantation*. 2010 Aug 15. 90(3): 298-305. - Suggests that 6MWD </= 300 m and RAP >/= 14 mm Hg is better predictor of wait list mortality than LAS scoring system.
20. McGoon MD and Miller DP. Eur Respir Rev. 2012; 21(123):8-18.
21. *Ann Int Med* 115: 343 1991
22. Weill D, et al. A consensus document for the selection of lung transplant candidates: 2014 An update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2015; 34:1–15
23. Nathan, SD., Lung Transplantation- Disease-Specific Considerations for Referral', CHEST 2005; 127: 1006-1016.
24. OPTN Policy 10: Allocation of Lungs, 10.1.F.i Lung Disease Diagnosis Groups, Effective Date 9/1/2016

If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Lung transplant is a last resort treatment for end stage lung disease. The first human transplant was conducted in 1965. The first successful single lung transplant was done in 1983.

The diseases treated by lung transplants include:

- chronic obstructive pulmonary disease (COPD), including emphysema;
- idiopathic pulmonary fibrosis;
- cystic fibrosis;
- idiopathic (formerly known as "primary") pulmonary hypertension;

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- alpha 1-antitrypsin deficiency;
- replacing previously transplanted lungs that have since failed;
- other causes, including bronchiectasis and sarcoidosis.

Prior to 2005, donor lungs were allocated by the United Network for Organ Sharing on a first-come, first-serve basis to patients on the transplant list. This was replaced by the current system, in which prospective lung recipients of age of 12 and older are assigned a lung allocation score or LAS, which takes into account various measures of the patient's health. The new system allocates donated lungs according to the immediacy of need rather than how long a patient has been on the transplant list. Patients who are under the age of 12 are still given priority based on how long they have been on the transplant waitlist. The length of time spent on the list is also the deciding factor when multiple patients have the same lung allocation score.

Patients who are accepted as good potential transplant candidates must carry a pager with them at all times in case a donor organ becomes available. These patients must also be prepared to move to their chosen transplant center at a moment's notice and relocate to within close proximity of the center. Such patients may be encouraged to limit their travel within a certain geographical region in order to facilitate rapid transport to a transplant center.

Evidence and Source Documents

The scientific literature is periodically reviewed, and patient selection criteria are updated when new efficacy data becomes available.

Kaiser Permanente Committee on Medically Emerging Technology:
Transplant, Lung, Double-7/12/91-Double lung transplantation is efficacious for appropriately selected patients.
Transplant, Lung, Single-7/12/91 Single lung transplantation is efficacious for appropriately selected patients.

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
32850	Donor pneumonectomy(s) (including cold preservation), from cadaver donor
32851	Lung transplant, single; without cardiopulmonary bypass
32852	Lung transplant, single; with cardiopulmonary bypass
32853	Lung transplant, double (bilateral sequential or en bloc); without cardiopulmonary bypass
32854	Lung transplant, double (bilateral sequential or en bloc); with cardiopulmonary bypass

Medicare – **Considered not medically necessary**
Non-Medicare – Considered medically necessary when criteria in the applicable policy statements listed above are met

CPT® or HCPC Codes	Description
0494T	Surgical preparation and cannulation of marginal (extended) cadaver donor lung(s) to ex vivo organ perfusion system, including decannulation, separation from the perfusion system, and cold preservation of the allograft prior to implantation, when performed
0495T	Initiation and monitoring marginal (extended) cadaver donor lung(s) organ perfusion system by physician or qualified health care professional, including physiological and laboratory assessment (eg, pulmonary artery flow, pulmonary artery pressure, left atrial pressure, pulmonary vascular resistance, mean/peak and plateau airway pressure, dynamic compliance and perfusate gas analysis), including bronchoscopy and X ray when performed; first two hours in sterile field
0496T	Initiation and monitoring marginal (extended) cadaver donor lung(s) organ perfusion system by physician or qualified health care professional, including physiological and laboratory assessment (eg, pulmonary artery flow, pulmonary artery pressure, left atrial pressure, pulmonary vascular resistance, mean/peak and plateau airway pressure, dynamic compliance and perfusate gas analysis), including bronchoscopy and X ray when performed; each additional hour (List separately in addition to code for primary procedure)

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S2060	Lobar lung transplantation *S codes not covered by Medicare

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
05/1996	04/06/2010[MDCRPC], 02/10/2011[MDCRPC], 12/06/2011[MDCRPC], 05/01/2012[MDCRPC], 03/05/2013[MDCRPC], 01/07/2014[MDCRPC], 11/04/2014 [MPC], 09/01/2015[MPC], 07/05/2016[MPC], 05/02/2017[MPC], 03/06/2018[MPC], 03/05/2019[MPC], 03/03/2020[MPC], 03/02/2021[MPC] , 03/01/2022[MPC], 03/07/2023[MPC]	01/10/2022

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
03/05/2019	MPC approved to adopt KP National Criteria for Lung Transplant
09/03/2019	MPC approved to change General Principles 1.3 to *Uncontrollable infection is a contraindication to transplant* as recommended by KP National Transplant Services.
03/03/2020	MPC approved proposed changes from KP National Transplant Services
04/06/2021	MPC approved proposed changes from KP National Transplant Services. Requires 60-day notice, effective date September 1, 2021.
01/10/2022	MPC approved proposed changes from KP National Transplant Services. 60-day notice is not required.

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Clinical Review Criteria

Lymphedema Therapy/ Lymphedema Therapy Training

- Complete Decongestive Therapy
- Lymphatic Venous Anastomosis (LVA) for the Treatment of Lymphedema

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Criteria

Complete Decongestive Therapy (CDT) is comprised of four components: Manual lymph drainage (MLD), compression bandaging, exercises and skin care. The goals of CDT are to reduce lymphedema, increase mobility and range of motion (ROM), decrease the risk of cellulitis, and ultimately providing for a better quality of life. The goal of CDT training is to educate the patient and/or the caregiver to be successful in performing decongestive techniques. In the process of learning lymphedema therapy techniques, the patient's lymphedema may improve and stabilize. However, the goal of therapy and training is to transfer the knowledge and skills to the patient, or their caregiver so ongoing decongestive techniques can be performed by the patient or their caregiver, not to necessarily completely decongest the affected limb. Ongoing responsibility for completion and maintenance of decongestion is with the patient and/or the caregiver.

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article	Lymphedema Decongestive Treatment (A52959)

For Non-Medicare Members

* CDT training is not routinely covered prophylactically, but patients at risk (such as having recent surgical removal of lymph nodes) who are "Stage 0" can be approved for up to 2 visits for patient education on future management

Complete Decongestive therapy is considered medically necessary if **ALL of the following** are met:

1. The treating or consulting practitioner (within the scope of their practice) documents a diagnosis of primary or secondary lymphedema and specifically orders CDT training ***and***

2. The patient or patient's caregiver has the ability to understand and provide home-based exercise and management, as the patient and/or caregiver will need to be able to manage the condition on their own after discharge ***and***

3. CDT training services must be performed by a licensed PT or OT that has received specific training for this service ***and***

4. The frequency and duration of services must be necessary and reasonable. CDT services are comprised of up to 15 sessions over a 2-12-week period ***and***

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5. A CDT course of training is generally expected to occur no more than once per lifetime. However, if medically necessary, refresher training will be approved for 1-2 sessions to review CDT techniques and measure for compression garments

Continued therapy may be indicated if ONE of the following are met:

1. 15 visits can extend beyond 12 weeks, if treatment is interrupted by chemotherapy or radiation therapy ***or***
2. Severe lymphedema that is showing progress with decreasing limb girth, more appointments may be approved if **ALL of the following** are met:
   a. Documentation of the patient's condition before, during and after therapy supports that progress was measurably sustainable ***and***
   b. Documentation indicates clear objective evidence of improvement, generally within the first week or 10 days of therapy (changes in weight, extremity circumference, etc.) ***and***
   c. Member or their caregiver has not yet mastered and demonstrated understanding of complex decongestive therapy techniques. For continued training to be approved, there must be documentation of the amount of further training required and an assessment if the patient or caregiver will be able to learn these techniques in a reasonable period of time.
   d. The goal of lymphedema therapy is not to fully decongest the affected limb, rather it is to transfer the skills and knowledge of lymphedema therapy techniques to the member or their caregiver.

Complete Decongestive Therapy is NOT covered when:

1. Therapy is limited to exercise or elevation of the affected area and is not CDT
2. Therapy does not include ongoing patient education
3. Therapy treatment is designed principally for temporary benefit
4. The patient or patient caregiver do not have the capacity to learn and perform CDT techniques within a reasonable amount of time

Covered Diagnosis

1. Primary lymphedema
2. Secondary lymphedema caused by:
   a. destruction of lymph nodes by radiation therapy or surgery for treatment of cancer.
   b. destruction of lymph system by:
      - trauma or
      - recurrent episodes of cellulitis in the affected limb (two episodes of cellulitis requiring antibiotic or
      - the result of severe chronic venous insufficiency

Lymphatic Venous Anastomosis (LVA) for the Treatment of Lymphedema:

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

If requesting these services, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist
- Last 6 months of radiology if applicable

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Background

Primary lymphedema refers to lymphedema that is caused by the imperfect or abnormal development/lymphatic dysplasia of the lymph vascular system. Primary lymphedema may be due to such causes as Milroy's Disease, Meige's Disease, Turner Syndrome Noonan Syndrome, Klippe-Trenaunay Syndrome, Parks Weber Syndrome, Prader-Willi Syndrome, Emberger Syndrome and other genetic and non- genetic syndromes (also known as hereditary and sporadic lymphedema). Secondary lymphedema is caused by known factors that damage the lymphatic system. Causes of secondary lymphedema include Filariasis, surgery and/or radiation for cancer, cancer, trauma, infection, and chronic venous insufficiency. Obesity is an independent risk factor for

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lymphedema. The most common cause of secondary lymphedema in developed countries is treatment for cancer, especially breast cancer, due primarily to the removal and/or damage of lymph nodes, and damage to lymph vessels. Complete decongestive therapy can be effective for both primary and secondary lymphedema.

Differential diagnosis must include medical conditions which cause swelling which are *not* considered lymphedema and should be treated medically. These conditions include hepatic/renal disorders, congestive heart failure, venous obstruction (DVT) and in some cases, immobility of the limb where the muscle pump is not active, hypoproteinemia, malnutrition, malabsorption syndromes, sepsis, allergic reactions, lipedema, myxedema (disorder of the thyroid), fluid retention syndrome, neurological conditions which can cause weakness or paralysis resulting in immobility of the limbs and even as a side-effect of certain medications and self-inflicted swelling.

Lymphedema can co-occur with other conditions and may be amenable to CDT treatment, especially if the condition is chronic and medical treatment has not completely resolved the edema. **Chronic venous insufficiency** can lead to lymphedema because as the increased amount of fluid in the interstitium which is filtered from the capillaries begins to overwhelm the lymphatic system and can cause damage to the lymphatics, this usually occurs in Stage 2 of CVI. If the conditions are chronic and swelling continues, they may be amenable to a course of CDT.

Evidence and Source Documents

Medicare B Issues Notice 177, Page 14, 15, 16

Lymphatic Venous Anastomosis (LVA) for the Treatment of Lymphedema

BACKGROUND

Lymphedema is the accumulation of fluid in the lymphatic system. Lymphedema is an imbalance between interstitial fluid production and the transport capacity of the lymphatic system ("The diagnosis and treatment of peripheral lymphedema: 2013 Consensus Document of the International Society of Lymphology," 2013). It is caused by congenital anomalies of the lymphatic vessels or any factors that damage the lymphatic system. Lymphedema is classified as primary or secondary depending on etiology. Primary lymphedema is due to a congenital malformation of the lymphatic vessels. It manifests, more commonly, by edema of the lower limbs at birth which can be present up to two years after birth. Secondary lymphedema is due to infection, injury/trauma, inflammation, obesity, cancer and cancer treatment, and chronic venous insufficiency.

Patients may experience swelling, pain, discomfort, heaviness, limited range of motion, and skin lesions. The diagnosis is made by history, physical exam, and measurements (Mehrara, B. et al., 2019).

The treatment of lymphedema can be difficult. However, the foundation of treatment is conservative and multimodal. Multimodal treatment consists of general measures along with compression therapy and physiotherapy. General measures include self-monitoring, limb elevation, maintenance of adequate body weight through diet and exercise, avoidance of skin infection or injury, avoidance of limb constriction. Compression therapy includes bandaging, compression garments, and intermittent pneumatic compression. Physiotherapy is comprised of manual lymphatic drainage and complete decongestive therapy (Mehrara, B. et al., 2019).

Complete decongestive therapy, also called complex decongestive therapy, complex decongestive physiotherapy, or decongestive lymphatic therapy is comprised of two phases: the first phase which is the treatment phase involves manual lymphatic drainage, limb compression, skin care, and exercise. This occurs every day five days per week and lasts two to four weeks. The second phase also called the maintenance phase entails compression garments, self-compression bandaging at night, skin care, exercise, and, if necessary, self-manual lymphatic drainage (Mehrara, B. et al., 2019). The treatment is provided by a health care professional. However, patients or caregivers can treat themselves especially in the second phase of the treatment after being trained.

Medical Technology Assessment Committee (MTAC)

Lymphatic Venous Anastomosis

06/20/2011: MTAC REVIEW

Evidence Conclusion: There is insufficient published evidence to determine the efficacy and safety of lymphatic venous anastomosis in the treatment breast cancer-related lymphedema.

Articles: The literature on the on lymphatic venous anastomosis (LVA) for the treatment of breast cancer-related lymphedema (BCRL) is very limited; the search did not reveal any meta-analyses or randomized controlled trials that evaluated efficacy or safety of the procedure. The empirical study published on the LVA for the treatment (BCRL) was a small case series with ten patients.

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The use of lymphatic venous anastomosis (LVA) for the treatment of post-breast cancer lymphedema does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Complete decongestive therapy for the treatment of lymphedema
04/08/2019: MTAC REVIEW
Evidence Conclusion:

- Low evidence indicates no difference between complete decongestive therapy and compression bandaging or garments in terms of reduction in limb volume, edema volume, limb-related volume change, QOL, and arm function in patients with secondary lymphedema due to breast cancer treatment on the short and mid-terms (≤1 year).
- There is insufficient evidence for or against the effectiveness of complete decongestive therapy training in term of lymphedema reduction.
- Moderate quality study suggests that decongestive lymphedema therapy may be safe.

Articles: PubMed was searched from 2012 to March 20, 2019 with the search terms Complete decongestive therapy OR complex decongestive therapy OR complex decongestive physiotherapy OR decongestive lymphatic therapy. The search was limited to English language publications and human populations. The reference lists of relevant studies were reviewed to identify additional publications. RCTs and observational studies were included as filters. See Evidence Table.

The use of Complete decongestive therapy for the treatment of lymphedema does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Hayes Technology Brief

Hayes, Inc. Hayes Technology Brief. Microsurgical Treatment of Lymphedema Following Breast Cancer Surgery. Lansdale, PA: Hayes, Inc.; 7/2013

Interregional New Technologies Committee (INTC) Review

02/02/2021: SCPMG Evidenced-Based Medicine
Overall Conclusion:

- The body of literature on LYMPHA for prevention of secondary extremity lymphedema consists of six comparative studies (including 2 RCTs) and eight non-comparative studies and involved a total of 1,067 participants (range: N=10 to N=380). Follow-up periods ranged from 3 months to 4 years. Most studies involved breast cancer patients, but several studies included patients with other types of cancer.
- The included studies were at high risk of bias and most had small sample sizes. There was also heterogeneity in terms of cancer type, lymphedema classification, treatment courses, and follow-up times. However, the studies consistently demonstrated substantial reductions in risk of lymphedema occurrence with the LYMPHA, compared with standard care.
- Incidence of lymphedema in the included studies ranged from 0% to 12.5%, with lymphedema occurring transiently in some patients and persisting in others. The highest rate of persistent lymphedema was 9% (in a retrospective case series, N=27). The overall quality of the evidence on the efficacy of LYMPHA was found to be low.
- Four studies (1 small RCT; 1 small prospective case series; 2 retrospective) reporting safety outcomes did not indicate any serious concerns regarding safety or complications associated with LYMPHA for prevention of secondary lymphedema. The overall quality of the evidence on the safety of LYMPHA is very low.
- We applied the ROBIS (i.e., risk of bias in systematic reviews) tool to the Hayes, Inc. assessment and found risk of bias in their review to be low.
- Given the overall low quality of the body evidence on LYMPHA, there remains a need for large, high-quality comparative studies or RCTs to draw a conclusion regarding the efficacy and safety of LYMPHA for prevention of secondary lymphedema, compared with standard care.

Applicable Codes

Complete Decongestive Therapy (CDT) - Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description

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97140	Manual therapy techniques (eg, mobilization/ manipulation, manual lymphatic drainage, manual traction), 1 or more regions, each 15 minutes
97535	Self-care/home management training (eg, activities of daily living (ADL) and compensatory training, meal preparation, safety procedures, and instructions in use of assistive technology devices/adaptive equipment) direct one-on-one contact, each 15 minutes
S8950	Complex lymphedema therapy, each 15 minutes

Lymphatic Venous Anastomosis (LVA) - Considered not medically necessary:

CPT® or HCPC Codes	Description
No specific codes – often submitted as *38999 Unlisted procedure, hemic or lymphatic system*	

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Date Created	Date Reviewed	Date Last Revised
01/1996	06/01/2010 MDCRPC, 04/05/2011 MDCRPC, 02/07/2012 MDCRPC ,12/04/2012 MDCRPC , 10/01/2013 MPC,08/05/2014 MPC,05/05/2015 MPC, 03/01/2016MPC, 05/03/2016MPC, 03/7/2017MPC, 01/09/2018MPC, 12/04/2018MPC, 12/03/2019MPC , 12/01/2020MPC,12/07/2021MPC ,12/06/2022MPC , 12/09/2023MPC	05/11/2023

MDCRPC Medical Director Clinical Review and Policy Committee
MPC Medical Policy Committee

Revision History	Description
05/05/2015	The criteria were completely revised to mirror Medicare guidelines to support payment for comprehensive decongestive therapy only.
05/03/2016	Merged CDT & LVA criteria into one document under Lymphedema Therapy
04/13/2017	Added Hayes Technology Brief Review
03/05/2019	MPC approved to expand criteria to treat members with lymphedema caused by other diagnosis other than cancer
04/08/2019	MTAC review for Complete Decongestive Therapy for the treatment of lymphedema was added
09/12/2022	INTC Review for Lymphovenous Anastomosis (LVA) (LYMPHA) for Prevention of Lymphedema from 02/01/2021 was added
05/11/2023	Updated format for clarity

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Clinical Review Criteria
Massage Therapy

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None

Medicare covers massage when delivered by a physical therapist as part of the rehabilitation plan of care. It is not covered when delivered by a massage therapist who is not licensed as a physical therapist.

For Non-Medicare Members

A. Massage therapy is indicated when **ALL of the following** are met:
   1. An assessment and diagnosis documents objective physical and functional limitations.
   2. It will have physical therapeutic benefits.
   3. It has been ordered by the treating physician.
   4. The condition or the level of function can be expected to improve significantly within a reasonable and generally predictable period of time with massage treatment.

OR

B. The patient is terminally ill, and the therapy is needed for comfort.

Massage therapy is not covered when:

1. It is provided for prevention, recreation (spa therapy) or stress reduction.
2. It is directed at the maintenance of current level of functioning.
3. The patient has achieved therapeutic goals or is not showing meaningful progress.

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Background

This service is covered when it is described as a benefit in the consumer's coverage contract and the consumer receives a health plan referral. Special work groups that have included licensed massage therapists identified the clinical conditions and screening criteria in order to determine clinical appropriateness for the service.

Low back pain (LBP) is a major health problem in the modern society. More than two thirds of the population will experience low back pain at some time in their lives. LBP is usually benign and self-limiting; almost 90% of all patients with acute low back pain will get better quickly regardless of therapy. The remaining 10% may develop chronic back pain and disability.

LBP is associated with a complex dysfunction and impaired endurance of the paraspinal muscles. Different therapies including exercise and spinal manipulation are often recommended, yet their clinical effectiveness has not been documented. Research on the effectiveness of these therapies has yielded inconsistent results.

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The use of massage therapy for back pain has a long history. Massage therapy may have the potential to increase the blood flow in the muscles, enhance muscle tone, reduce muscle fatigability, and improve muscle endurance. It may relax the mind and increase the pain threshold. Massage is considered a safe treatment with no risk or adverse effects. It is, however, contraindicated when several other conditions are present, including acute inflammations, skin infections, unhealed fractures, and burns.

Massage is rubbing or kneading part of the body usually with the hands to stimulate circulation and make the muscles or joints suppler. It is also defined as soft tissue manipulation using the hands or a mechanical device. Massage can be applied to the lumbar region only or to the whole body. It is usually used as an adjunct therapy for other physical treatments; however, many massage therapists use it as the only intervention. Examples of soft tissue massage are Shiatsu, Rolfing, Swedish massage, reflexology, myofascial release, craniosacral therapy, and Bindege webs massage. Massage therapy is applied through various techniques including friction, kneading, hacking, petrissage, neuromuscular, trigger, and pressure points.

Massage therapists are licensed by the state of Washington. Licensure requires a minimum of 500 hours of training at an accredited school of massage therapy.

Medical Technology Assessment Committee (MTAC)

Massage Therapy in the Treatment of Chronic Neck and Back Pain

11/2001: MTAC REVIEW

Evidence Conclusion: Two of the studies reviewed show that massage is an effective therapy for non-specific subacute and chronic low back pain (Cherkin, Preyde). Cherkin's study did not compare massage to a placebo or no treatment. Preyde's study, which compared massage to sham treatment, had a short follow-up duration. On the other hand, Pope et al found no significant difference between massage, spinal manipulation, corset, and transcutaneous muscle stimulation (TMS). Various confounding factors may affect the outcome of massage therapy including the type of massage given, number and duration of treatment sessions, experience of the therapists, size of massage area, amount of pressure, as well as the type of injury or problem, chronicity, level of stress, and other aggravating factors. Many of the studies reviewed did not address or adjust for these variables. Further research is needed to study the patients' variables and to help ascertain which type of low back pain will respond best to massage therapy. Studies with a longer-term follow-up are also needed to determine the elements and techniques of massage therapy that will give the most benefit. Use of a control group with a placebo or no treatment would also strengthen the validity of the results.

Articles: The search yielded 32 articles. There were two systematic reviews, with no statistical pooling or meta-analysis due to the heterogeneity of the studies. There were eight randomized, controlled trials. Massage was the main therapy under investigation in only two of the RCTs revealed by the search. *The studies selected for critical appraisal were:* Cherkin, D., Eisenberg, D., et al. Randomized trial comparing traditional Chinese medical acupuncture, therapeutic massage, and self-care education for chronic low back pain. Arch Intern Med 2001; 161: 1081-1088 See Evidence Table. Preyde, M., Effectiveness of massage therapy for subacute low-back pain: a randomized controlled trial. CMAJ 2000; 162: 1815-20 See Evidence Table. Pope, M.H., et al. A prospective randomized three-week trial of spinal manipulation, transcutaneous muscle stimulation, massage, and corset in the treatment of subacute low back pain. Spine 1994; 22: 2571-2577 See Evidence Table.

The use of massage therapy in the treatment of chronic neck and back pain meets the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
97124	Therapeutic procedure, 1 or more areas, each 15 minutes; massage, including effleurage, petrissage and/or tapotement (stroking, compression, percussion)
97140	Manual therapy techniques (eg, mobilization/ manipulation, manual lymphatic drainage, manual traction), 1 or more regions, each 15 minutes
with type of service massage	

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11/20/2002	10/5/2010 MDCRPC, 08/02/2011 MDCRPC, 06/05/2012 MDCRPC, 04/02/2013 MDCRPC, 02/04/2014 MPC,12/02/2014 MPC, 10/06/2015MPC, 08/02/2016MPC, 06/06/2017MPC, 04/03/2018MPC, 03/05/2019MPC, 03/03/2020MPC, 03/02/2021MPC, 03/01/2022MPC , 03/07/2023MPC	06/21/2007

MDCRPC Medical Director Clinical Review and Policy Committee
MPC Medical Policy Committee

Revision History	Description

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Clinical Review Criteria
Medically Necessary Services

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Criteria

For Medicare Members

Kaiser Permanente follows CMS coverage guidance when available per the CMS **Medicare Coverage Database** search tool. Where there is a conflict between this document and Medicare national and/or local coverage documentation, the Medicare source materials will apply. If there is no Medicare guidance, the information below applies.

For Non-Medicare Members

The Medically Necessary Services policy is meant to provide guidance regarding coverage determinations for select services of limited or questionable clinical value not subject to separate clinical review criteria. The policy addresses a finite scope of specific service codes which are listed within this document.

"Medically Necessary" or "Medical Necessity" shall mean pre-service, concurrent or post-service reviews may be conducted. Once a service has been reviewed, additional reviews may be conducted. Appropriate and clinically necessary services, as determined by KFHPWA/KFHPWAO's medical director according to generally accepted principles of good medical practice, which are rendered to a member for the diagnosis, care or treatment of a medical condition and which meet the standards set forth below. The fact that one of our covered providers has prescribed, recommended, or approved a service or supply does not, in itself, make it medically necessary or covered under the member's plan.

To be reasonable and medically necessary, services and supplies must meet the following requirements:

- Appropriate to prevent, diagnose, or treat your condition, illness, or injury
- Appropriate and consistent with the associated diagnosis and which, in accordance with accepted medical standards in the State of Washington, could not have been omitted without adversely affecting the member's condition or the quality of health services rendered
- Not primarily for the personal comfort or convenience of the patient, the family, or the provider
- There is not a preferred alternative service or sequence of services which is either more effective, cost effective, safer or that produces similar results.
- Requests inpatient care, could not have been provided in a provider's office, the outpatient department of a hospital or a non-residential facility without affecting the member's condition or quality of health services rendered
- Not part of or associated with scholastic education or vocation training of the patient
- Not primarily for research and data accumulation
- Not experimental or investigational

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The length and type of the treatment program and the frequency and modality of visits covered shall be determined by KFHPWA/KFHPWAO's medical director. In addition to being medically necessary, to be covered, services and supplies must be otherwise be included as a covered service and not excluded from coverage.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

This policy is designed to address medical guidelines that are appropriate for the majority of individuals with a particular disease, illness, or condition. Each person's unique clinical circumstances may warrant individual consideration, based on review of applicable medical records.

Medical policies are designed to supplement the terms of a member's contract. The member's contract defines the benefits available; therefore, medical policies should not be construed as overriding specific contract language. In the event of conflict, the contract shall govern.

Medical policies do not constitute medical advice, nor the practice of medicine. Rather, such policies are intended only to establish general guidelines for coverage and reimbursement under Kaiser Permanente plans. Application of a medical policy to determine coverage in an individual instance is not intended and shall not be construed to supersede the professional judgment of a treating provider. In all situations, the treating provider must use his/her professional judgment to provide care he/she believes to be in the best interest of the patient, and the provider and patient remain responsible for all treatment decisions.

Applicable Codes

The following services have been determined to have little to no clinical value. Due to low utilization, explicit clinical review criteria have been archived. If a request is received, the service will be reviewed for medical necessity using the above policy.

Date of Archive	Clinical Criteria	Codes
Effective August 1st, 2024	Chelation Therapy	M0300, J3520, J0600
	Infrared Thermography	93740
	Renal Sympathetic Nerve Ablation	0338T, 0339T
12/1/2023	Cryosurgery- Breast	19105
	Axial Lumbar Interbody Fusion System	22586
	Collagen Meniscus Implant	G0428
	Continuous 24-hour monitoring of Intraocular Pressure	0198T, 0329T
	Diaphragmatic/Phrenic Pacing	L8696
	Exoskeleton	K1007
	Intradiscal Electrothermal Therapy (IDET)	22526, 22527
	Magnetic Resonance Guided Focused Ultrasound for Treatment of Uterine Fibroids (MRgFUS)	0071T, 0072T
	Microvolt T-Wave Alternans	93025
	Radioimmunoscintigraphy	78800
	Retinal (Implant) Prosthesis System	0100T
	Scintimammography	S8080
	Thermal Capsulorrhaphy for Shoulder Instability	S2300
	Transmyocardial Laser Revascularization for Treatment of Severe Angina	33140, 33141
03/01/2022	In Lieu of Hospital Admission to Skilled Nursing Facility (ILOH)	No specific codes
	MIBG Imaging for Heart Failure	0331T, 0332T
	Pneumatic Vest for Chronic Low Back Pain (Orthotrac)	No specific codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPCS Codes	Description

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15773	Grafting of autologous fat harvested by liposuction technique to face, eyelids, mouth, neck, ears, orbits, genitalia, hands, and/or feet; 25 cc or less injectate
15774	Grafting of autologous fat harvested by liposuction technique to face, eyelids, mouth, neck, ears, orbits, genitalia, hands, and/or feet; each additional 25 cc injectate, or part thereof (List separately in addition to code for primary procedure)
39499	Unlisted procedure, mediastinum
42299	Unlisted procedure, palate, uvula
53899	Unlisted procedure, urinary system
57465	Computer-aided mapping of cervix uteri during colposcopy, including optical dynamic spectral imaging and algorithmic quantification of the acetowhitening effect (List separately in addition to code for primary procedure)
61850	Twist drill or burr hole(s) for implantation of neurostimulator electrodes, cortical
61860	Craniectomy or craniotomy for implantation of neurostimulator electrodes, cerebral, cortical
96931	Reflectance confocal microscopy (RCM) for cellular and sub-cellular imaging of skin; image acquisition and interpretation and report, first lesion
96932	Reflectance confocal microscopy (RCM) for cellular and sub-cellular imaging of skin; image acquisition only, first lesion
96933	Reflectance confocal microscopy (RCM) for cellular and sub-cellular imaging of skin; interpretation and report only, first lesion
96934	Reflectance confocal microscopy (RCM) for cellular and sub-cellular imaging of skin; image acquisition and interpretation and report, each additional lesion (List separately in addition to code for primary procedure)
96935	Reflectance confocal microscopy (RCM) for cellular and sub-cellular imaging of skin; image acquisition only, each additional lesion (List separately in addition to code for primary procedure)
96936	Reflectance confocal microscopy (RCM) for cellular and sub-cellular imaging of skin; interpretation and report only, each additional lesion (List separately in addition to code for primary procedure)
0106T	Quantitative sensory testing (QST), testing and interpretation per extremity; using touch pressure stimuli to assess large diameter sensation
0107T	Quantitative sensory testing (QST), testing and interpretation per extremity; using vibration stimuli to assess large diameter fiber sensation
0108T	Quantitative sensory testing (QST), testing and interpretation per extremity; using cooling stimuli to assess small nerve fiber sensation and hyperalgesia
0109T	Quantitative sensory testing (QST), testing and interpretation per extremity; using heat-pain stimuli to assess small nerve fiber sensation and hyperalgesia
0110T	Quantitative sensory testing (QST), testing and interpretation per extremity; using other stimuli to assess sensation
0174T	Computer-aided detection (CAD) (computer algorithm analysis of digital image data for lesion detection) with further physician review for interpretation and report, with or without digitization of film radiographic images, chest radiograph(s), performed c
0175T	Computer-aided detection (CAD) (computer algorithm analysis of digital image data for lesion detection) with further physician review for interpretation and report, with or without digitization of film radiographic images, chest radiograph(s), performed r
0202T	Posterior vertebral joint(s) arthroplasty (eg, facet joint[s] replacement), including facetectomy, laminectomy, foraminotomy, and vertebral column fixation, injection of bone cement, when performed, including fluoroscopy, single level, lumbar spine
0208T	Pure tone audiometry (threshold), automated; air only
0209T	Pure tone audiometry (threshold), automated; air and bone
0210T	Speech audiometry threshold, automated;
0211T	Speech audiometry threshold, automated; with speech recognition
0212T	Comprehensive audiometry threshold evaluation and speech recognition (0209T, 0211T combined), automated
0220T	Placement of a posterior intrafacet implant(s), unilateral or bilateral, including imaging and placement of bone graft(s) or synthetic device(s), single level; thoracic
0221T	Placement of a posterior intrafacet implant(s), unilateral or bilateral, including imaging and placement of bone graft(s) or synthetic device(s), single level; lumbar
0234T	Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; renal artery

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0235T	Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; visceral artery (except renal), each vessel
0236T	Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; abdominal aorta
0237T	Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; brachiocephalic trunk and branches, each vessel
0238T	Transluminal peripheral atherectomy, open or percutaneous, including radiological supervision and interpretation; iliac artery, each vessel
0263T	Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; complete procedure including unilateral or bilateral bone marrow harvest
0264T	Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; complete procedure excluding bone marrow harvest
0265T	Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, one leg, including ultrasound guidance, if performed; unilateral or bilateral bone marrow harvest only for intramuscular autologous bone marrow ce
0266T	Implantation or replacement of carotid sinus baroreflex activation device; total system (includes generator placement, unilateral or bilateral lead placement, intra-operative interrogation, programming, and repositioning, when performed)
0267T	Implantation or replacement of carotid sinus baroreflex activation device; lead only, unilateral (includes intra-operative interrogation, programming, and repositioning, when performed)
0268T	Implantation or replacement of carotid sinus baroreflex activation device; pulse generator only (includes intra-operative interrogation, programming, and repositioning, when performed)
0269T	Revision or removal of carotid sinus baroreflex activation device; total system (includes generator placement, unilateral or bilateral lead placement, intra-operative interrogation, programming, and repositioning, when performed)
0270T	Revision or removal of carotid sinus baroreflex activation device; lead only, unilateral (includes intra-operative interrogation, programming, and repositioning, when performed)
0271T	Revision or removal of carotid sinus baroreflex activation device; pulse generator only (includes intra-operative interrogation, programming, and repositioning, when performed)
0272T	Interrogation device evaluation (in person), carotid sinus baroreflex activation system, including telemetric iterative communication with the implantable device to monitor device diagnostics and programmed therapy values, with interpretation and report (
0273T	Interrogation device evaluation (in person), carotid sinus baroreflex activation system, including telemetric iterative communication with the implantable device to monitor device diagnostics and programmed therapy values, with interpretation and report (
0278T	Scrambler therapy for pain
0308T	Telescope implant for eye
0330T	Image taken of cornea in eye
0333T	Visual evoked potential, screening of visual acuity, automated, with report
0342T	Blood component removal
0347T	Place devices in bone
0348T	Double x-ray of spine
0349T	Double x-ray of arm(s)
0350T	Double x-ray of leg(s)
0351T	Optical coherence tomography of breast or axillary lymph node, excised tissue, each specimen; real-time intraoperative
0352T	Optical coherence tomography of breast or axillary lymph node, excised tissue, each specimen; interpretation and report, real-time or referred
0353T	Optical coherence tomography of breast, surgical cavity; real-time intraoperative
0354T	Optical coherence tomography of breast, surgical cavity; interpretation and report, real-time or referred
0362T	Behavior identification supporting assessment, each 15 minutes of technicians' time face-to-face with a patient, requiring the following components: administration by the physician or other qualified health care professional who is on site; with the assi
0378T	Visual field eye exam

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0379T	Visual field eye exam
0397T	Endoscopic retrograde cholangiopancreatography (ERCP), with optical endomicroscopy (List separately in addition to code for primary procedure)
0398T	Magnetic resonance image guided high intensity focused ultrasound (MRgFUS), stereotactic ablation lesion, intracranial for movement disorder including stereotactic navigation and frame placement when performed
0419T	Destruction neurofibromata, extensive, (cutaneous, dermal extending into subcutaneous); face, head and neck, greater than 50 neurofibromata
0420T	Destruction neurofibromata, extensive, (cutaneous, dermal extending into subcutaneous); trunk and extremities, extensive, greater than 100 neurofibromata
0422T	Tactile breast imaging by computer-aided tactile sensors, unilateral or bilateral
0424T	Insertion or replacement of neurostimulator system for treatment of central sleep apnea; complete system (transvenous placement of right or left stimulation lead, sensing lead, implantable pulse generator)
0425T	Insertion or replacement of neurostimulator system for treatment of central sleep apnea; sensing lead only
0426T	Insertion or replacement of neurostimulator system for treatment of central sleep apnea; stimulation lead only
0427T	Insertion or replacement of neurostimulator system for treatment of central sleep apnea; pulse generator only
0428T	Removal of neurostimulator system for treatment of central sleep apnea; pulse generator only
0429T	Removal of neurostimulator system for treatment of central sleep apnea; sensing lead only
0430T	Removal of neurostimulator system for treatment of central sleep apnea; stimulation lead only
0431T	Removal and replacement of neurostimulator system for treatment of central sleep apnea, pulse generator only
0432T	Repositioning of neurostimulator system for treatment of central sleep apnea; stimulation lead only
0433T	Repositioning of neurostimulator system for treatment of central sleep apnea; sensing lead only
0434T	Interrogation device evaluation implanted neurostimulator pulse generator system for central sleep apnea
0435T	Programming device evaluation of implanted neurostimulator pulse generator system for central sleep apnea; single session
0436T	Programming device evaluation of implanted neurostimulator pulse generator system for central sleep apnea; during sleep study
0437T	Implantation of non-biologic or synthetic implant (eg, polypropylene) for fascial reinforcement of the abdominal wall (List separately in addition to code for primary procedure)
0439T	Myocardial contrast perfusion echocardiography; at rest or with stress, for assessment of myocardial ischemia or viability (List separately in addition to code for primary procedure)
0440T	Ablation, percutaneous, cryoablation, includes imaging guidance; upper extremity distal/peripheral nerve
0441T	Ablation, percutaneous, cryoablation, includes imaging guidance; lower extremity distal/peripheral nerve
0442T	Ablation, percutaneous, cryoablation, includes imaging guidance; nerve plexus or other truncal nerve (eg, brachial plexus, pudendal nerve)
0444T	Initial placement of a drug-eluting ocular insert under one or more eyelids, including fitting, training, and insertion, unilateral or bilateral
0445T	Subsequent placement of a drug-eluting ocular insert under one or more eyelids, including re-training, and removal of existing insert, unilateral or bilateral
0450T	Insertion of aqueous drainage device, without extraocular reservoir, internal approach, into the subconjunctival space; each additional device (List separately in addition to code for primary procedure)
0464T	Visual evoked potential, testing for glaucoma, with interpretation and report
0465T	Suprachoroidal injection of a pharmacologic agent (does not include supply of medication)
0469T	Retinal polarization scan, ocular screening with on-site automated results, bilateral
0472T	Device evaluation, interrogation, and initial programming of intra-ocular retinal electrode array (eg, retinal prosthesis), in person, with iterative adjustment of the implantable device to test functionality, select optimal permanent programmed values wi

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0473T	Device evaluation and interrogation of intraocular retinal electrode array (eg, retinal prosthesis), in person, including reprogramming and visual training, when performed, with review and report by a qualified health care professional
0481T	Injection(s), autologous white blood cell concentrate (autologous protein solution), any site, including image guidance, harvesting and preparation, when performed
0485T	Optical coherence tomography (OCT) of middle ear, with interpretation and report; unilateral
0486T	Optical coherence tomography (OCT) of middle ear, with interpretation and report; bilateral
0488T	Preventive behavior change, online/electronic structured intensive program for prevention of diabetes using a standardized diabetes prevention program curriculum, provided to an individual, per 30 days
0489T	Autologous adipose-derived regenerative cell therapy for scleroderma in the hands; adipose tissue harvesting, isolation and preparation of harvested cells including incubation with cell dissociation enzymes, removal of non-viable cells and debris, determi
0490T	Autologous adipose-derived regenerative cell therapy for scleroderma in the hands; multiple injections in one or both hands
0501T	Noninvasive estimated coronary fractional flow reserve (FFR) derived from coronary computed tomography angiography data using computation fluid dynamics physiologic simulation software analysis of functional data to assess the severity of coronary artery
0502T	Noninvasive estimated coronary fractional flow reserve (FFR) derived from coronary computed tomography angiography data using computation fluid dynamics physiologic simulation software analysis of functional data to assess the severity of coronary artery
0503T	Noninvasive estimated coronary fractional flow reserve (FFR) derived from coronary computed tomography angiography data using computation fluid dynamics physiologic simulation software analysis of functional data to assess the severity of coronary artery
0504T	Noninvasive estimated coronary fractional flow reserve (FFR) derived from coronary computed tomography angiography data using computation fluid dynamics physiologic simulation software analysis of functional data to assess the severity of coronary artery
0509T	Electroretinography (ERG) with interpretation and report, pattern (PERG)
0515T	Insertion of wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming, and imaging supervision and interpretation, when performed; electrode only
0516T	Insertion of wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming, and imaging supervision and interpretation, when performed; electrode only
0517T	Insertion of wireless cardiac stimulator for left ventricular pacing, including device interrogation and programming, and imaging supervision, when performed; pulse generator component(s) (battery and/or transmitter) only
0518T	Removal of only pulse generator component(s) (battery and/or transmitter) of wireless cardiac stimulator for left ventricular pacing
0519T	Removal and replacement of wireless cardiac stimulator for left ventricular pacing; pulse generator component(s) (battery and/or transmitter)
0520T	Removal and replacement of wireless cardiac stimulator for left ventricular pacing; pulse generator component(s) (battery and/or transmitter), including placement of a new electrode
0521T	Interrogation device evaluation (in person) with analysis, review and report, includes connection, recording, and disconnection per patient encounter, wireless cardiac stimulator for left ventricular pacing
0522T	Programming device evaluation (in person) with iterative adjustment of the implantable device to test the function of the device and select optimal permanent programmed values with analysis, including review and report, wireless cardiac stimulator for lef
0523T	Intraprocedural coronary fractional flow reserve (FFR) with 3D functional mapping of color-coded FFR values for the coronary tree, derived from coronary angiogram data, for real-time review and interpretation of possible atherosclerotic stenosis(es) inter
0524T	Endovenous catheter directed chemical ablation with balloon isolation of incompetent extremity vein, open or percutaneous, including all vascular access, catheter manipulation, diagnostic imaging, imaging guidance and monitoring
0525T	Insertion or replacement of intracardiac ischemia monitoring system, including testing of the lead and monitor, initial system programming, and imaging supervision and interpretation; complete system (electrode and implantable monitor)

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0526T	Insertion or replacement of intracardiac ischemia monitoring system, including testing of the lead and monitor, initial system programming, and imaging supervision and interpretation; electrode only
0527T	Insertion or replacement of intracardiac ischemia monitoring system, including testing of the lead and monitor, initial system programming, and imaging supervision and interpretation; implantable monitor only
0528T	Programming device evaluation (in person) of intracardiac ischemia monitoring system with iterative adjustment of programmed values, with analysis, review, and report
0529T	Interrogation device evaluation (in person) of intracardiac ischemia monitoring system with analysis, review, and report
0530T	Removal of intracardiac ischemia monitoring system, including all imaging supervision and interpretation; complete system (electrode and implantable monitor)
0531T	Removal of intracardiac ischemia monitoring system, including all imaging supervision and interpretation; electrode only
0532T	Removal of intracardiac ischemia monitoring system, including all imaging supervision and interpretation; implantable monitor only
0533T	Continuous recording of movement disorder symptoms, including bradykinesia, dyskinesia, and tremor for 6 days up to 10 days; includes set-up, patient training, configuration of monitor, data upload, analysis and initial report configuration, download revi
0534T	Continuous recording of movement disorder symptoms, including bradykinesia, dyskinesia, and tremor for 6 days up to 10 days; set-up, patient training, configuration of monitor
0535T	Continuous recording of movement disorder symptoms, including bradykinesia, dyskinesia, and tremor for 6 days up to 10 days; data upload, analysis and initial report configuration
0536T	Continuous recording of movement disorder symptoms, including bradykinesia, dyskinesia, and tremor for 6 days up to 10 days; download review, interpretation and report
0537T	Chimeric antigen receptor T-cell (CAR-T) therapy; harvesting of blood-derived T lymphocytes for development of genetically modified autologous CAR-T cells, per day
0538T	Chimeric antigen receptor T-cell (CAR-T) therapy; preparation of blood-derived T lymphocytes for transportation (eg, cryopreservation, storage)
0539T	Chimeric antigen receptor T-cell (CAR-T) therapy; receipt and preparation of CAR-T cells for administration
0540T	Chimeric antigen receptor T-cell (CAR-T) therapy; CAR-T cell administration, autologous
0541T	Myocardial imaging by magnetocardiography (MCG) for detection of cardiac ischemia, by signal acquisition using minimum 36 channel grid, generation of magnetic-field time-series images, quantitative analysis of magnetic dipoles, machine learning-derived cl
0542T	Myocardial imaging by magnetocardiography (MCG) for detection of cardiac ischemia, by signal acquisition using minimum 36 channel grid, generation of magnetic-field time-series images, quantitative analysis of magnetic dipoles, machine learning-derived cl
0543T	Transapical mitral valve repair, including transthoracic echocardiography, when performed, with placement of artificial chordae tendineae
0544T	Transcatheter mitral valve annulus reconstruction, with implantation of adjustable annulus reconstruction device, percutaneous approach including transseptal puncture
0545T	Transcatheter tricuspid valve annulus reconstruction with implantation of adjustable annulus reconstruction device, percutaneous approach
0547T	Bone-material quality testing by microindentation(s) of the tibia(s), with results reported as a score
0552T	Low-level laser therapy, dynamic photonic and dynamic thermokinetic energies, provided by a physician or other qualified health care professional
0553T	Percutaneous transcatheter placement of iliac arteriovenous anastomosis implant, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention
0554T	Bone strength and fracture risk using finite element analysis of functional data, and bone-mineral density, utilizing data from a computed tomography scan; retrieval and transmission of the scan data, assessment of bone strength and fracture risk and bone
0555T	Bone strength and fracture risk using finite element analysis of functional data, and bone-mineral density, utilizing data from a computed tomography scan; retrieval and transmission of the scan data

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0556T	Bone strength and fracture risk using finite element analysis of functional data, and bone-mineral density, utilizing data from a computed tomography scan; assessment of bone strength and fracture risk and bone mineral density
0557T	Bone strength and fracture risk using finite element analysis of functional data, and bone-mineral density, utilizing data from a computed tomography scan; interpretation and report
0558T	Computed tomography scan taken for the purpose of biomechanical computed tomography analysis
0559T	Anatomic model 3D-printed from image data set(s); first individually prepared and processed component of an anatomic structure
0560T	Anatomic model 3D-printed from image data set(s); each additional individually prepared and processed component of an anatomic structure (List separately in addition to code for primary procedure)
0561T	Anatomic guide 3D-printed and designed from image data set(s); first anatomic guide
0562T	Anatomic guide 3D-printed and designed from image data set(s); each additional anatomic guide (List separately in addition to code for primary procedure)
0564T	Oncology, chemotherapeutic drug cytotoxicity assay of cancer stem cells (CSCs), from cultured CSCs and primary tumor cells, categorical drug response reported based on percent of cytotoxicity observed, a minimum of 14 drugs or drug combinations
0567T	Permanent fallopian tube occlusion with degradable biopolymer implant, transcervical approach, including transvaginal ultrasound
0568T	Introduction of mixture of saline and air for sonosalpingography to confirm occlusion of fallopian tubes, transcervical approach, including transvaginal ultrasound and pelvic ultrasound
0569T	Transcatheter tricuspid valve repair, percutaneous approach; initial prosthesis
0570T	Transcatheter tricuspid valve repair, percutaneous approach; each additional prosthesis during same session (List separately in addition to code for primary procedure)
0581T	Ablation, malignant breast tumor(s), percutaneous, cryotherapy, including imaging guidance when performed, unilateral
0583T	Tympanostomy (requiring insertion of ventilating tube), using an automated tube delivery system, iontophoresis local anesthesia
0587T	Percutaneous implantation or replacement of integrated single device neurostimulation system including electrode array and receiver or pulse generator, including analysis, programming, and imaging guidance when performed, posterior tibial nerve
0588T	Revision or removal of integrated single device neurostimulation system including electrode array and receiver or pulse generator, including analysis, programming, and imaging guidance when performed, posterior tibial nerve
0589T	Electronic analysis with simple programming of implanted integrated neurostimulation system (eg, electrode array and receiver), including contact group(s), amplitude, pulse width, frequency (Hz), on/off cycling, burst, dose lockout, patient-selectable par
0590T	Electronic analysis with complex programming of implanted integrated neurostimulation system (eg, electrode array and receiver), including contact group(s), amplitude, pulse width, frequency (Hz), on/off cycling, burst, dose lockout, patient-selectable pa
C9746	Transperineal implantation of permanent adjustable balloon continence device, with cystourethroscopy, when performed and/or fluoroscopy, when performed

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed	Date Last Revised
07/05/2023	07/11/2023,	11/30/2023

MPC Medical Policy Committee

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Revision History	Description
07/11/2023	MPC approved to adopt a new policy to address a specific service or procedure that may no longer be necessary or in line with current standards of care. This criteria page will maintain historical information and guide clinicians during their review process.
08/30/2023	Updated policy with a clarifying preamble with the intent of this policy.
11/30/2023	Added applicable codes; effective 12/1/2023
3/12/2024	MPC approved to archive policies for Chelation therapy (M0300, J3520, J0600), Infrared Thermography (93740), and Renal Sympathetic Nerve Ablation (0338T, 0339T); services will be reviewed against this Medically Necessary Services policy effective August 1st, 2024. Requires 60-day notice.

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Clinical Review Criteria
Medicare Only – Miscellaneous Criteria

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medical service.

**Note: This list is not all-inclusive – refer to the Medicare Coverage Database for additional coverage documentation.*

Category	Location of Policy	Name of Policy and Link
Durable Medical Equipment	NCD	• Ambulatory Blood Pressure Monitoring 20.19 • Ambulatory EEG Monitoring 160.22-Retired • Hospital Beds 280.7 • Peridex CAPD Filter Set 230.13
	LCD	• Hospital Beds and Accessories L33820 • Urological Supplies L33803 *(addresses InFlow device A4341/A4342)*
	Decision Memo	• Ambulatory blood Pressure Monitoring (ABPM)
Radiology	NCD	• Bone (Mineral) Density Studies 150.3 • Microvolt T-Wave Alternans (MTWA) 20.3
	LCD	• Magnetic-Resonance-Guided Focused Ultrasound Surgery (MRgFUS) for Essential Tremor (L37738)
Laboratory	NCD	• Alpha-fetoprotein 190.25 • Chimeric Antigen Receptor (CAR) T-cell Therapy 110.24 • Human Tumor Stem Cell Drug Sensitivity Assays 190.7
	LCD	• B-type Natriuretic Peptide (BNP) Testing (L34038) • Vitamin D Assay Testing L34051 • Measurement of Salivary Hormones(L36857)
	Decision Memo	• Chimeric Antigen Receptor (CAR) T-cell Therapy for Cancers (CAG-00451)
Other Diagnostic Tests	NCD	• Cardiac Output Monitoring by Thoracic Electrical Bioimpedance (TEB) 20.16 • Challenge Ingestion Food Testing 110.12 • Collagen Crosslinks, any Method 190.19 • Displacement Cardiography 20.24 • HIS Bundle Study 20.13
	LCD	• Polysomnography and Other Sleep Studies L34040
Surgical Procedures	NCD	• Arthroscopic Lavage and Arthroscopic Debridement for the Osteoarthritic Knee 150.9 • Blood Brain Barrier Osmotic Disruption for Treatment of Brain Tumors 110.20 • Cardiac Pacemakers: Single Chamber and Dual Chamber Permanent Cardiac Pacemakers 20.8.3 • Carotid Body Resection/Carotid Body Denervation 20.18 • Ultrasonic Surgery 50.8 • Vertebral Artery Surgery 20.1 • Lung Volume Reduction Surgery (Reduction Pneumoplasty) 240.1

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Date Sent: 3/29/24
These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage.
Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

Category	Location of Policy	Name of Policy and Link
		• Partial Ventriculectomy 20.26 • Percutaneous Transluminal Angioplasty (PTA) 20.7 • Phrenic Nerve Stimulator 160.19 • Transmyocardial Revascularization (TMR) 20.6
	LCD	• Injection - Tendon, Ligament, Ganglion Cyst, Tunnel Syndromes and Morton's Neuroma L34076
	LCA	• Arthroscopic Lavage and Arthroscopic Debridement for Osteoarthritic Knees A54063
Medical Procedures	NCD	• Apheresis (Therapeutic Pheresis) 100.14 • Abortion 140.1 • Verteporfin (Photosensitive Drugs) 80.3
Rehabilitation Services	NCD	• Inpatient Hospital Pain Rehabilitation Programs 10.3 • Intensive Behavioral Therapy for Cardiovascular Disease 210.11 • Intensive Behavioral Therapy for Obesity 210.12 • Outpatient Hospital Pain Rehabilitation Programs 10.4
Others	Manuals	• Hospice Chapter 9

Date Created	Date Reviewed	Date Last Revised
04/13/2009	04/13/2009[MDCRPC], 05/03/2011[MDCRPC], 08/02/2011[MDCRPC], 06/05/2012[MDCRPC], 04/02/2013[MDCRPC], 02/04/2014[MPC], 04/01/2014[MPC], 05/06/2014[MPC], 07/01/2014[MPC], 10/06/2015[MPC], 08/02/2016[MPC], 06/06/2017[MPC], 04/03/2018[MPC], 04/02/2019[MPC], 04/07/2020[MPC], 04/06/2021[MPC], 04/05/2022[MPC], 04/04/2023[MPC]	12/21/2023

[MDCRPC] Medical Director Clinical Review and Policy Committee

[MPC] Medical Policy Committee

Revision History	Description of Change
04/30/2015	Added Transcatheter Mitral Valve Repair
05/26/2015	Added Oral Appliances for Obstructive Sleep Apnea
09/08/2015	Revised LCD B-type Natriuretic Peptide (BNP) Testing L34057 and L34038, Medicare Non-Covered Services 34886, Vitamin D Assay Testing LCD L34094 and L34051, Polysomnography and Other Sleep Studies LCD L34040, Facet Joint Injections, Medial Branch Blocks, and Facet Joint Radiofrequency Neurotomy LCD L34995, Injection - Tendon, Ligament, Ganglion Cyst, Tunnel Syndromes and Morton's Neuroma L34076, Oral Appliances for Obstructive Sleep Apnea L33611
01/27/2016	Added LCD L35457 and L34980
04/11/2017	Added Decision Memo for Leadless Pacemakers
08/03/2017	Added NCD for Leadless Pacemakers
06/12/2019	Added LCD L37738
04/07/2020	Removed Leadless Pacemakers, Implantable Automatic Defibrillators and Hyperthermia for Treatment of Cancer categories since they have their own individual KPWA criteria.
12/02/2022	Added LCD L39242 replacing retired LCD L34980
03/01/2023	Added NCD 160.22 Ambulatory EEG Monitoring - Retired
03/23/2023	Review for Endothelial Cell Photography is no longer required.
04/18/2023	Removed Magnetic Resonance Imaging NCD 220.2 due to having independent criteria pages for MRI. Removed Epidural Steroid injections for Pain management L39242 due to having independent criteria page for ESI.
12/21/2023	Added NCD Microvolt T-Wave Alternans (MTWA) 20.3, Lung Volume Reduction Surgery (Reduction Pneumoplasty) 240.1, Partial Ventriculectomy 20.26, Percutaneous Transluminal Angioplasty (PTA) 20.7, Transmyocardial Revascularization (TMR) 20.6

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Medicare Medical Policy Development

Kaiser Permanente Medicare Advantage Medical Policies identify the clinical criteria for determining when medical services are considered 'reasonable and necessary' (medically necessary). Medicare Advantage plans are required by CMS to provide the same medical benefits to Medicare Advantage members as Original Medicare. As such, whenever possible, Medicare Advantage Medical Policies are based on Medicare coverage manuals, National Coverage Determinations (NCDs), and Local Coverage Determinations (LCDs) when available. If there is no applicable NCD or LCD for the service under review, then per CMS other evidence-based criteria may be applied. In addition, each member's unique, clinical situation is considered in conjunction with current CMS guidelines

Kaiser Permanente Medicare Medical Policy Hierarchy

The following hierarchy is used to determine Kaiser Permanente Medicare Advantage (MA) Medical Policy:

- *CMS Coverage Manuals or other CMS-based Resource*
  Coverage provisions in interpretive manuals are instructions that are used to further define when and under what circumstances items or services may be covered (or not covered). Other CMS-based resources include, but are not limited to, documentation such as Medicare Learning Network (MLN) and Federal Register (FR) publications.

- *National Coverage Determinations (NCD)*
  For some services, procedures, and technologies, CMS has developed an NCD, which is to be applied on a national basis for all Medicare beneficiaries. Once published in a CMS program instruction, the NCD is binding on all Medicare Advantage plans. (1)

- *Local Coverage Determinations (LCD), Articles (LCA), and other contractor-based bulletins*
  When there is no NCD or other coverage provision outlining medical necessity criteria within a Medicare manual, or when there is a need to further define an NCD, then the Medicare Administrative Contractor (MAC) for a service area may develop an LCD. (2) Noridian Healthcare Solutions (Noridian) is the designated MAC for the state of Washington.

- *Retired LCD/LCD*
  LCDs are retired due to lack of evidence of current problems with utilization, or in some cases because the material is addressed by a National Coverage Determination (NCD), a coverage provision in a CMS interpretative manual or an article. Most LCDs are not retired because they are incorrect. The guidance in the retired LCD may still be helpful in assessing medical necessity. (3)

- *Commercial Medical Policies*
  In coverage situations where there is no NCD, LCD, or guidance on coverage in original Medicare manuals, a Medicare Advantage Organization (MAO) may adopt the coverage policies of other MAOs in its service area. (4)
  However, if the MAO decides not to use coverage policies of other MAOs in its service area, the MAO:
  - Must make its own coverage determination;
  - Must provide CMS an objective evidence-based rationale relying on authoritative evidence such as:
    - Studies from government agencies (e.g., the FDA);
    - Evaluations performed by independent technology assessment groups (e.g. BCBSA); and
    - Well-designed controlled clinical studies that have appeared in peer review journals; and
  - In providing its justification, the MAO may not use conclusory statements with no accompanying rationale (e.g., "It is our policy to deny coverage for this service.")

- *MCG™ Care Guidelines*
  If no policy criteria are available within an NCD, LCD, coverage manual, or existing medical policy for the services in question, MCG™ guidelines may be applied at the discretion of the physician reviewer.

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Kaiser Permanente may consider some services to have insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies (and/or) provides better long-term outcomes than current standard services/therapies. When a procedure or device is deemed to have "insufficient evidence" by Kaiser Permanente, the term "insufficient evidence" does not mean the procedure or device has not been approved by the Food and Drug Administration (FDA). Rather, it means the procedure or device does not meet Kaiser Permanente's objective, evidence-based technology assessment based on authoritative evidence. See the Kaiser Permanente Medical Technology Assessment Committee for further details regarding their evidence-based evaluation process.

Noridian may also provide coverage or non-coverage guidance in a Part B News Article published on the noridianmedicare.com website. Thus, these articles may be used in Medicare Advantage coverage decisions even though they are not in the form of an LCD or an LCA.

In some instances, one Medicare A/B MAC processes all of the claims for a particular Medicare-covered item or service for all Medicare beneficiaries around the country. This generally occurs when there is only one provider of a particular item or service (for example, certain pathology and lab tests furnished by independent laboratories). In this situation, MA plans must follow the coverage policy reflected in an LCD issued by the A/B MAC that enrolled the provider and processes all of the Medicare claims for that item or service. (5)

For genetic and molecular diagnostic testing, Noridian has implemented the guidelines published by Palmetto GBA under the Molecular Diagnostic (MolDX) Program for their Jurisdiction F (J-F) service area. (6). MolDX guidelines, when available, should be applied to requests for genetic and molecular diagnostic testing. In the absence of a guideline for a genetic test the above hierarchy will apply.

References:

1. Medicare Managed Care Manual, Pub. #100-16, Chapter 4 – Benefits and Beneficiary Protections, §90.2 - Definitions Related to National Coverage Determinations (NCDs)
2. Medicare Managed Care Manual, Pub. #100-16, Chapter 4 – Benefits and Beneficiary Protections, §90.4 - Local Coverage Determinations (LCDs)
3. Medicare Managed Care Manual, Pub. #100-16, Chapter 4 - Benefits and Beneficiary Protections, §90.4.1 – MAC with Exclusive Jurisdiction over a Medicare Item or Service
4. Noridian MolDX Website https://med.noridianmedicare.com/web/jfb/policies/moldx
5. Medicare Managed Care Manual, Pub. #100-16, Chapter 4 - Benefits and Beneficiary Protections, §90.5 - Creating New Guidance
6. LCD Retirement Clarification https://med.noridianmedicare.com/web/jfb/article-detail/-/view/10546/lcd-retirement-clarification

[5] - 90.5 – Creating New Guidance

(Rev. 120, Issued: 01-16-15, Effective: 01-01-15, Implementation: 01-01-15)

In coverage situations where there is no NCD, LCD, or guidance on coverage in original Medicare manuals, a Medicare Advantage Organization (MAO) may adopt the coverage policies of other MAOs in its service area. However, if the MAO decides not to use coverage policies of other MAOs in its service area, the MAO:

- Must make its own coverage determination;
- Must provide CMS an objective evidence-based rationale relying on authoritative evidence such as:
  - Studies from government agencies (e.g., the FDA);
  - Evaluations performed by independent technology assessment groups (e.g. BCBSA); and
  - Well-designed controlled clinical studies that have appeared in peer review journals; and
  - In providing its justification, the MAO may not use conclusory statements with no accompanying rationale (e.g., "It is our policy to deny coverage for this service.")

The requirement that an MA plan provide coverage for all Medicare-covered services is not intended to dictate care delivery approaches for a particular service. MA plans may encourage enrollees to see more cost-effective provider types than would be the typical pattern in original Medicare, as long as those providers are licensed and working within the scope of their licenses and the plan complies with the provider anti-discrimination rules set forth in 42 CFR §422.205.

An MA plan's flexibility to deliver care using cost-effective approaches should not be construed to mean that Medicare coverage policies do not apply to the MA program. If original Medicare covers a service only when certain conditions are met, then such conditions must be met in order for the service to be considered part of the

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original Medicare benefits component of an MA plan. An MA plan may cover the same service when the conditions are not met, but these benefits would then be defined as supplemental.

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Date Created	Date Reviewed	Date Last Revised
01/18/2017	09/04/2018[MPC], 09/03/2019[MPC], 09/01/2020[MPC], 09/07/2021[MPC], 09/06/2022[MPC] , 09/05/2023[MPC]	09/03/2019

[MPC] Medical Policy Committee

Revision History	Description
09/03/2019	Updated policy to reflect changes in Medicare Managed Care Manuals

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Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Micronutrient Panel Testing
Intracellular micronutrient analysis

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article	None
Kaiser Permanente Medical Policy	Due to the absence of an active NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Clinical Review Criteria, "***Micronutrient Panel Testing"*** for medical necessity determinations. Refer to the Non-Medicare criteria below.

For Non-Medicare Members

There is insufficient evidence in the published medical literature to show that micronutrient testing provides better long-term outcomes than current standard services/therapies.

Micronutrient testing, also known as functional intracellular analysis, essential metabolic analysis, intracellular micronutrient analysis, or leukocyte nutrient analysis, is a blood test consisting of multiple micronutrient levels intended to assess nutritional deficiencies and offer supplementation suggestions. Micronutrient tests are considered **not medically necessary**.

Some examples of commercially available micronutrient tests include but are not limited to the following:

- Genova Diagnostics ION Profile®
- IntraCellular Diagnostics EXA Test®
- SpectraCell Laboratories Micronutrient Test
- VibrantAmerica Micronutrients

If requesting review for this service, please send the following documentation:

- Last 6 months of clinical notes from requesting provider &/or specialist

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Background

Micronutrient testing assesses the level of multiple nutrients in the body. These panels may include measurement of numerous vitamins, minerals, amino acids, fatty acids, oxidation products, organic acids, toxins and antioxidants. The test results are proposed to help determine the cause of various symptoms, such as hair loss and fatigue, and various disease processes. Antioxidant function testing (e.g., Spectrox™) has been proposed as a method to evaluate the ability of cells to resist damage caused by free radicals and other forms of oxidative stress. SpectraCell Laboratories, Inc., (Houston, TX) offers a micronutrient testing panel proposed to measure how micronutrients function within the white blood cell. The Individual Optimal Nutrition (ION) (Genova Diagnostics, Asheville, NC) is a blood test that measures levels of vitamins, minerals, antioxidants, and organic, fatty, and amino acids. ExaTest®, offered by IntraCellular Diagnostics, Inc® (Medford. OR) is an intracellular tissue analysis of mineral electrolytes. The test is proposed to provide information on mineral electrolyte deficiencies or imbalances not available by blood testing. The analysis is made from an epithelial cell scraping from the sublingual area. The sample is analyzed using high energy photos (x-rays).

Currently, there is insufficient evidence in the published, peer-reviewed, scientific literature to establish the clinical utility of nutrient panel testing or antioxidant function testing or to demonstrate that the use of such testing results in improved health outcomes.

Applicable Codes

Micronutrient Test (identified by the volume of lab tests for vitamins, minerals, amino acids, antioxidants, and metabolites for diagnoses such as fatigue)

The following is a list of codes that will not be covered when billed for a Micronutrient Test. This is not an all-inclusive list.

CPT® Codes	Description
82136	Amino acids, 2 to 5 amino acids, quantitative, each specimen
82180	Ascorbic acid (Vitamin C), blood
82306	Vitamin D; 25 hydroxy, includes fraction(s), if performed
82310	Calcium; total
82379	Carnitine (total and free), quantitative, each specimen
82495	Chromium
82525	Copper
82607	Cyanocobalamin (Vitamin B-12)
82652	Vitamin D; 1, 25 dihydroxy, includes fraction(s), if performed
82725	Fatty acids, nonesterified
82746	Folic acid; serum
82978	Glutathione
83735	Magnesium
83785	Manganese
84207	Pyridoxal phosphate (Vitamin B-6)
84252	Riboflavin (Vitamin B-2)
84255	Selenium
84425	Thiamine (Vitamin B-1)
84446	Tocopherol alpha (Vitamin E)
84590	Vitamin A
84591	Vitamin, not otherwise specified
84597	Vitamin K
84630	Zinc
86353	Lymphocyte transformation, mitogen (phytomitogen) or antigen induced blastogenesis

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
05/05/2020	05/05/2020 MPC, 05/04/2021 MPC, 05/03/2022MPC, 05/02/2023MPC	05/05/2020

MPC Medical Policy Committee

Revision History	Description
05/05/2020	MPC approved to adopt new non-coverage policy. Requires 60-day notice, effective date 9/1/2020.

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Clinical Review Criteria
Minimally Invasive Lumbar Decompression

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	Percutaneous image-guided lumbar decompression (PILD) for lumbar spinal stenosis (150.13)
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article	Decision Memo for PERCUTANEOUS IMAGE-GUIDED LUMBAR DECOMPRESSION for Lumbar Spinal Stenosis (CAG-00433R)

For Non-Medicare Members

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

If requesting review for this service, please send the following documentation:

- Last 6 months of clinical notes from requesting provider &/or specialist

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Lumbar spinal stenosis (LSS) is one of the most common degenerative diseases of the lumbar spine, and the most common indication for spinal surgery in elderly patients. LSS is a condition where the dural sac and nerve roots are compressed by a combination of degenerative features including bulging of the intervertebral discs, hypertrophy of the facet joints, and thickening of the ligamentum flavum. In LSS the space within the spinal canal narrows leading to asymptomatic compression of the nerves and ultimately symptomatic neurogenic claudication, which is described as pain, paresthesia, weakness or heaviness radiating to lower extremities that occurs with walking or prolonged standing. The severity of these symptoms varies widely among patients, and may be disabling in some (Deer 2011, Brown 2012, Popov 2012, Wong 2012).

Conservative therapies for LSS include rest, pain medication, and physical therapy with or without epidural steroid injections. If these therapies fail, the patient may be advanced to more invasive surgical procedures. The goal of any surgical treatment of LSS is the relief of symptoms by adequate neural decompression while preserving as much of the anatomy, stability, and biomechanics of the lumbar spine as possible. Until the last decade, open spinal surgery was the standard treatment of LSS. The traditional surgical approach involves performing a wide, bilateral decompression laminectomy and resection of the medial portion of the facet joints to decompress the affected neural elements. This can successfully alleviate nerve compression symptoms but has the drawback of

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the open approach including the amount of soft tissue dissection, blood loss, postoperative pain, muscular atrophy, and potential for iatrogenic instability of the spinal segment (Popov 2012).

A number of less-invasive surgical techniques have been developed in recent years as an alternative to the traditional spine surgeries to limit the injury to the patient's native anatomy and reduce complication rates. These procedures are particularly attractive to spine surgeons for their small-skin incision, minimization of soft tissue injury, reduction of blood loss, infection rates, hospitalization time, narcotic usage, and minimization of physiological stress on the patient. Minimally invasive lumbar decompression techniques include the unilateral lumbar laminotomy for bilateral decompression, micro-endoscopic decompressive laminectomy, and lumbar micro-decompression (Deer 2010, Payer 2011, Smith 2012).

The *mild* ® (Minimally Invasive Lumbar Decompression) procedure (Vertos Medical Inc., Aliso Viejo, California) is a minimally invasive alternative to open or endoscopic lumbar decompression in the treatment of lumbar spinal stenosis. *Mild* ® treats LSS by removing small but adequate portions of the interlaminar bone (laminotomy) and partial excision (debulking) of the ligamentum flavum (LF) to restore space in the spinal canal while minimizing trauma to the surrounding tissue and bony structure. The procedure is typically performed under intravenous sedation monitored anesthesia and fluoroscopic guidance. The *mild* ® device kit is comprised of a single-use 6 gauge (5.1 mm diameter) *mild*® portal cannula with trocar to access into the soft tissue of the posterior lumbar spine, followed by a Bone Sculptor Ronguer which is used to precisely sculpt small pieces of lamina prior to tissue resection of the hypertrophic ligamentum flavum, then the *mild*® Tissue Sculpture is used to remove ligamentous and fibrous tissues from the hypertrophic ligamentum flavum (Deer 2010, 2011, Wong 2012).

The Vertos Medical *mild* ® Device Kit was FDA approved through the 510k process as a set of specialized surgical instruments intended to be used to perform lumbar decompressive procedures for the treatment of various spinal conditions (FDA website accessed June 26, 2012).

Medical Technology Assessment Committee (MTAC)

Minimally Invasive Lumbar Decompression

08/20/2012: MTAC REVIEW

Evidence Conclusion: There is insufficient published evidence to determine that *mild* ® Vertos procedure leads to similar or better outcomes than traditional surgery among in patients with symptomatic spinal stenosis who failed conservative therapy. There is limited published literature on the procedure. No published randomized controlled trials compared the procedure to the traditional surgical approach, or to other less invasive surgical techniques. The only published RCT to date was a small study that compared the outcomes of *mild* ® procedure to epidural steroid injection (ESI) in patients with symptomatic spinal stenosis and painful lower limb neurogenic claudication. The authors indicated that patients had to fail conservative therapy to be included in the trial, yet the procedure was compared to epidural steroid injection (ESI), which is considered a conservative management. In addition, the epidural steroid was delivered through interlaminar injections and not the preferable transforaminal route to maintain blinding (according to the author). The other published studies were prospective or retrospective case series with potential biases and were all funded by Vertos Medical the manufacturer of *mild*® *device*.

Articles: The literature search revealed one small RCT that compared the *mild*® procedure with epidural steroid injection, two multicenter observational studies with no control group, and few small prospective and retrospective case series. The RCT and the prospective multicenter observational study with one-year follow-up were selected for critical appraisal: Brown LL. A double-blind, randomized, prospective study of epidural steroid injection vs. the *mild* ® procedure in patients with symptomatic lumbar spinal stenosis. *Pain Practice*. 2012; 12:333-341. See Evidence Table. Mekhail N, Vallejo R, Coleman MH, et al. Long-term results of percutaneous lumbar decompression *mild* ® for spinal stenosis. *Pain Practice*.2012;12:184-193. See Evidence Table.

The use of minimally invasive lumbar decompression for treatment of spinal stenosis does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Interregional New Technologies Committee

MILD PROCEDURE FOR LUMBAR SPINAL STENOSIS

INTC Review: June 30, 2023

Evidence Conclusion:

There is insufficient evidence regarding the efficacy and safety of the mild® procedure by Vertos Medical, Inc. (MILD) for lumbar spinal stenosis (LSS), compared with treatment alternatives. The certainty of the body of evidence is low, given limitations of the available studies. Additional details on the studies can be found in the TPMG New Medical Technology assessment report.

Applicable Codes

Medicare - Considered Medically Necessary when criteria in the applicable policy statements listed above are met
Non-Medicare - Considered Not Medically Necessary

CPT® Codes	Description
62380	Endoscopic decompression of spinal cord, nerve root(s), including laminotomy, partial facetectomy, foraminotomy, discectomy and/or excision of herniated intervertebral disc, 1 interspace, lumbar
62287	Decompression procedure, percutaneous, of nucleus pulposus of intervertebral disc, any method utilizing needle-based technique to remove disc material under fluoroscopic imaging or other form of indirect visualization, with discography and/or epidural injection(s) at the treated level(s), when performed, single or multiple levels, lumbar
0275T	Percutaneous laminotomy/laminectomy (interlaminar approach) for decompression of neural elements, (with or without ligamentous resection, discectomy, facetectomy and/or foraminotomy), any method, under indirect image guidance (eg, fluoroscopic, CT), single or multiple levels, unilateral or bilateral; lumbar

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Creation Date	Review Dates	Date Last Revised
09/04/2012	09/04/2012[MDCRPC], 10/02/2012[MDCRPC], 08/06/2013[MPC], 06/03/2014[MPC], 04/07/2015[MPC], 02/02/2016[MPC], 12/06/2016[MPC], 10/03/2017[MPC], 09/04/2018[MPC], 09/03/2019[MPC], 09/01/2020[MPC], 09/07/2021[MPC], 09/06/2022[MPC], 09/05/2023[MPC]	06/15/2022

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
09/01/2020	Removed CPT code 0274T
06/15/2022	Added 62287 CPT code (per neurosurgery consultation this is more accurate than 62380); 62380 will no longer require review after 11/1/2022

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Clinical Review Criteria
Transcatheter Mitral Valve Repair (TMVR)

- MitraClip

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Transcatheter Edge-to-Edge Repair (TEER) for Mitral Valve Regurgitation (20.33)
Local Coverage Determinations (LCD)	None
Local Coverage Article	None
Decision Memo	Transcatheter Mitral Valve Repair (TMVR) (CAG-00438R)

For Non-Medicare Members

Transcatheter mitral valve repair using a device approved by the U.S. Food and Drug Administration for use in mitral valve repair may be considered medically necessary for patients with symptomatic, primary mitral regurgitation who are considered at prohibitive risk for open surgery.

Prohibitive risk for open mitral valve repair surgery may be determined based on the following:

- The documented presence of a Society for Thoracic Surgeons predicted mortality risk of 12% or greater

AND/OR

- The documented presence of a logistic EuroSCORE of 20% or greater

Transcatheter mitral valve repair with a device approved by the U.S. Food and Drug Administration may be considered medically necessary for patients with heart failure and moderate-to-severe or severe* symptomatic secondary mitral regurgitation despite the use of maximally tolerated guideline-directed medical therapy**.

* Moderate to severe or severe MR may be determined by:

- Grade 3+ (moderate) or 4+ (severe) MR confirmed by echocardiography
- New York Heart Association (NYHA) functional class II, III, or IVa (ambulatory) despite the use of stable maximal doses of guideline-directed medical therapy and cardiac resynchronization therapy (if appropriate) administered in accordance with guidelines of professional societies.

**Optimal guideline directed medical therapy (GDMT) - see reference below:
https://www.jacc.org/doi/10.1016/j.jacc.2020.11.022

Transcatheter mitral valve repair is considered investigational in all other situations.

Reference

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the American College of Cardiology. Retrieved February 11, 2022, from https://www.jacc.org/doi/10.1016/j.jacc.2020.11.022

If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist
- Name of the Food and Drug Administration (FDA) approved device to be used

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Transcatheter mitral valve repair (TMVR) is used in the treatment of mitral regurgitation. A TMVR device involves clipping together a portion of the mitral valve leaflets as treatment for reducing mitral regurgitation (MR); currently MitraClip® is the only one with Food and Drug Administration (FDA) approval.

U.S. FDA–MitraClip Clip Delivery System (MitraClip CDS) (Abbott Vascular, Menlo Park, CA): The MitraClip CDS received FDA approval through the PMA process on October 24, 2013. It is indicated for the percutaneous reduction of significant symptomatic mitral regurgitation (MR ≥ 3+) due to primary abnormality of the mitral apparatus (degenerative MR) in patients who have been determined to be at prohibitive risk for mitral valve surgery by a heart team, which includes a cardiac surgeon experienced in mitral valve surgery and a cardiologist experienced in mitral valve disease, and in whom existing comorbidities would not preclude the expected benefit from reduction of the mitral regurgitation. The device is contraindicated in patients who cannot tolerate procedural anticoagulation or post procedural antiplatelet regimen, and those with active endocarditis of the mitral valve, rheumatic mitral valve disease, or evidence of intracardiac, inferior vena cava or femoral venous thrombus.

The MitraClip system consists of implant catheters and the MitraClip device, a permanent implant that attaches to the mitral valve leaflets. The procedure results in a double opening of the mitral valve that allows greater closure and reduces mitral regurgitation.

Medical Technology Assessment Committee (MTAC)

MitraClip System

BACKGROUND

Mitral regurgitation (MR) is the second most common valvular heart disease after aortic stenosis. The natural history of severe MR without surgical intervention is poor, leading to worsening LV failure, pulmonary hypertension, atrial fibrillation and death. It is reported that without surgical treatment, patients with severe symptomatic MR have an annual mortality rate of 5% per year, and as high as 60% at 5 years if associated with significant heart failure (Mauri 2010).

MR is broadly categorized as primary or secondary. Primary MR, also known as degenerative MR (DMR), describes an abnormality of the leaflets varying from a prolapse of an isolated segment in a normally shaped valve, to multiple segment prolapse involving one or both leaflets in a valve with significant excessive tissue and large annular size. Secondary MR, also known as functional MR (FMR), is secondary to left ventricular (LV) remodeling with structurally preserved mitral leaflets. Surgical mitral valve repair/replacement remains the gold standard for the treatment of symptomatic MR, though it has some controversy in FMR due to the lack of clear survival benefit and high recurrence rates of MR at 1 year after surgery. Current guidelines recommend MV surgery in patients with moderate to severe (grade 3+) or severe (4+) MR associated with symptoms or evidence of LV dysfunction. Surgical repair of the valve before the onset of limiting symptoms or LV dysfunction can restore normal life expectancy and quality of life. The conventional surgery for MV repair/replacement is an open-heart surgery performed under cardiopulmonary bypass. It is reported that as many as 49% of patients in need of MR repair or replacement are considered at high surgical risk and are denied surgical treatment due to their age, advanced LV systolic dysfunction, previous bypass surgeries, or significant comorbidities. Patients who do not qualify for surgical correction of the MV are treated with medical therapy alone, which may reduce their symptoms, but does not stop the disease progression (Estevez-Loureiro 2013 Mauri 2013, Vakil 2013, Wan 2013, Munkholm-Larsen 2014). In the past 15 years, percutaneous valve therapy has been advancing rapidly especially for the aortic and pulmonic valve replacement. This development of percutaneous mitral valve (MV) therapies has been slower due to the anatomy of the MV and its relationship with the left ventricle. A number of devices for MV repair have been introduced as potential alternatives to open surgical procedures; many have failed, and more

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are at different stages of investigation. Percutaneous or minimally invasive repair systems target the MV leaflets, annulus or the left ventricle, e.g. the Neochord DS1000, the Carillon Mitral Contour System, and the MitraClip system. The latter is the only one in clinical use across the United States and Europe (Munkholm-Larsen 2014, Rana 2015).
The concept of the MitraClip system (Abbott Vascular, Menlo Park, California) is based on the edge-to-edge repair technique developed by Alfieri and colleagues in the early 2000s. This technique involves suturing of the middle scallops of the anterior and posterior MV leaflets resulting in a double orifice valve. The MitraClip is a single-sized system that consists of a 4mm wide cobalt chromium clip with two foldable arms designed to grasp the moving leaflets; a 10Fr delivery catheter, with a radiopaque distal tip, and a 24-Fr steerable sleeve. The procedure is performed in the cardiac catheterization laboratory under general anesthesia, anticoagulation, and fluoroscopic and transesophageal echocardiographic guidance. The MV is accessed via the femoral vein and right atrium then to the left atrium via a transseptal puncture. The system is advanced into the left ventricle and the clip is deployed for permanent approximation of the anterior and posterior MV leaflets creating a double orifice MV during diastole. Reduction in MR is assessed by echocardiography during the procedure, and more than one clip may be used at the operator's discretion. At the end, the catheters are withdrawn, and the patient treated with aspirin for 6 months and clopidogrel for 30 days (Wan 2013, Vakil 2013, Munkholm-Larsen 2014, Rana 2015).
Several anatomic parameters must be satisfied to determine the appropriate patients for the procedure. These differ for patients with DMR and FMR. Anatomical criteria for DMV include flail width and gap size, prolapse location, length of posterior MV leaflet (PMVL) and MV orifice size. The criteria for MV anatomy include coaptation depth and length, the MV orifice size, and the MV transvalvular gradient. Lesions ideal for MitraClip lie within the central portion at the coaptation line, have a flail width <15 mm with a flail gap <10mm, and as the MitraClip reduces the MV orifice, the preimplantation area should be >40 mm^2. A hypoplastic posterior leaflet is a contraindication, and heavy calcification, fibrosis, or deep clefts within the clip grasping area have potential for clip implantation failure. The percutaneous MV repair with the MitraClip system depends heavily on echo-imaging during the implantation and early on for assessing the suitability for clip placement, which is the cornerstone for the success of the technique. It has been reported that some technical aspects of the MitraClip implantation remain operator dependent and have not been fully standardized, and that the correct strategy for patients with complex valve anatomy remains controversial (Paranskaya 2013, Rana 2015).
The MitraClip treatment of MR is less invasive than surgery but may be associated with potentially life-threatening complications. The incidence of the reported procedure-related complications is generally low and varies considerably between studies. These included bleeding that require >2 units of blood transfusion (the most common), vascular access site complications, transseptal puncture
(which may also cause to aortic root needle puncture), partial clip detachment, clip attachment to a single leaflet, leaflet injury or laceration, mitral valve stenosis, mitral valve injury, acute heart failure, and stroke (Bakker 2013).
According to the device manufacturer and the FDA (approval in October, 2013), MitraClip implantation is indicated for the percutaneous reduction of significant symptomatic mitral regurgitation (MR ≥ 3+) due to primary abnormality of the mitral valve (degenerative MR), who have been determined to be at prohibitive risk for mitral valve surgery by a heart team, which includes a cardiac surgeon experienced in mitral valve surgery and a cardiologist experienced in mitral valve disease, and in whom existing comorbidities would not preclude the expected benefit from reduction of the mitral regurgitation. It is contraindicated in patients who cannot tolerate anticoagulation required during the procedure or antiplatelet therapy required after the procedure; in patients with active MV endocarditis; rheumatic MV disease; and in patients with evidence of femoral venous, inferior vena cava, or intracardiac thrombus. (http://mitraclip.com, and FDA webpage accessed July 17, 2015)

08/17/2015: MTAC REVIEW
MitraClip System
Evidence Conclusion:
There is evidence from EVEREST II RCT with 4 years of follow-up, that the implantation of MitraClip is less effective than surgery in improving the mitral regurgitation in patients with moderate or severe symptomatic mitral valve regurgitation who are suitable candidates for conventional surgery. The is low quality, but consistent evidence from observational studies and registries that implantation of MitraClip in patients with symptomatic moderate or severe symptomatic mitral valve regurgitation who are at high surgical risk, is feasible and is associated with clinical improvement and relatively low risk of major adverse events. However, there is no evidence to date to determine the durability of clinical improvements and optimal criteria for patient selection. There is insufficient evidence to determine the outcomes of MitraClip device by etiology of mitral regurgitation (FMR or DMR). Two ongoing RCTs (COPAT in the US and RESHAPE-HF trial in Europe) are comparing MitraClip implantation versus medical therapy in high surgical risk patients, and their results may provide more evidence on the relative safety and efficacy of implanting the device in these patients.
Articles: The literature search revealed EVEREST I feasibility trial; EVEREST II randomized controlled with four publications (the last of which reported on 4-years follow-up outcomes); 4 other nonrandomized
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comparative studies with retrospective controls including EVEREST II High Risk Study (HRS); a number of uncontrolled studies; a meta-analysis that pooled the results of the RCT and comparative studies; 3 systematic reviews (2 on the safety and efficacy of MitraClip in patients at high surgical risk, and one for patients with severe MR); and a number of industry-supported or industry-independent registries (REALISM, ACCESS Europe, Everest High-risk register) TRAMI German registry, and GRASP registry),The EVEREST II RCT, the EVEREST II HRS, and the meta-analysis that examined the safety and efficacy of MitraClip for patients at high surgical risk were selected for critical appraisal. Feldman T, Foster E, Glower DD, et al for the EVEREST II Investigators. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med*. 2011 Apr 14; 364(15):1395-406. See Evidence Table 1. Mauri L, Garg P, Massaro JM, Foster E, et al. The EVEREST II Trial: design and rationale for a randomized study of the evalve mitraclip system compared with mitral valve surgery for mitral regurgitation. *Am Heart J*. 2010 Jul; 160 (1):23-29. See Evidence Table 1. Philip F, Athappan G, Tuzcu EM, et al. MitraClip for severe symptomatic mitral regurgitation in patients at high surgical risk: a comprehensive systematic review. *Catheter Cardiovasc Interv*. 2014 Oct; 84(4):581-590. See Evidence Table 3. Mauri L, Foster E, Glower DD, et al. for the EVEREST II Investigators. 4-year results of a randomized controlled trial of percutaneous repair versus surgery for mitral regurgitation. *J Am Coll Cardiol*. 2013 Jul 23; 62(4):317-328. See Evidence Table 1. Wan B, Rahnavardi M, Tian DH, et al. A meta-analysis of MitraClip system versus surgery for treatment of severe mitral regurgitation. *Ann Cardiothorac Surg.* 2013. Nov; 2(6):683-692. Whitlow PI, Feldman T, Pederson WS et al on behalf of the EVEREST II Investigators. Acute and 12-Month Results with Catheter-Based Mitral Valve Leaflet Repair: The EVEREST II (Endovascular Valve Edge-to-Edge Repair) High Risk Study. *J Am Coll Cardiol*. 2012. January; 59:130–139. See Evidence Table 2.

The use of the MitraClip System does meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
0345T	Transcatheter mitral valve repair percutaneous approach via the coronary sinus
33418	Transcatheter mitral valve repair, percutaneous approach, including transseptal puncture when performed; initial prosthesis
33419	Transcatheter mitral valve repair, percutaneous approach, including transseptal puncture when performed; additional prosthesis(es) during same session (List separately in addition to code for primary procedure)

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check.**

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Date Created	Date Reviewed	Date Last Revised
05/13/2015	09/01/2015[MPC], 06/07/2016[MPC], 04/04/2017[MPC], 02/06/2018[MPC], 02/05/2019[MPC], 02/04/2020[MPC], 02/02/2021[MPC] 02/01/2022[MPC], 02/07/2023[MPC]	01/05/2021

[MPC] Medical Policy Committee

Revision History	Description
01/05/2021	MPC approved to adopt changes to criteria to include symptomatic secondary mitral regurgitation and high-risk score for traditional surgery. Requires 60-day notice, effective date 06/01/2021.

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Clinical Review Criteria
Monitored Anesthesia Care (MAC) for Gastrointestinal Endoscopic Procedures

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	4/09/2018 Noridian Retired LCD for Monitored Anesthesia Care (MAC) (L34100). These services still need to meet medical necessity as outlined in the LCD and will require review. LCDs are retired due to lack of evidence of current problems, or in some cases because the material is addressed by a National Coverage Decision (NCD), a coverage provision in a CMS interpretative manual or an LCD. Most LCDs are not retired because they are incorrect. The criteria should be still referenced when making an initial decision. However, if the decision is appealed, the retired LCD cannot be specifically referenced. Maximus instead looks for “medical judgment” which could be based on our commercial criteria or literature search. Medical necessity review is no longer required for Medicare members. However, providers are expected to validate medical necessity per Medicare’s guidance in retired LCD L34100 (see above).
Local Coverage Article	None

For Non-Medicare Members

No medical necessity review required.

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Background

Each year in the United States, 145,000 people will be diagnosed with colon cancer; 54,000 will die. Getting recommended colorectal cancer screening could potentially save the lives of up to 60% of these patients. Increasing patient participation in routine screening is a matter of serious concern.

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With the increased emphasis on prevention and the importance of the role of colonoscopy as a tool there is a need to evaluate the use of monitored anesthesia care in conjunction with endoscopic evaluation. Kaiser Permanente has developed this policy in response to our findings.

Medical Technology Assessment Committee (MTAC)

Monitored Anesthesia Care (MAC) for Gastrointestinal Endoscopic Procedures

2/22/2010: MTAC REVIEW

Evidence Conclusion: The following are conclusions based on a review of several systematic reviews, meta-analyses, randomized controlled trials, and published internal data on sedation involving propofol compared to standard sedation: There is good evidence of improved patient satisfaction and reductions in discharge and recovery times with propofol used alone or in combination with other agents compared to standard sedation for colonoscopy exams. There is fair evidence from a KP SCAL-based comparative study of improved cecal intubation rates with propofol used as a single agent for sedation during colonoscopy. The evidence is of insufficient quantity or quality to draw definitive conclusions on differences in polyp detection. There is less comparative data on EGD procedures, but some evidence of improved recovery and patient satisfaction with propofol sedation. The evidence is of insufficient quantity and/or quality to draw definitive conclusions on comparative risk of serious adverse events, including death, neurologic injury, endotracheal intubations, bleeding, and colonic perforations during these procedures. There does not appear to be a significant difference in the risk of cardiopulmonary and respiratory events with propofol compared to standard sedation and no evidence of greater risk for serious adverse events for either colonoscopy or EGD procedures in lower risk patients (ASA I or II). Following the review of one systematic review and two comparative observational studies, the evidence is of insufficient quantity and quality to draw definitive conclusions on the safety of anesthesiologist- versus non anesthesiologist-directed or administered propofol sedation in GI endoscopy. Controlled prospective studies with standardized protocols, patient selection, and reporting are needed. Serious Adverse Events. The best available comparative evidence from the United States is a large observational registry study that suggests comparable rates of serious adverse events for anesthesiologist-directed propofol under monitored anesthesia care and gastroenterologist-administered propofol during colonoscopy procedures (0.16% and 0.14%) but a significantly increase risk of serious adverse events with gastroenterologist-administered propofol for upper endoscopy procedures, including EGDs (0.16% vs 0.5%). However, it is likely that these events differentially occurred in higher risk patients (ASAI III) who were also included in the study. Overall Cardiopulmonary Adverse Events. There is evidence from the same study of a significant increased risk of overall cardiopulmonary events with endoscopic-administered propofol in ASA I or II patients undergoing colonoscopy and upper endoscopy. The majority of the cardiopulmonary events are most likely to be of minor clinical consequence, but the challenge remains to identify which cardiopulmonary events are more likely to result in serious adverse events and what risk factors are specific to upper versus lower endoscopy procedures. The evidence is of insufficient quantity and quality to draw conclusions on the safety of RN-administered propofol as compared to standard sedation for colonoscopy and EGD in ASA I and II patients. Based on a review of several systematic reviews and randomized controlled trials, there is no evidence of a significant increase in risk of adverse events with propofol compared to standard sedation and the risks appear to be comparable. However, these studies were not adequately sampled to detect or compare rates of serious adverse events. Comparative data from large and well-designed observational studies is needed. The existing series of RN-administered propofol are large and report low rates of adverse events.

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MDCRPC voted to adopt the Kaiser evidence review conclusions.

MONITORED ANESTHESIA CARE (MAC) FOR CHRONIC MARIJUANA USERS UNDERGOING GASTROINTESTINAL ENDOSCOPIC PROCEDURES

BACKGROUND

Marijuana use

Marijuana is the most commonly used federally illegal drug in the United States. Its use has significantly increased across the country in recent years, especially among young people and in the states that have legalized the recreational cannabis use. It is estimated that approximately 3 in 10 people who use marijuana have marijuana use disorder, the risk of which is higher among those who begin using it before the age of 18, The National Survey on Drug Use and Health National Institute on Drug Abuse estimated that 5.1% (or about 14.2 million people) aged 12 or older in 2020 had a cannabis use disorder in the past 12 months (2020 National Survey on Drug Use and Health National Institute on Drug Abuse and CDC website).

Th term “Marijuana” is commonly used interchangeably with “Cannabis”; however, they don’t mean exactly the same thing. Cannabis refers to all products derived from the plant Cannabis sativa that includes more than 500 compounds among which are cannabinoids, terpenoids, and flavonoids. Marijuana on the other hand refers to the dried flowers, leaves, stems, and seeds of the cannabis plant that contain substantial amounts of tetrahydrocannabinol (THC) that is primarily responsible for the effects of marijuana on a person’s mental state. The main cannabinoids in the cannabis are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), each with its own effects and uses. THC is the main psychoactive compound in cannabis and is responsible for the “high” that most people associate with cannabis. CBD is also a psychoactive cannabinoid, but is non-intoxicating and non-euphoric, i.e., does not cause a “high”. It is often used to help reduce inflammation and pain, and also to ease nausea, migraine, seizures, and anxiety. (Andre et al, 2016, Boninin et al, 2018, Bakshi, et al 2019, Balant, et al 2021, Irvine , et al 2022, and the CDC website

Marijuana use has negative clinical effects on different body organs and systems including the respiratory, cardiovascular, and central nervous system, gastrointestinal tract, and others. These vary by the quantity and chronicity of the marijuana used. However, it can be difficult to the quantity the active compound of the marijuana consumed as the formulations of the products and their CBD-to-THC-content ratios are very heterogeneous. Research suggests that cannabis users require significantly higher doses of sedation for upper endoscopic procedures compared with nonusers. Propofol, a primary anesthetic agent, is metabolized through similar enzymatic pathways as the THC and cannabis users may present a higher-than-normal risk for subanesthetic dosing, leading to greater incidence of awareness or recall. They are also at a higher risk of adverse events such as bronchospasm, laryngospasm, tachycardia, and others (Twardowski, et al 2019, Imasogie et al 2021, Ladha et al, 2021).

With the increasing prevalence of cannabis use among adults, and with the known effects of marijuana on the different systems it is important that anesthesia professionals consider the potential effects of cannabis use when providing perioperative care to chronic marijuana users.

Monitored anesthesia care (MAC)

Monitored anesthesia care is defined by the American Society of Anesthesiologists (ASA) as a planned procedure during which the patient undergoes local anesthesia together with sedation, and analgesia provided by an anesthesiologist. I.e., it is an anesthesia technique combining local anesthesia with parenteral drugs for sedation and analgesia. The purpose of the conscious sedation during MAC is providing the patient with safe sedation, comfort, and control of pain and anxiety. The patients under conscious sedation maintain ventilatory and cardiovascular function and are able to respond to verbal and tactile stimulation. The discretion and judgment of an experienced anesthesiologist are required for the safety and efficacy as the airway of the patient is not

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secured. The attending anesthesiologist should be aware of the possibility of airway obstruction, desaturation, or even aspiration due to the possibility of deep sedation after infusion of a combination of two or more drugs (GHISI, et al 2005, Sohn and Ryu 2016. In contrast, moderate sedation /analgesia (conscious sedation) is a drug induced depression of consciousness during which patients respond purposefully to verbal commands alone or with
light tactile stimulation. No interventions are required to maintain a patent airway, spontaneous ventilation is adequate and cardiovascular function is usually maintained.

MAC allows for the safe administration of a maximal depth of sedation more than that provided during moderate sedation. The qualified anesthesiologist /provider is able to adjust the sedation level from full consciousness to general anesthesia during the procedure according to the patient needs and procedural requirements. An essential component of MAC is the periprocedural anesthesia assessment and understanding of the comorbidities and management of the patient's actual or anticipated physiological instabilities during a diagnostic or therapeutic procedure. MAC may include the administration of sedatives and/or analgesics often used for moderate sedation, however the qualified MAC provider is focused exclusively and continuously on the patient for any attendant airway, hemodynamic and physiologic instabilities, and must be prepared and qualified to convert to general anesthesia. The provider's ability to intervene to rescue a patient's airway from any sedation-induced compromise is required. On the other hand, moderate sedation is not expected to induce the level of sedation that would impair the patient's respiratory function or ability to maintain the integrity of his or her airway, and the moderate sedation provider or anesthesiologist focus is on the procedure itself. (ASA 2018)

The use of MAC is increasing for a variety of diagnostic and therapeutic procedures in and outside of the operating room due to the rapid postoperative recovery with the use of relatively small amounts of sedatives and analgesics compared to general anesthesia. Procedures performed with MAC include eye surgery, otolaryngologic surgery, cardiovascular procedures, pain procedures, and endoscopy. Sedation and analgesia during MAC are provided by an anesthesia care team following the same preoperative evaluation, perioperative management, monitoring, and postoperative recovery care used for general or regional anesthesia (Sohn and Ryu 2016).

Some researchers found that the overall rate of complications during and after MAC may be similar to that for general anesthesia. These potential complications associate with MAC include
- Respiratory complications, including airway obstruction, respiratory depression with hypoxemia and hypercarbia, and aspiration due to depression of airway reflexes.
- Cardiovascular compromise, including hypotension, cardiac ischemia, cardiac arrest, and arrhythmias.
- Complications related to patient movement
- Burn injuries, particularly involving the head and neck
- Local anesthetic systemic toxicity (LAST

10/10/2022: MTAC REVIEW
Evidence Conclusion: To date, there are no published literature on the comparative efficacy and safety of monitored anesthesia care and moderate sedation for patients on chronic marijuana use undergoing gastrointestinal endoscopic procedures.

Additional research is needed to determine the efficacy and safety of MAC in these patients.
Articles: The literature search did not reveal any published RCTs or observational studies that compared the outcomes of MAC versus moderate conscious sedation for GI endoscopic procedures in adults on chronic marijuana use. The published literature mainly discussed the effects of cannabis use on the anesthesia risk, the dose of propofol required, the need for using adjuncts such as fentanyl and ketamine, and or the risk of adverse cardiac or respiratory events during or immediately after anesthesia.

The use of Monitored Anesthesia Care (MAC) For Chronic Marijuana Users Undergoing Gastrointestinal Endoscopic Procedures does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Medical necessity no longer required:

CPT® Codes	Description

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00731	Anesthesia for upper gastrointestinal endoscopic procedures, endoscope introduced proximal to duodenum; not otherwise specified
00811	Anesthesia for lower intestinal endoscopic procedures, endoscope introduced distal to duodenum; not otherwise specified
00812	Anesthesia for lower intestinal endoscopic procedures, endoscope introduced distal to duodenum; screening colonoscopy
00813	Anesthesia for combined upper and lower gastrointestinal endoscopic procedures, endoscope introduced both proximal to and distal to the duodenum

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
09/10/2012	10/02/2012[MDCRPC], 08/06/2013[MPC], 06/03/2014[MPC], 04/07/2015[MPC], 05/05/2015[MPC], 03/01/2016[MPC], 01/03/2017[MPC], 11/07/2017[MPC] , 09/04/2018[MPC], 09/03/2019[MPC], 09/01/2020[MPC] , 09/07/2021[MPC], 09/06/2022[MPC]	05/02/2023

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
05/05/2015	Slight changes were made to the existing policy, which included the following: • Removal of the 70-age limit • Definition of pediatric age group as 16 years and younger • Clarification of “high dose” & “unstable” • “as documented by anesthesia” language was added
09/08/2015	Revised LCD L34100
10/3/2016	Added prolonged procedure clarification
09/06/2017	Changed BMI to 40
10/19/2017	Added examples of prolonged procedures
04/09/2018	MA retired LCD 34100
05/23/2018	Removed the language regarding the Mallampati score
09/04/2018	Added specific language regarding marijuana use
05/05/2020	MPC approved to adopt updates to align with ASA class ASGE recommendations. Requires 60-day notice, effective date 9/1/2020. Removed deleted CPT codes 00740 and 00810 and added CPT code 00732.
06/16/2020	Removed 00732 (ERCP)
11/02/2021	MPC approved to remove the prior-authorization requirement for Medicare members, effective January 1, 2022.
09/06/2022	MPC approved the MAC criteria update for ASA class from IV to III and the inclusion of coverage for members with current suboxone use. 60-day notice required; effective 2/1/2023.
12/06/2022	Updated MAC effective date to 3/1/2023 per Provider Relations.
12/07/2022	Added MTAC Review for Monitored Anesthesia Care (MAC) For Chronic Marijuana Users Undergoing Gastrointestinal Endoscopic Procedures to criteria.
05/02/2023	MPC approved to support KPWA executive leaderships recommendation to remove prior authorization and medical necessity criteria for MAC. 60-day notice expedited; effective September 1, 2023.

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Clinical Review Criteria

Magnetic Resonance Enterography (MR per OS) for the Diagnosis and Monitoring of Crohn's and Celiac Diseases

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Magnetic Resonance Imaging (MRI) (220.2)
Local Coverage Determinations (LCD)	None

For Non-Medicare Members

Kaiser Permanente considers magnetic resonance enterography medically necessary to evaluate and monitor Crohn's disease and other small bowel disorders and does not require medical necessity review.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract. In 80% of cases it involves the small bowel, more specifically the ileum, and is characterized by luminal, transmural and mesenteric abnormalities. Crohn's usually manifests in early adulthood and typically runs a relapsing and remitting course. Initial diagnosis aims at establishing and characterizing the disease including the location, extent of inflammation, and the presence of stenosis, fistulae or abscesses. Several modalities such as radiology, endoscopy, and serologic markers are being used to diagnose and assess the disease activity. None is recognized as a gold standard, but radiological procedures including small bowel series and fluoroscopic enteroclysis continue to lead the diagnostic tools that examine the small bowel in its entirety. Because there is no known cure, and the condition is typically relapsing, patients with Crohn's disease normally undergo several radiological investigations during the course of the disease to monitor the treatment response, recurrence, and /or development of complications (Negaard 2007, 2008, Masselli 2006, Lin 2008).

Celiac disease is a gluten-sensitive enteropathy of the gastrointestinal tract that affects the small intestine in genetically susceptible individuals at any age. The disease is relatively common in European countries and occurs less frequently in the US. Celiac disease has a wide range of nonspecific clinical manifestations which make it challenging to diagnose. Its may be silent and go clinically undetected or present with symptoms that range from fatigue and abdominal pain to weight loss, diarrhea, and malabsorption with steatorrhea. In children it may be associated with apathy, anorexia, and muscle wasting. It is reported that a small-intestine biopsy is mandatory to confirm the diagnosis of celiac disease. Imaging plays a role in suggesting celiac disease in adults with intestinal disorders, and in ruling out complicating lesions in patients with known disease (Paolantonio 2007).

The traditional imaging techniques used to evaluate the small bowel are the conventional barium studies e.g. small bowel follow-through or conventional enteroclysis (CE) Historically CE has been the radiological method of

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choice. It was found to be highly accurate for diagnosing Crohn's disease and detecting partially or non-obstructive lesions that may not be demonstrated by cross-sectional imaging techniques. The procedure involves distension of the entire small bowel with barium suspension which when adequate, would allow the radiological demonstration of mucosal abnormalities and provide functional information on the ability of the small bowel to distend. CE, however, exposes the patient to ionizing radiation, may be hindered by the overlapping bowel loops, and does not provide information on the transmural and extramural extension, or other complications of the disease such as fistulae and abscesses (Schreyer 2004, Bernstein 2005, Masselli 2008).

Computed tomographic (CT) enterography, magnetic resonance (MR) enterography, and MR enteroclysis are emerging techniques for small bowel imaging. They have a benefit over traditional barium fluoroscopic techniques in their ability to visualize superimposed bowel loops and extraluminal extensions, and complications. CT provides excellent temporal and spatial high-resolution images of the small bowel, and is less susceptible to motion artifacts than MRI, but at the cost of radiation exposure. MRI on the other hand, has several advantages over CT, such as its superior tissue contrast, ability to provide direct cross-sectional imaging in multiple planes, functional or real-time examination of the bowel, and lack of ionizing radiation exposure which is particularly important in Crohn's patients who need repeated evaluation. The real-time imaging can be helpful in evaluating the progress of bowel filling with contrast agents during enteroclysis, determining the ability of the narrowed areas to distend, and improving differentiation of contractions from strictures. In addition, the gadolinium contrast agents used in MRI are known to have an excellent safety profile and can be used in patients with iodine contrast allergies, renal insufficiency, or during pregnancy. MRI, however, has inferior spatial and temporal resolution compared to CT, and its image quality may be degraded by artifacts from bowel peristalsis. Other reported constraints for MRI use include the limited number and access to MR scanners as well as its high cost (Rieber 2000, Bruining 2006, Fidler 2007).

MRI for small bowel disease may be performed by MR enteroclysis (luminal contrast) or MR enterography (MRI per OS, oral contrast). MR enteroclysis requires the fluoroscopic passage of a nasojejunal catheter and controlled administration of significant volumes (up to 3 liters) of enteric contrast agents. The small bowel can be filled with manual injection or hand-held infusion pumps while the patient is in the scanner. The procedure is associated with significant patient discomfort particularly due to the catheter introduction and manipulation, as well as the profuse diarrhea which results from the infused contrast medium. Moreover, the continuous infusion of the contrast agent may result in gastro-esophageal reflux especially in the obstructed patient, leading to potential vomiting and aspiration (Negaard 2007, Lohan 2007).

To achieve a compromise between patient tolerability and reproducible diagnostic image acquisition, MRI techniques with oral contrast (MR enterography) have been introduced. For this procedure, the patient is required to ingest a large amount of fluid (1.5-2 liters) to distend the stomach and small bowel in continuity. Various substances and volumes have been added to the oral solutions to increase the bowel distension. It is reported that there is no agreement on the optimal oral contrast, but investigators found that high osmolarity of the contrast e.g. mannitol, improves the bowel distension. MR enterography may be associated with adverse effects such as diarrhea, nausea, abdominal pain, ileus due to the increased fluid content, and other side effects (Masselli 2006, Lohan 2007).

Medical Technology Assessment Committee (MTAC)

Magnetic Resonance Enterography (MR per OS)

02/02/2009: MTAC REVIEW

Evidence Conclusion: Most of the published studies on MR imaging of the small bowel used the enteroclysis technique that requires intubation of the proximal small bowel followed by the administration of contrast agent. Few studies performed MR enterography where the contrast material is ingested orally. Different modalities for the diagnosis of Crohn's disease were used as reference standards, as there is no non-surgical gold standard to date.

In the studies reviewed, MR imaging was used for patients with suspected or confirmed Crohn's disease to characterize the disease, assess the extent and severity of bowel inflammation, and detect any stenosis, fistula, or other associated lesions. In both MR techniques, good distension of the small bowel loops during examination is essential to accurately evaluate the bowel wall pathology because collapsed loops may hide the disease or falsely identify a collapsed segment as a thickened wall. Negaard et al's study (2007) included 40 participants with known or suspected Crohn's. All participants were examined with both MR techniques, and the diagnosis of the disease was based on clinical evaluation, ileoscopy with histopathology, capsule endoscopy, or surgery. The study had several limitations, no comparison was made to with conventional enteroclysis, and lesions in jejunum and proximal ileum were not evaluated. Moreover, the reference standards were performed 2-3 months after the

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MR imaging, which may affect the presence or absence of some disease-related findings. The overall results of the study show that bowel distension was statistically significantly inferior in MR enterography compared to MR enteroclysis at both the jejunal and ileal levels. The difference was, however, insignificant for the terminal ileum. The accuracy of the two MR imaging techniques had similar sensitivity in assessing the intestinal wall thickness, enhancement and ulcer detection, when compared to reference standards used in the study. MR enteroclysis was more sensitive and specific than MR enterography in detecting intestinal stenosis, but less specific for the three other measures. MR enterography was associated with bowel obstruction in two patients one of which required abdominal surgery to treat the condition. Masselli and colleagues' study (2008) compared the diagnostic accuracy of MR enterography, with MR enteroclysis, and conventional enteroclysis as a reference standard in 40 patients with histologically proven Crohn's disease. All participants underwent conventional enteroclysis and either the MR enteroclysis or enterography on an alternating basis. The study was small and had several limitations. Its overall results show that conventional enteroclysis detected significantly more mucosal and mural abnormalities, but less mesenteric findings vs. MR enteroclysis and MR enterography. There was no significant difference between the two MR imaging techniques in the image quality, or assessment of mural stenosis and fistulae. However, MR enterography was statistically significantly inferior in bowel distension vs. MR or conventional enteroclysis. It was also inferior to MR enteroclysis in detecting the involved affected segments, superficial erosions, and deep ulcers. Conclusions: The published studies indicate that MR enterography may be inferior to conventional and MR enteroclysis in bowel distension, and detection of some associated lesions. There is insufficient evidence to determine the role of MR enterography in the diagnosis or assessment of celiac disease. There is insufficient evidence to determine the role of MR enterography in monitoring patients with Crohn's or celiac disease. There is insufficient evidence to determine the safety of the MR enterography in patients with Crohn's or celiac disease.
Articles: The literature search revealed over three hundred publications. The majority was reviews, articles that dealt with the technical aspects of the tests, or that were unrelated to the current review. The studies on the use of MR imaging for the evaluation of small bowel diseases mainly included patients with Crohn's disease; only one small retrospective case series evaluated the test for patients with celiac disease. The literature on MR enterography was very limited compared to MR enteroclysis. One study compared both MR techniques (enteroclysis and enterography) to conventional enteroclysis, and one to a combination of reference standards. The technology was also compared to capsule endoscopy or CT enterography in two small studies. The test was mainly used for the initial assessment of known or suspected Crohn's. Only one small study that included patients with recurrent disease was identified, but there were no published studies on the use of MR enterography for monitoring treatment response. The studies that compared MR enterography of the small bowel to conventional enteroclysis and/or MR enteroclysis, and that had more valid methodology and data analysis, were selected for critical appraisal. Negaard A, Paulson V, Sandvick L, et al. A prospective randomized comparison between two MRI studies of the small bowel in Crohn's disease, the oral contrast methods and MR enteroclysis. Eur Radiol 2007;17:2294-2301. See Evidence Table. Masselli G, Casciani E, Polettini E, et al. Comparison of MR enteroclysis with MR enterography and conventional enteroclysis in patients with Crohn's disease. Eur Radiol. 2008;18:438-47. See Evidence Table.

The use of Magnetic Resonance Enterography (MR per OS) for the diagnosis and monitoring of Crohn's and celiac diseases does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Applicable Codes

Medical Necessity Review not required:

CPT® or HCPC Codes	Description
No Specific Codes	

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised

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03/12/2009	05/03/2011 MDCRPC, 08/02/2011 MDCRPC, 06/05/2012 MDCRPC, 04/02/2013MDCRPC, 02/04/2014 MPC, 12/02/2014 MPC, 10/06/2015MPC, 08/02/2016MPC, 06/06/2017MPC, 04/03/2018MPC, 04/07/2020MPC, 04/06/2021MPC, 04/05/2022MPC, 04/04/2023MPC	05/04/2021

MDCRPC Medical Director Clinical Review and Policy Committee

MPC Medical Policy Committee

Revision History	Description
06/06/2017	MPC approved criteria for medical necessity
05/04/2021	MPC approved to remove the medical necessity review requirement for Magnetic Resonance Enterography. Requires 60-day notice, effective date 10/1/2021.

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KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Brain MRI

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Criteria

For Medicare Members

This policy does not apply to Medicare members.

For Non-Medicare Members

***Site of Care review also applies -** See the High-end imaging Site of Care Medical Policy

Magnetic resonance imaging (MRI) studies of the brain may be medically necessary when the following criteria are met:

I. **Evaluation of headache:**
Brain MRI is not indicated for any of the following headache diagnoses in the absence of focal neurological deficits: migraine, cluster headache, tension-type headache, or chronic stable headache**.**
MRI can be considered for 1 or more of the following –
   a. Chronic headache with a change in character/pattern (e.g., more frequent, increased severity, or duration) not explained after evaluation of common causes (e.g., medication overuse syndrome or cervicogenic headache) and failure to respond to standard medical management
   b. Suspected aneurysm rupture/leak or AVM. Typically described as a new onset (< 48 hours) of “worst headache in my life” or “thunderclap” headache. A thunderclap type headache is a sudden onset new headache reaching maximum intensity within 2-3 minutes, lasting more than 5 minutes.
   c. Prior history of stroke or intracranial bleed with sudden onset of severe headache
   d. New onset of headache and any of the following:
      i. Onset of headache before age 6 years
      ii. Onset of headache after age 50 years not explained after evaluation of common causes (e.g., medication overuse syndrome or cervicogenic headache)
      iii. A combination of acute, new, or fluctuating neurologic deficits such as unilateral sensory deficits, unilateral limb weakness, speech difficulties, visual loss, lack of coordination, gait disturbance, seizures, otherwise unexplained vomiting, otherwise unexplained acute hypertension, cranial nerve abnormality, mental status changes, or with papilledema or other signs of increased intracranial pressure
      iv. Clinical signs and symptoms strongly suggesting metastatic cancer as the cause of the headache
      v. Significantly immunocompromised patient (i.e., patient with HIV or immunosuppression)
      vi. Patients with risk factors for cerebral venous thrombosis:
         1. Pregnancy or post-partum
         2. Known history of active coagulation disorder (e.g., sickle cell crisis, or clinical signs of active coagulation disorder)
      vii. Fever or meningismus with suspected CNS cause
      viii. Reproducible headache immediately preceded by physical exertion, sexual activity, Valsalva maneuver, or positional change, e.g., leaning forward
   e. MRI can be considered in a **pediatric age (0-16 years old)** patient with worsening headache and **1 or more** of the following:
      i. Occipital location

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ii. Age < 6 years
iii. Repeatedly awakens child from sleep or is present upon awakening

II. **Acute, new, or fluctuating neurologic symptoms or deficits** such as **1 or more** of the following:
a. Ataxia or gait disturbance without other cause
b. Change in speech or language (e.g., dysarthria, aphasia)
c. Cranial nerve palsy (not otherwise explained (e.g., Bell's Palsy or diabetic CN III palsy)
d. Focal sensory /motor deficit suggesting brain or spinal cord cause (e.g., unilateral numbness or paresthesia's of face, arm and leg *OR* arm and leg)
e. Horner syndrome (unilateral miosis, ptosis, facial anhidrosis)
f. Papilledema
g. New visual disturbance (e.g., diplopia, visual field defect, nystagmus, visual loss)

III. **Evaluation of known or suspected seizure disorder and 1 or more** of the following:
a. New onset of a seizure (first focal seizure or first unprovoked generalized seizures)
b. Newly identified change in seizure activity/pattern not otherwise explained.
c. Medically refractory epilepsy
d. Preoperative evaluation when surgery being considered
e. Seizure in child younger than 2 years, excluding those with febrile seizures

IV. **Evaluation of movement disorders** – **Not indicated for **typical** Parkinson's Disease, essential tremor, primary dystonia, restless leg syndrome, or tics/spasms which can be duplicated at will*
a. Evaluation of suspected Parkinson's with atypical feature(s) or unresponsive to levodopa
b. Evaluation of new non-Parkinson symptoms in known Parkinson's disease complicating the evaluation of the current condition
c. Evaluation of other movement disorder to exclude a structural lesion (e.g., suspected Huntington disease, chorea, atypical parkinsonian syndromes, hemiballismus, secondary dystonia)
d. Prior to surgery or deep brain stimulation in patient with known Parkinson disease

V. **Evaluation of new or acutely worsened cognitive impairment with unclear cause (to rule out large frontal tumor or frontal stroke). Not indicated if the patient has a classic Alzheimer 's history of several years of progressive decline. CT may be sufficient if MRI cannot be done. Must meet ALL of the following:**
a. Change in mental status with a mental status score of either Mini-Mental State Exam (MMSE) or Montreal Cognitive Assessment (MoCA) of less than 26 or other similar mental status instruments showing at least mild cognitive impairment **AND**
b. A completed medication review and exclusion of medical causes (e.g., thyroid function testing, liver function testing, complete blood count, electrolytes, and B12) without cause found

VI. **Evaluation of known or suspected inflammatory disease or infection** (e.g., meningitis or abscess) for **1 of the following:**
a. Intracranial abscess or brain infection with acute altered mental status OR positive lab findings (such as elevated WBC's) OR follow up assessment during or after treatment completed
b. Meningitis with positive signs and symptoms (such as fever, headache, mental status changes, stiff neck) OR positive lab findings (such as abnormal lumbar puncture fluid exam)
c. Suspected encephalitis with a headache, altered mental status OR positive lab finding, (such as elevated WBC's)
d. Endocarditis with suspected septic emboli
e. Central nervous system (CNS) involvement in members with known or suspected vasculitis or autoimmune disease with positive lab findings

VII. **Evaluation of vertigo/dizziness** *All patients should have full neurologic examination, medication review, orthostatic vitals, and Dix-Hallpike test for peripheral vertigo prior to consideration of MRI.
MRI can be considered appropriate if **1 or more** of the following signs or symptoms suggestive of a CNS lesion:
a. Brainstem findings (e.g., dysarthria, Horner syndrome, double vision, vertical nystagmus) **OR**
b. Cerebellar findings (e.g., ataxia/incoordination of voluntary movements, intention tremor, disorder of equilibrium or gait, diminished muscle tone) **OR**
c. Focal neurologic findings (e.g., weakness, numbness, paresthesia's on one side of body) **OR**

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d. Acute or rapidly progressing unilateral hearing loss

VIII. **Evaluation of syncope, with 1 or more of the following:**
a. Concurrent bowel or bladder incontinence
b. Witnessed tonic-clonic seizure
c. Strong clinical suspicion of symptomatic third ventricular cyst

IX. **Precocious puberty** (central), as indicated by **ALL of the following**:
a. Clinical findings suggestive of central precocious puberty
b. Patient has been evaluated by pediatric endocrinologist

X. Global developmental delay or developmental delay with abnormal neurological examination (initial evaluation)

XI. Other indications for a brain MRI
a. Multiple sclerosis – known or strong clinical suspicion after discussion with neurology
   i. Frequency after diagnosis: annually to monitor for new lesions or following clinical flare up
b. Trauma to the head with acute, new, or fluctuating neurologic findings
c. Brain tumor, mass, or metastasis – known or strong clinical suspicion based on history and physical exam
d. Routine surveillance of previously diagnosed brain tumor based on treatment plan from neuroscience specialty or oncology
e. Initial evaluation of stroke/TIA
f. Evaluation of known or suspected congenital abnormality with any acute, new, or fluctuating neurologic, motor, or mental status changes (hydrocephalus, craniosynostosis)
g. Evaluation of suspected acute subarachnoid hemorrhage (SAH) if CT scan is non-diagnostic
h. Evaluation of known or suspected cerebrospinal fluid (CSF) leakage
i. Follow-up of a recent brain hemorrhage to check for underlying tumor or AVM
j. Immunocompromised member (e.g., transplant recipients, HIV with CD4 < 200, primary immunodeficiency syndromes, hematologic malignancies) with focal neurologic symptoms, headaches, behavioral, cognitive, or personality changes
k. Pre-operative evaluation for brain/skull surgery, stereotactic radiosurgery
l. Post-operative/procedural evaluation - A follow-up study may be needed to help evaluate a member's progress after treatment, procedure, intervention or surgery. Documentation requires a medical reason that clearly indicates why additional imaging is needed for the type and area(s) requested
m. Suspected acoustic neuroma include IAC protocol (to ensure that imaging looks in detail at that part of the anatomy)
n. Anatomy or structural defect evaluation – e.g., when Chiari malformation is clinically suspected
o. Suspected intracranial vasculitis
p. Evaluation of neurological signs or symptoms in sickle cell disease
q. Unexplained acute unilateral hearing loss after other reasonable causes ruled out
r. Optic neuritis – consider orbit MRI in addition to brain MRI
s. Abnormal eye findings on physical or neurologic examination (e.g., papilledema, pathologic nystagmus, ocular nerve palsies, new onset anisocoria, visual field deficit)
t. Horner's syndrome with symptoms localizing the lesion to the central nervous system
u. Trigeminal neuralgia if medication is not effective or if atypical features/exam (e.g., bilateral, hearing loss, dizziness/vertigo, visual changes, sensory loss, numbness, pain >2 min, pain outside trigeminal nerve distribution, progression)
v. Bell's palsy - only if atypical signs, or no improvement at four months, or facial twitching/spasms prior to onset
w. Psychological changes with neurological deficits on exam or after completion of a full neurological assessment by a neurologist that suggests a possible neurologic cause
x. Multiple cranial neuropathies.

If requesting this service (*or these services*), please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist

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Background

MRI can detect a variety of conditions of the brain such as cysts, tumors, bleeding, swelling, developmental and structural abnormalities, infections, inflammatory conditions, or problems with the blood vessels. It can determine if a shunt is working and detect damage to the brain caused by an injury or a stroke.

MRI of the brain can be useful in evaluating problems such as persistent headaches, dizziness, weakness, and blurry vision or seizures, and it can help to detect certain chronic diseases of the nervous system, such as multiple sclerosis.

In some cases, MRI can provide clear images of parts of the brain that can't be seen as well with an X-ray, CAT scan, or ultrasound, making it particularly valuable for diagnosing problems with the pituitary gland and brain stem.

Applicable Codes

Non-Medicare - Considered Medically Necessary when criteria in the applicable policy statements listed above are met
Medicare – Medical Necessity Review not required

CPT® or HCPCS Codes	Description
70551	Magnetic resonance (eg, proton) imaging, brain (including brain stem); without contrast material
70552	Magnetic resonance (eg, proton) imaging, brain (including brain stem); with contrast material(s)
70553	Magnetic resonance (eg, proton) imaging, brain (including brain stem); without contrast material, followed by contrast material(s) and further sequences

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed	Date Last Revised
02/01/2022	02/01/2022[MPC],02/07/2023[MPC]	

[MPC] Medical Policy Committee

Revision History	Description
02/01/2022	MPC approved to adopt criteria for Brain MRI for non-Medicare members. Requires 60-day notice, effective date 07/01/2022.

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KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Breast MRI with and without Computer-Aided Detection (CAD)

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Magnetic Resonance Imaging (MRI) (220.2)
Local Coverage Determinations (LCD)	None
Local Coverage Article	None
KPWA Medical Policy	Due to the absence of a NCD, LCD, or other coverage guidance specific to breast MRI, KPWA has chosen to use their own Clinical Review Criteria for ***indications for breast MRI***, for medical necessity determinations. Use the Non-Medicare criteria below.

Effective until November 1, 2023

For Non-Medicare Members

I. Breast MRI may be indicated for **One or more of the following**:
   A. Breast abnormality evaluation needed, as indicated by **One or more of the following**:
      Note: If an area of distortion is found on mammography, a breast ultrasound should be the next step to confirm. If breast ultrasound shows a correlate, that area can then be biopsied under ultrasound guidance. If a breast ultrasound biopsy cannot be done of the area for some reason or is unsuccessful, and tomosynthesis guided or stereotactic guided breast biopsy is also not an option, consultation with a breast surgeon is recommended. MRI is not indicated in this situation.
      1. A single 6-month MRI for f/u if requested by the radiologist who attempted or performed the original MRI guided biopsy
      2. Breast MRI is covered for members with suspected silicone (not saline) implant leaks or rupture when **ALL** of the following have been met:
         a. Implants were placed as a result of **ONE of the following**:
            - Medically necessary lumpectomy or complete or partial mastectomy due to disease, injury or illness (such as breast cancer, chronic and severe fibrocystic disease, or infection unresponsive to medical therapy, chest wall surgery, or trauma) resulting in significant deformity;
            - Prophylactic mastectomy to prevent the onset of breast cancer when a clinical determination has been made that there is a high risk for breast cancer
         b. Records must document need for this test for evaluation and management
         c. A recent mammogram and/or ultrasound (depending on local breast center protocol) does not confirm leakage
         d. The leakage is not the result of a cosmetically placed implant as this would be a complication of a non-covered service
         e. It is not being requested for routine surveillance of a silicone implant

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B. Breast cancer diagnosis (new within the last 3 months) and **ONE or more** of the following:

1. After positive nipple-areolar biopsy for Paget disease, to define extent of disease and identify additional disease
2. Assessment of tumor response to neoadjuvant (preoperative) chemotherapy to determine appropriateness of breast-conserving surgery to assist with surgical planning
3. Evaluation of a newly diagnosed invasive breast cancer (e.g., lobular, ductal) (see below**).
4. Evaluation of a newly diagnosed DCIS and there is documentation that the patient is requesting breast conserving surgery (see below**).
5. Post lumpectomy, (within 6 weeks) for assessment of residual disease with the finding of close or positive margins on pathology.

C. Occult breast cancer, suspected (e.g., unknown primary), as indicated by **ALL of the following**:
1. Diagnosis of adenocarcinoma or carcinoma not otherwise specified in **ONE or more of the following**:
   a. Axillary lymph nodes
   b. Supraclavicular lymph nodes
2. Mammogram and breast ultrasound show no evidence of cancer.
3. No palpable breast mass suitable for biopsy

D. Annual MRI for breast cancer screening for **One or more of the following**:

Not indicated for patients who have undergone bilateral mastectomy for risk reduction or for treatment.

1. A lifetime risk of 20% or greater, as defined by validated models such as the following models: Tyrer-Cuzick, Gail Model, BRCAPro, Claus.
   a. The specific risk model must be documented in the clinical notes
   b. If member has had breast or ovarian cancer diagnosed after age 50, calculate the risk *prior* to the diagnosis
2. BRCA1 or BRCA2 mutation carrier
3. Personal history of radiation to chest between ages 10 and 30 years
4. Annual MRI is indicated for individual with a personal history of breast cancer (including DCIS), diagnosed at or before age 50 and treated with breast conservation therapy of the affected breast (lumpectomy). Patients treated with mastectomy (unilateral or bilateral) would not routinely qualify.
5. Other high-risk family history of breast cancer, as indicated by **ONE or more of the following**:
   - Male relative with breast cancer
   - Untested first-degree relative [A*] of BRCA1 or BRCA2 mutation carrier
   - Woman not of Ashkenazi Jewish ancestry, with **ONE or more of the following**:
     i. First-degree [A*] or second-degree [B*] relative with breast cancer and **ONE or more of the following**:
        - Diagnosed at age 45 years or younger
        - Diagnosed at age 50 years or younger, with limited family history [C*]
        - Diagnosed at age 50 years or younger, who in turn has one or more close blood relatives [D*] with breast cancer, with at least one diagnosed at age 50 years or younger (29)
        - Diagnosed at age 50 years or younger, who in turn has one or more close blood relatives [D*] with epithelial ovarian [E*] cancer diagnosed at any age
        - Diagnosed at age 60 years or younger, with triple-negative breast cancer [F*]
        - Epithelial ovarian [E*] cancer
   - First-degree [A*] or second-degree [B*] relative with 2 breast primaries, with the first primary diagnosed at age 50 years or younger
   - First-degree [A*] or second-degree [B*] relative with breast cancer diagnosed at any age, who in turn has **One** or more of the following:
     i. Two or more close blood relatives [D*] with breast or epithelial ovarian [E*] cancer diagnosed at any age
     ii. One or more close male blood relatives [D*] with breast cancer

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- First-degree [A] or second-degree relative [B*] with breast cancer who is of ethnicity associated with deleterious mutations, including Icelandic, Hungarian, Swedish, and Dutch
- First-degree [A*] or second-degree relative [B*] with breast or ovarian cancer diagnosed at any age, who in turn has 2 or more close blood relatives [D*] with pancreatic cancer diagnosed at any age

a. First-degree [A*] or second-degree relative [B*] with pancreatic cancer diagnosed at any age, who in turn has 2 or more close blood relatives [D*] with ONE or more of the following:
   - Breast cancer diagnosed at any age
   - Ovarian cancer diagnosed at any age
   - Pancreatic cancer diagnosed at any age

b. Third-degree relative [H*] with breast or epithelial ovarian [E*] cancer, who in turn has **ONE or more of the following**:
   - One close blood relative [D*] with epithelial ovarian [E*] cancer and another close blood relative [D*] with breast cancer diagnosed at age 50 years or younger
   - Two or more close blood relatives [D*] with breast cancer, with at least one diagnosed at age 50 years or younger
   - Two or more close blood relatives [D*] with epithelial ovarian [E*] cancer

c. Woman of Ashkenazi Jewish ancestry, with **One or more of the following**:
   - One or more first-degree relatives [A*] with breast cancer or epithelial ovarian cancer
   - Two or more second-degree relatives, [B*] on same side of family, [I*] with breast cancer
   - Two or more second-degree relatives, [B*] on same side of family, [I*] with epithelial ovarian cancer

d. Patient has diagnosis of, or has first-degree relative [A] with, **One or more of the following**:
   - Bannayan-Riley-Ruvalcaba syndrome
   - Cowden syndrome
   - Li-Fraumeni syndrome

Effective November 1, 2023

I. Breast MRI may be indicated for **ONE or more of the following**:

A. Breast abnormality evaluation needed, as indicated by **ONE or more of the following**:
Note: If an area of distortion is found on mammography, a breast ultrasound should be the next step to confirm. If breast ultrasound shows a correlate, that area can then be biopsied under ultrasound guidance. If a breast ultrasound biopsy cannot be done of the area for some reason or is unsuccessful, and tomosynthesis guided or stereotactic guided breast biopsy is also not an option, consultation with a breast surgeon is recommended. MRI is not indicated in this situation.

1. A single 6-month MRI for f/u if requested by the radiologist who attempted or performed the original MRI guided biopsy
2. Breast MRI is covered for members with suspected silicone (not saline) implant leaks or rupture when **ALL** of the following have been met:
   a. Implants were placed as a result of **ONE of the following**:
      - Medically necessary lumpectomy or complete or partial mastectomy due to disease, injury or illness (such as breast cancer, chronic and severe fibrocystic disease, or infection unresponsive to medical therapy, chest wall surgery, or trauma) resulting in significant deformity;
      - Prophylactic mastectomy to prevent the onset of breast cancer when a clinical determination has been made that there is a high risk for breast cancer
   b. Records must document need for this test for evaluation and management
   c. A recent mammogram and/or ultrasound (depending on local breast center protocol) does not confirm leakage
   d. The leakage is not the result of a cosmetically placed implant as this would be a complication of a non-covered service
   e. It is not being requested for routine surveillance of a silicone implant
3. Nipple Discharge, a breast MRI is indicated when **ALL of the following** conditions are met:
   a. Discharge is clear or bloody
   b. Discharge is unilateral and coming from a single duct
   c. Discharge is spontaneous (i.e., does not happen only with expression) and persistent (i.e., not a single episode)

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d. Discharge is reproducible on exam
e. Mammography and ultrasound have been completed and did not detect a pathologic etiology. *If mammography, ultrasound or ductography were done, and was abnormal, MRI would not be indicated

B. Breast cancer diagnosis (new within the last 3 months) and **ONE or more** of the following:

1. After positive nipple-areolar biopsy for Paget disease, to define extent of disease and identify additional disease
2. Assessment of tumor response to neoadjuvant (preoperative) chemotherapy to determine appropriateness of breast-conserving surgery to assist with surgical planning
3. Evaluation of a newly diagnosed invasive breast cancer (e.g., lobular, ductal) (see below**).
4. Evaluation of a newly diagnosed DCIS and there is documentation that the patient is requesting breast conserving surgery (see below**).
5. Post lumpectomy, (within 6 weeks) for assessment of residual disease with the finding of close or positive margins on pathology.

C. Occult breast cancer, suspected (e.g., unknown primary), as indicated by **ALL of the following**:
1. Diagnosis of adenocarcinoma or carcinoma not otherwise specified in **ONE or more of the following**:
   a. Axillary lymph nodes
   b. Supraclavicular lymph nodes
2. Mammogram and breast ultrasound show no evidence of cancer.
3. No palpable breast mass suitable for biopsy

D. Annual MRI for breast cancer screening for **One or more of the following**:

Not indicated for patients who have undergone bilateral mastectomy for risk reduction or for treatment.

1. A lifetime risk of 20% or greater, as defined by validated models such as the following models: Tyrer-Cuzick, Gail Model, BRCAPro, Claus.
   a. The specific risk model must be documented in the clinical notes
   b. If member has had breast or ovarian cancer diagnosed after age 50, calculate the risk *prior* to the diagnosis
2. Carrier of high-risk[A] breast cancer gene mutation (including but not limited to: BRCA1, BRCA2, CDH1, PALB2, PTEN, STK11, TP53)
3. Personal history of radiation to chest between ages 10 and 30 years
4. Annual MRI is indicated for individual with a personal history of breast cancer (including DCIS), diagnosed at or before age 50 and treated with breast conservation therapy of the affected breast (lumpectomy). Patients treated with mastectomy (unilateral or bilateral) would not routinely qualify.
5. Other high-risk family history of breast cancer, as indicated by **ONE or more of the following**:
   - Male relative with breast cancer
   - Untested first-degree relative [A*] of BRCA1 or BRCA2 mutation carrier
   - Woman not of Ashkenazi Jewish ancestry, with **ONE or more of the following**:
     ii. First-degree [A*] or second-degree [B*] relative with breast cancer and **ONE or more of the following**:
     - Diagnosed at age 45 years or younger
     - Diagnosed at age 50 years or younger, with limited family history [C*]
     - Diagnosed at age 50 years or younger, who in turn has one or more close blood relatives [D*] with breast cancer, with at least one diagnosed at age 50 years or younger (29)
     - Diagnosed at age 50 years or younger, who in turn has one or more close blood relatives [D*] with epithelial ovarian [E*] cancer diagnosed at any age
     - Diagnosed at age 60 years or younger, with triple-negative breast cancer [F*]
     - Epithelial ovarian [E*] cancer

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- First-degree [A*] or second-degree [B*] relative with 2 breast primaries, with the first primary diagnosed at age 50 years or younger
- First-degree [A*] or second-degree [B*] relative with breast cancer diagnosed at any age, who in turn has **One** or more of the following:
  i. Two or more close blood relatives [D*] with breast or epithelial ovarian [E*] cancer diagnosed at any age
  ii. One or more close male blood relatives [D*] with breast cancer
- First-degree [A] or second-degree relative [B*] with breast cancer who is of ethnicity associated with deleterious mutations, including Icelandic, Hungarian, Swedish, and Dutch
- First-degree [A*] or second-degree relative [B*] with breast or ovarian cancer diagnosed at any age, who in turn has 2 or more close blood relatives [D*] with pancreatic cancer diagnosed at any age

a. First-degree [A*] or second-degree relative [B*] with pancreatic cancer diagnosed at any age, who in turn has 2 or more close blood relatives [D*] with ONE or more of the following:
   - Breast cancer diagnosed at any age
   - Ovarian cancer diagnosed at any age
   - Pancreatic cancer diagnosed at any age

b. Third-degree relative [H*] with breast or epithelial ovarian [E*] cancer, who in turn has **ONE or more of the following**:
   - One close blood relative [D*] with epithelial ovarian [E*] cancer and another close blood relative [D*] with breast cancer diagnosed at age 50 years or younger
   - Two or more close blood relatives [D*] with breast cancer, with at least one diagnosed at age 50 years or younger
   - Two or more close blood relatives [D*] with epithelial ovarian [E*] cancer

c. Woman of Ashkenazi Jewish ancestry, with **One or more of the following**:
   - One or more first-degree relatives [A*] with breast cancer or epithelial ovarian cancer
   - Two or more second-degree relatives, [B*] on same side of family, [I*] with breast cancer
   - Two or more second-degree relatives, [B*] on same side of family, [I*] with epithelial ovarian cancer

d. Patient has diagnosis of, or has first-degree relative [A] with, **One or more of the following**:
   - Bannayan-Riley-Ruvalcaba syndrome
   - Cowden syndrome
   - Li-Fraumeni syndrome

* See below for the definition:
A - First-degree relatives consist of male or female parents, siblings, or children
B - Second-degree relatives consist of male or female grandparents, grandchildren, aunts, uncles, nieces, nephews, or half- siblings
C - Examples of a limited family history include fewer than 2 first-degree or second-degree female relatives or fewer than 2 female relatives in either maternal or paternal ancestry surviving beyond 45 years of age. (
D - Close blood relatives include first-degree, second-degree, or third-degree relatives on the same side of the family
E - A triple-negative breast cancer is one that is estrogen receptor-negative, progesterone receptor-negative, and human epidermal growth factor receptor 2-negative
F - Two primaries may be either bilateral disease or 2 or more clearly separate ipsilateral tumors, either synchronous or asynchronous
H - Third-degree relatives consist of first cousins, great-aunts, great-uncles, great-grandchildren, or great-grandparents
I - Each side of the family, maternal or paternal, should be considered independently

**Ideally, this should be ordered after discussion with the patient about risks and benefits or per recommendation of a multidisciplinary care conference, if available.

"Don't routinely order breast MRI in new breast cancer patients." per The American Society of Breast Surgeons Choosing Wisely initiative:

After a new diagnosis of breast cancer, breast MRI can be useful in selected patients to aid treatment decisions. However, there is a lack of evidence that routine use of MRI lessens cancer recurrence, death from cancer or the need for re-operation after lumpectomy surgery. The routine use of MRI is associated with an increased need for subsequent breast biopsy

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procedures, delays in time to treatment and higher cost of care. Increased mastectomy rates can occur if the MRI finds additional cancers or indeterminate findings cause patient anxiety, leading to patient requests for mastectomy.

(https://www.choosingwisely.org/clinician-lists/breast-surgeons-mris-in-new-breast-cancer-patients/)

Routine Surveillance of Silicone Breast Implants
Breast MRI is not covered for routine surveillance of silicone breast implants. The FDA made a recommendation (not a requirement) when they re-approved silicone implant use that members receive periodic breast MRIs. The FDA did not fund this screening. The choice of silicone vs saline is a patient preference and the use of MRI in this case cannot be described as medically necessary.

Computer-aided detection applied to breast MRI
No longer requires review

If requesting this service, please send the following documentation to support medical necessity:

- Documentation to support medical necessity (i.e., family history, prior treatment, genetic testing results, other imaging studies and diagnostic results, etc.)
- Applicable CPT code(s)

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Background

Breast Cancer Screening and Lesions:
Mammography has been the standard tool used for breast cancer imaging. Community breast cancer screening programs have found an overall sensitivity of 75% and a specificity of 92%. The sensitivity of mammography in randomized trials is in the range of 68-88% (Elmore et al., 2005).

Due to limitations in the sensitivity of mammography, there has been research into alternative imaging modalities, particularly for women at high-risk of breast cancer. Interest in more accurate screening tests has grown since the identification of the BRCA1 and BRCA2 genes in the mid-1990s. Population-based studies have found that women with BRCA1 mutations have a approximately a 65% risk of developing breast cancer by age 70, and women with BRCA2 mutations have a 45% risk (Saslow et al., 2006). Mammography may not be adequate for detecting breast cancer in women with the BRCA1/2 mutation. In a study of BRCA1/2 mutation carriers who underwent annual mammography, screening detected only 5 out of 9 cases of breast cancer; the remaining were interval cancers (Brekelmans et al., 2001).

Contrast-enhanced magnetic resonance imaging (MRI) is proposed as an adjunct to mammography for women at high-risk of breast cancer. Breast MRI involves the injection of a contrast agent, usually gadolinium. Breast carcinomas tend to enhance, or get brighter, following injection of the contrast agent. MRI may be able to detect small breast lesions missed by mammography. However, contrast-enhanced MRI may not be able to distinguish between breast carcinoma and benign disease which also enhance, thus reducing the specificity of MRI.

The American Cancer Society (ACS) issued guidelines in May 2007 on breast screening with MRI as an adjunct to mammography (Saslow et al., 2007). The recommendations include:

- Annual screening for women with a lifetime risk of ≥20-25%, BRCA mutation or untested first-degree relative of BRCA carrier.
- No recommendation for or against screening women with a lifetime risk of 15-20%.
- Recommendation against screening women with <15% lifetime risk due to insufficient evidence.

The ACS recommends the BRCAPRO or other model largely dependent on family history be used to determine lifetime risk. BRCAPRO is a computer program on a statistical model for estimating an individual's probability of carrying a BRACA1/2 mutation on the basis of their own cancer status, and the history of breast and ovarian cancer among her first- and second-degree relatives (Berry et al., 2002). Other risk models, such as the Gail model risk calculator, which is also based on family history, may be easier to use in the primary care setting. An individual's risk level may vary with the different models (Saslow et al., 2007).

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The Kaiser Permanente breast clinic already generally recommends MRI screening for women with known BRCA mutations, who are a first-degree relative of a BRCA carrier but are untested or have a 30-49% lifetime risk.

Silicone Implant Leakage:
Silicone-gel breast implants were first available for commercial use in the early 1960s. It is estimated that 1.5 to 2 million women in the United States have received an artificial breast implant, and the number is growing. Almost four-fifths of these women received the implant for cosmetic purposes to enhance or remodel breast shape, or to correct traumatic or congenital deformities. In only 20% of the cases they received it for breast reconstruction after mastectomy. At least three major generations and over 200 models of silicone gel-filled breast implants have been manufactured. The differences between the generations are primarily in the types of silicone gel and thickness of elastometric shell. The first generation of silicone gel-filled implants (early 1960s to the mid 1970s) had a thick elastometric shell with firm silicone gel. The second generation (mid 1970s to late 1980s) had a thin elastometric shell, and a less viscous gel. The third generation (mid 1980s to date) has a multilayer shell with a barrier layer and thick cohesive viscous silicone gel. In 1993 a newer generation of highly cohesive silicone implants (Style 410) was developed, however it is widely used in Europe and other countries, but not in the US (Brown 2002, Belli 2002, Scaranelo 2004, Gamper 2007, Gorczyca 2007).

Silicone implants may have psychological benefits but could be associated with local complications and systemic effects. Local implant-related complications include wound infection, hematomas, sensory nerve injury, capsular contracture, and implant rupture. The latter is a well-known complication and could range from focal rupture involving pinhole sized holes, through large visible tears, to complete disintegration of the implant shell. Implant rupture can be divided into two major categories: intracapsular (80-90% of all ruptures) and extracapsular. Unlike rupture, gel bleed is microscopic escape of silicone particles through the intact silicone envelope, in the absence of gross holes or tears. This is usually confined to the fibrous capsule that forms around the implant. Implant age, and design were found to be the most important factors associated with rupture. Other potential causes of rupture include trauma, mammography, and history of closed capsulotomy. The age of implant at rupture varied between reports between 4 and 22 years, with means also varying between studies from 11 to 16 years (Cher 2001, Samuels 1994, Gorczyca 2007).

Silicone gel-implant rupture may be clinically silent and pass unnoticed by the patient and the physician. It could remain undetected for years especially when it is contained within the fibrous capsule. A symptomatic rupture may present with local symptoms as breast pain, nodules, capsular contracture, and change in symmetry, size, or shape of the breast. Silicone gel granulomas and chronic disseminated granulomatous inflammation have been associated with implant rupture and gel migration. The potential health implications of silicone implant rupture are greatly debated. Some researchers reported that seepage of silicone and distant migration of the free silicone may lead to serious symptoms and foreign body reactions. Others indicated that it is harmless and does not lead to significant clinical symptoms or activate the humoral immune system (Ahn 2003, Holmich 2004, Gampper 2007).

The clinical diagnosis of asymptomatic implant rupture can be challenging. It was reported that less than one third of ruptures in asymptomatic patients can accurately be detected by experienced plastic surgeons. The gold standard for diagnosing an implant rupture is removal and examination of the implant. Mammography, ultrasonography, computed tomography, and magnetic resonance imaging have all been used in the diagnosis of silicone breast implant rupture. Each was reported to have its specific indications, advantages, and limitations. The type of silicone implant may also be a factor in choosing the modality for evaluating its integrity.

Mammography is a rapid inexpensive test, used routinely for screening, and can easily detect free silicone within the breast parenchyma due to extracapsular rupture. It, however, has a small radiation risk, and limited ability to detect intracapsular rupture which accounts for 80-90% of implant failures. The dense silicone is not easily penetrated by the X-ray energies used for typical screening mammography (Samuels 1994, Gampper 2007, Gorczyca 2007).

Ultrasonography is inexpensive, does not use ionizing radiation, can detect intracapsular rupture, and may also detect small amounts of free silicone mixed within the surrounding breast tissues. However, its usefulness for detecting implant rupture depends on the experience of the operator, type of equipment used, as well as other technical factors. It was also reported that ultrasonography may have its limitations in the evaluation of the posterior aspect of the implant, pectoralis muscle and chest wall (Belli 2002, Gorczyca 2007).

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MRI does not use ionizing radiation, has the ability to detect implant rupture, and to localize extensive free silicone. It can also be used with severe capsular contracture. Specialized breast coils increase the image quality and reduce scan time. However, it was reported that MRI cannot detect microscopic silicone leakage (gel bleeds). It is expensive, less available, less comfortable for the patient, and cannot be used among those with pacemakers, or other internal metallic devices that are not compatible with the MRI. Some patients may be claustrophobic and are unable to complete the examination (Beekman 1999, Gorczyca 2007, Gampper 2007)

FDA recommends MRI, with a dedicated breast coil and a magnet of at least 1.5 Tesla, as the current method of choice for detecting silent rupture of silicone gel implant. This is recommended to be performed three years after the implant, then every 2 years thereafter. The FDA also recommends the removal of ruptured breast implants.

With Computer-Aided Detection (CAD):
(Background information quoted from Blue Cross Blue Shield Association Technology Evaluation Center, BCBSA TEC report, June 2006)

Over the past decade, MRI of the breast has been studied in a variety of clinical settings, including both benign and malignant conditions of the breast…While MRI has a very high sensitivity for detecting lesions, its specificity is variable and often quite low because of the difficulty in distinguishing between benign and malignant lesions. The sensitivity for detection of invasive carcinoma overall is above 90%, while specificities between 37% and 90% have been reported (Deurloo et al. 2005a). The low specificity is particularly challenging in younger women, who are more likely to have enhancing benign lesions (Gilhuijs et al., 2002) …

Some investigators have incorporated additional criteria into the determination of MRI results in an attempt to increase the specificity without compromising sensitivity (Liberman 2004; Nunes et al. 2001). Descriptive features of lesion morphology such as those used in X-ray mammography may be helpful in this regard. For example, lesions with irregular or spiculated margins are characteristically malignant, while lesions with smooth, regular margins are usually benign (Nunes et al. 1997a) …CAD systems for MRI… provide easier ways of interpreting the patterns of contrast enhancement and washout across a series of images, which in turn may help identify lesions and their likelihood of being malignant. In contrast to CAD systems used with mammography, CAD for MRI is not aimed primarily at identifying lesions for consideration by a radiologist. Unlike the subtle appearance of lesions on mammography, most cancers enhance on MRI. The challenge is determining which lesions are benign and which are malignant. A large number of images are produced during MRI of the breast: images are taken at varying 'depths' throughout each breast multiplied by the number of times the breast is imaged to capture different time points in the enhancement process… Radiologists view the images to detect suspicious areas, and then they can pick a region of interest and look at the enhancement pattern. However, there may be variations across radiologists in the regions of interest selected and in the precise definition of the region of interest. CAD systems, in contrast, use color-coding and differences in hue to indicate the patterns of enhancement for each pixel in the breast image. It thereby may allow the radiologist to analyze the enhancement patterns systematically, although there is some question about how effective it is in reducing interobserver variability (Gabriel et al. 2005). Some CAD programs apparently incorporate morphological characteristics as well to estimate a probability of malignancy…"

There are several FDA-approved CAD systems for use with MRI of the breast. These include:

- CADstream (Confirma, Inc. Kirkland, WA). Originally cleared in 2003. CADstream version 4.0 was cleared in 2008.
- MRI Soft Tissue Motion Correction Software (Siemens Medical Solutions. Malvern, PA). Cleared September 2005.
- Z3D (Clario Medical Imaging): Cleared September 2008.

Medical Technology Assessment Committee (MTAC)

MRI in the Diagnosis of Breast Cancer and Breast Lesion

02/13/2002: MTAC REVIEW

Evidence Conclusion: All studies reviewed were retrospective, had several limitations, and data were obtained from records. Tan's study showed that MRI had an impact on the clinical management in almost one fifth of the patients. MRI findings were false positive among 61.5 % of the patients who underwent an additional surgery, which was a mastectomy in one case. Olson's study showed that MRI had a sensitivity of 95%, and specificity of 80%. These were based on data obtained from patients who underwent additional breast surgery, not all the sample. The clinical usefulness of a diagnostic test depends not only on its accuracy but also its reliability i.e. the consistency of interpretation on different occasions and by different observers. Mussurakis' study shows that all

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readers achieved a high sensitivity in cancer detection, their specificity however was much lower. The study also revealed a significant inter-observer variability in the interpretation of breast MRI. The high false positive rates, i.e. low specificity, and high inter-observer variability indicate that MRI, with its current limitations, is not an accurate or a reliable technology, compared to the gold standard of biopsy. Randomized trials, with a large study population will be required to confirm the findings and define the patients most likely to benefit from MRI. Moreover, further efforts are needed to improve, and standardize the indications, techniques, and image interpretation.
Articles: The search yielded 63 articles. Selection was based on study type. The majority were reviews, editorials, letters, and commentaries. The literature did not reveal any randomized controlled trials or longitudinal studies.
The following articles were selected for critical appraisal: Tan J E, Schnall M D, et al. Role of magnetic resonance imaging and magnetic resonance imaging-guided surgery in the evaluation of patients with early-stage breast cancer for breast conservation treatment. *Am J Clin Oncol* 1999; 22(4): 414-18 See Evidence Table. Olson JA, Morris EA, et al. Magnetic resonance imaging facilitates breast conservation for occult breast cancer. *Annals of Surgical Oncology* 2000; 7(6): 411-15 See Evidence Table. Mussurakis S et al. Observer variability in the interpretation of contrast enhanced MRI of the breast. *The British Journal of Radiology*1996; 69: 1009-16. See Evidence Table.

The use of MRI in the diagnosis of breast cancer and breast lesions does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

06/04/2007: MTAC REVIEW
MRI in the Diagnosis of Breast Cancer and Breast Lesion
Evidence Conclusion: The major prospective studies comparing screening asymptomatic women at moderate-to-high risk of breast cancer with MRI and mammography are summarized in Table 1. All of these studies were judged to be of reasonable validity. All studies were prospective and eligibility criteria included an assessment of risk based on genetic and family history factors. In addition, all of the studies included an independent evaluation of MRI and mammograms. The gold standard was biopsy/histology for positive tests in all studies. Gold standards for negative tests varied. Most studies used 1-year follow-up of negative tests to identify false negatives; Kuhl et al., 2005 used 6 months' follow-up. The Lehman et al., 2005 study was the weakest for several reasons. This is the only study in which the authors did not attempt to verify the accuracy of negative tests. In addition, only 4 cases of cancer were identified, a number too small for statistical analysis. The absolute difference in the breast cancer detection rate between combined testing with MRI and mammography and mammography alone ranged from 1% (Kriege et al., 2004) to 5% (Warner et al., 2004; Kuhl et al. 2005). The Kriege study included moderate-to-high risk women (≥15% lifetime risk) whereas the other two studies included only high-risk women. None of the studies reported whether the difference in the breast cancer detection rate with MRI plus mammography versus mammography alone was statistically significant. The recall rate (proportion of women called back for follow-up testing) ranged from 4% to 8% higher with MRI screening than with mammography-alone screening. None of the studies reported the recall rate with combined screening, but this would likely reflect the higher MRI rates. The sensitivity and specificity of combined screening with MRI and mammography versus mammography alone was reported in two studies. Leach et al., 2005 found a higher sensitivity with combined screening (94% versus 40%) and a lower specificity (77% versus 93%). Kuhl et al. (2005) also found a higher sensitivity with combined testing than mammography alone (93% versus 33%) and similar levels of specificity with the two methods (96% and 97%). Neither study reported p-values for the difference in sensitivity and specificity. The Kuhl et al., 2005 study did a sub-analysis by level of risk (see Table 2). The risk categories were moderate-risk (20% lifetime risk) and high-risk (21-40% lifetime risk). The sensitivity of combined screening was 100% in both the moderate and high-risk groups. This was substantially higher than the sensitivity with mammography alone, 50% for the moderate risk group and 25% for the high-risk group. Specificities of combined screening and mammography alone were similar for both risk levels. This analysis is limited in that it is based on a small number of cancer cases, only 6 for the moderate-risk group. This results in imprecise and unreliable statistics and should be viewed as preliminary data. For example, mammography correctly detected 3/6 cancers (50%); if only one additional cancer had been identified, the sensitivity would be dramatically altered to 4/6 (67%). Conclusion There is no high-grade evidence on whether combined screening with MRI and mammography improves health outcomes such as breast cancer mortality or overall mortality. The available evidence from 6 prospective studies suggests that combined screening of asymptomatic women at moderate-to-high risk of breast cancer with MRI plus mammography results in a 1-5% absolute increase in the cancer detection rate over mammography alone. The recall rate is substantially higher with MRI alone (4-8%) and would thus be higher with combined screening. Findings of 2 prospective studies are that combined screening substantially improves sensitivity compared to mammography alone and may decrease specificity. Data on women at moderate risk of breast cancer (≤20% lifetime risk) are insufficient to draw conclusions about detection rate or diagnostic accuracy.
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Articles: There were no randomized or non-randomized controlled trials that compared health outcomes in high-risk women who received screening with mammography alone versus screening with mammography plus MRI. As reported in the American Cancer Society review (Saslow et al., 2007), there were 6 published prospective studies examining diagnostic yield and/or sensitivity/specificity of mammography compared to MRI for asymptomatic women at moderate-to-high risk of breast cancer. These 6 studies were critically appraised and presented in a joint evidence table. The Kaiser Permanente national breast cancer screening guideline included the topic of breast MRI screening for high-risk women. They identified additional observational studies comparing mammography to MRI. These studies were not included in the MTAC review due to methodological limitations such as a retrospective design, small sample size or only a minority of the study population underwent MRI screening. *The studies reviewed include:* Kriege M et al. for the MRI Screening Study Group. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. NEJM 2004; 351: 427-437**.** See Evidence Table. Kuhl CK et al. Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk of breast cancer. J Clin Oncol 2005; 23: 8469-8476. See Evidence Table. Leach MO et al. for the MARIBS Study Group. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). Lancet 2005; 365: 1769-1778. See Evidence Table. Lehman CD et al. for the International Breast MRI Consortium Working Group. Screening women at high risk of breast cancer with mammography and magnetic resonance imaging. Cancer 2005; 103: 1898-1895. See Evidence Table. Sardanelli F et al. for the High Breast Cancer Italian Trial (HIBCRIT). Multicenter comparative multimodality surveillance of women at genetic-familial high risk for breast cancer (HIBCRIT Study). Radiology 2007; 242: 698-715. See Evidence Table. Warner E et al. Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound and mammography, and clinical breast examination. JAMA 2004; 292: 1317-1325. See Evidence Table.

The use of MRI in the screening of high risk patients for breast cancer and breast lesions does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

04/08/2008: MTAC REVIEW
MRI in the Diagnosis of Breast Cancer and Breast Lesion
Evidence Conclusion: *Diagnostic accuracy:* It is hard to determine the diagnostic accuracy of imaging studies used to assess the integrity of breast implants. Visual inspection of the implant after its surgical removal is considered the gold standard for ruptured implants. However, this would not apply to asymptomatic women, as it would not be appropriate or ethical to remove an implant with no evidence of leak or rupture. The majority of the studies on the diagnostic accuracy of MRI or other imaging tests were thus conducted among symptomatic women who requested or were advised to remove the implants. The meta-analysis and the studies reviewed show wide variations in the accuracy of MRI and its predictive values in detecting an implant rupture in symptomatic women. The studies had differences in the equipment used, imaging protocol, description of positive MRI, and surgical criteria for a diagnosis of rupture. There were also some interobserver variations as seen in Collis and colleagues' study (2007). Different generations of implants were used. These varied by manufacturer, model, longevity, long-term integrity of the implant, as well as the implantation site and position. The authors of the majority of studies did not indicate the generation of implants used. Only one study (Collis 2007) included patients who exclusively received the third-generation implants. Holmich (2005) also provided the proportion of women receiving each of the three implant generations. Results of studies among women who received earlier generation of implants might not be generalized to the generation(s) currently used. One other limitation of the studies is the inclusion of self-selected symptomatic women who were requesting removal or replacement of the implants. The higher prevalence of rupture among these women would overestimate the accuracy of the tests, and limit generalization of the results to similar groups of patients. The overall results of the published studies show that the sensitivity of MRI in detecting an implant rupture among symptomatic women ranged from 64% to 90%. The specificity of the test ranged from 43% to 100%, the positive predictive value from 57% to 100% and the negative predictive values from 79% to 90%. Ultrasound came next in its accuracy with a sensitivity ranging from 30% to 69% and specificity ranging from 64% to 81%. Mammography was found to have the lowest sensitivity ranging from 20% to 69%, but with a specificity of 82% to 93%. Collis et al's study among asymptomatic who responded to the invitation for MRI testing showed a wide variation in sensitivity (71-86%) and specificity (48-95%) depending on the radiologist who interpreted the test. This assessment was based only on implants that were surgically removed. *Diagnostic impact*: There is insufficient evidence to determine that MRI may influence the management decisions for detected implant leak. *Therapeutic impact:* There are no published studies on the impact of MRI detection of implant leak on health outcomes.
Conclusions:

- MRI is moderately to highly sensitive, and more specific in detecting implant rupture among self-selected groups of symptomatic women**.** i.e. in confirming ruptures when suspected.

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- There is insufficient evidence on the accuracy of MRI as a screening tool for detecting leak or rupture among asymptomatic women.
- There is insufficient evidence to determine that MRI may influence the management decisions for detected implant leak.
- There is insufficient evidence on the impact of MRI detection of implant leak on health outcomes.

Articles: The literature search revealed over 120 articles. Many were review articles or studies on and safety and durability of the silicone gel implants. The following questions were considered in screening the published articles:

1. What is the diagnostic accuracy of MRI in detecting silicone gel breast implant leak/rupture in asymptomatic and symptomatic women?
2. Would the detection of the implant rupture be using MRI influence management decisions?
3. Does the detection of the implant rupture using MRI have an impact on health outcome?

1. Diagnostic accuracy

The literature search revealed several studies dating back to the early 1990s. There were 2 meta-analyses, and a systematic review on the diagnostic accuracy of MRI for detecting implant rupture among symptomatic women. The more recent meta-analysis, as well as studies that were not included in the analysis and that verified MRI findings with visual inspection of implant after surgical removal were critically appraised. Two studies that included asymptomatic women with a breast implant were identified (Brown 2000, and Collis 2007). In Brown and colleagues' (2000), study, the majority (92%) of the implants was second generation implants, and in Collis et al's study all were 3rd generation implant type. Collis' study was selected for critical appraisal as the second-generation implants are known to be more prone to rupture, and the results of Brown's study may not be generalized to the other generations that are more commonly used.

2. Diagnostic impact

A small study on the clinical impact of MRI was identified and critically appraised.

3. Therapeutic impact

No studies on the impact of technology on patient outcomes were identified by the search.

The following studies were critically appraised:

Cher DJ, Conwell JA, Mandel JS. MRI for detecting silicone breast implant rupture: Meta-analysis and implications. *Ann Plast Surg* 2001; 47:367-380. See Evidence Table. Reynolds HE, Buckwalter KA, Jackson VP, et al. Comparison of mammography, sonography, and magnetic resonance imaging in the detection of silicone-gel breast implant rupture. *Ann Plast Surg.*1994; 33:247-257. See Evidence Table. Beekman WH, Hage JJ, van Amerongen AHM, et al. Accuracy of ultrasonography, and magnetic resonance imaging in detecting failure of breast implants filled with silicone gel. *Scand J Plast Reconstr Hand Surg* 1999; 33:415-418. See Evidence Table. Scaranelo AM, Marques AF, Smialowski EB, et al. Evaluation of the rupture of silicone breast implants by mammography, ultrasonography, and magnetic resonance imaging in asymptomatic patients: correlation with surgical findings. *Sao Paulo Med J* 2004; 122:41-47. See Evidence Table. Holmich LB, Vejborg I, Conrad C, et al. The diagnosis of breast rupture: MRI findings compared with findings of explanation. *Europ J Radiol*. 2005:213-225. See Evidence Table. Collis N, Phil M, Litherland J, et al. Magnetic resonance imaging and explantation investigation of long-term silicone gel implant integrity. *Plast Reconstr Surg* 2007; 120:1401-1406. See Evidence Table. Dobke MK, Middleton MS. Clinical impact of breast implant magnetic resonance imaging. *Ann Plast Surg.*1994; 33:241-246. See Evidence Table

The use of MRI in the detecting leakage from silicone implants does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

08/03/2009: MTAC REVIEW

MRI in the Diagnosis of Breast Cancer and Breast Lesion

Evidence Conclusion: Published studies by two research groups comparing the specificity of breast MRI with and without CAD assistance for distinguishing between benign and malignant lesions were reviewed. Williams et al. (2007) evaluated 155 breast lesions detected by MRI and found a statistically significant reduction in the false-positive rate (reduced 23%) with CAD enhancement at 100%. Meinel et al. (2006) evaluated 80 lesions and found a statistically significant increase in specificity (from 51% to 81%) when human readers were aided by CAD. A higher specificity (and corresponding low false-positive rate) would contribute to improved diagnosis since fewer women would be subject to unnecessary follow-up tests or procedures. No published studies, however, evaluated whether there was a reduction in the number of biopsies or other procedures, or whether use of CAD contributed to a change in diagnosis. The above findings are insufficient to draw conclusions about the use of CAD systems with breast MRI and its impact on health outcomes. The quantity of published studies is low, and sample sizes of individual studies are small. Only one research group, Williams et al. (2007) did a comparative analysis with a

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commercially available CAD system. Moreover, no studies are available on the impact of CAD-enhanced MRI on follow-up procedures or diagnosis.

Articles: The Pubmed search yielded 79 articles. One additional article was identified on the CADStream website (Lehman et al., 2006). BCBSA TEC conducted an assessment in 2006; their search in March of that year identified the same articles as the PubMed search. Most of the articles in the PubMed search were either review articles, dealt with related topics such as other types of cancer, or addressed CAD development of other technical aspects of CAD systems or MRI. Three empirical studies were identified that compared breast MR imaging with and without a CAD system. Two of the articles were published by the same research group (T. Lehman, W DeMartini, S Peacock and others) and the later article (2007) appears to also include lesions included in the earlier article (2006). The 2007 article by this group and the other comparative study were both critically appraised. References are as follows: Williams TC, DeMartini WB, Partridge SC et al. Breast MR imaging: Computer-aided evaluation program for discriminating benign from malignant lesions. Radiol 2007; 244: 94-103. See Evidence Table. Meinel LA, Stolpen AH, Berbaum KS et al. Breast MRI lesion classification: Improved performance of human readers with a backpropagation neural network computer-aided diagnosis (CAD) system. J Magn Reson Imaging 2007; 25: 89-95. See Evidence Table.

The use of computer-aided detection (CAD) applied to breast MRI does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Breast MRI surveillance in women with personal history of breast cancer

Date: 07/13/2020

Evidence Conclusion:

- There is insufficient evidence for or against annual surveillance breast MRI in less than 50 years old women with personal history of breast cancer who were diagnosed with invasive breast cancer.
- High-quality randomized controlled trials comparing annual surveillance breast MRI vs mammography in women <50 years old (even in women aged 50 years and older) with personal history of breast cancer who were diagnosed with invasive breast cancer are rare.
- In women (age 18+) with personal history of breast cancer, (some in this population had heterogeneously & extremely dense breast tissue, genetic/family history) who were diagnosed were invasive breast cancer or DCIS:
  - Although one cohort study indicates no difference in performance between annual surveillance MRI and mammography, retrospective studies suggest that MRI performance may be higher than mammography.
  - In addition, MRI results in increased recall and biopsy rates as well as false positive.
  - Cancer detection rate may be higher in patients undergoing MRI than in that undergoing mammography.
  - The findings also suggest that mammography combined with MRI may be more effective (with low specificity) than mammography alone but recall rate and biopsy rate are high.
  - It is also not clear who may benefit from surveillance breast MRI.
- Impact of MRI on survival was not assessed.

Articles: PubMed was searched through February 14, 2020 with the following search terms (with variations): (((Magnetic Resonance Imaging OR MRI)) AND (breast neoplasm OR breast cancer)) AND (follow-up OR postoperative). Search terms also included surveillance, follow-up, and breast MRI surveillance. The search was limited to English language publications and human populations. The search was filtered by RCTs, systematic review & meta-analysis, and observational studies. The reference lists of relevant studies were reviewed to identify additional publications. See Evidence Table.

The use of Breast MRI for surveillance in women with a personal history of breast cancer, diagnosed under the age of 50 does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
77046	Magnetic resonance imaging, breast, without contrast material; unilateral
77047	Magnetic resonance imaging, breast, without contrast material; bilateral

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77048	Magnetic resonance imaging, breast, without and with contrast material(s), including computer-aided detection (CAD real-time lesion detection, characterization and pharmacokinetic analysis), when performed; unilateral
77049	Magnetic resonance imaging, breast, without and with contrast material(s), including computer-aided detection (CAD real-time lesion detection, characterization and pharmacokinetic analysis), when performed; bilateral
C8903	Magnetic resonance imaging with contrast, breast; unilateral
C8905	Magnetic resonance imaging without contrast followed by with contrast, breast; unilateral
C8906	Magnetic resonance imaging with contrast, breast; bilateral
C8908	Magnetic resonance imaging without contrast followed by with contrast, breast; bilateral

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed0	Date Last Revised
02/13/2002	06/07/2011 MDCRPC, 04/03/2012MDCRPC, 05/01/2012MDCRPC, 08/07/2012MDCRPC, 03/05/2013MDCRPC, 09/03/2013MPC, 05/06/2014MPC, 03/03/2015MPC, 08/04/2015MPC, 06/07/2016MPC, 04/04/2017MPC, 02/06/2018MPC, 01/08/2019MPC, 01/07/2020MPC, 01/05/2021MPC, 01/04/2022MPC, 01/10/2023MPC	06/06/2023

MDCRPC Medical Director Clinical Review and Policy Committee
MPC Medical Policy Committee

Revision History	Description
05/14/2015	Changed Breast Cancer Diagnosis criteria to include language that clarifies cancer must be newly diagnosed within the last 3 months.
08/04/2015	Criteria was modified for clarifications regarding requests for MR biopsies
09/02/2016	Added indication, “it is not being requested for routine surveillance of a silicone implant,” to criteria
01/09/2017	Revised indication to “evaluate response to neoadjuvant chemotherapy”
10/18/2018	Criteria was modified for clarifications under breast abnormality evaluation
01/28/2019	Computer-aided detection applied to breast MRI No longer requires review
12/27/2019	Codes deleted 77058, 77059, C8904, C8907, 0159T
03/02/2021	Added July 2020 MTAC Review. MPC approved to adopt Breast MRI criteria for members with a personal history of breast cancer diagnosed at the age of 50 or younger and elected to have a lumpectomy or partial mastectomy. Requires 60-day notice, effective date 08/01/2021.
05/03/2022	MPC approved to revise the criteria to include educational additions for *Breast Cancer Diagnosis*
10/17/2022	Clarification of breast center protocols
06/06/2023	MPC approved modifications to the existing MRI Breast criteria to align with recommendations from multiple guideline statements, including NCCN, regarding certain types of nipple discharge and the need for breast MRI to detect cancer. Requires 60-day notice, effective date 11/01/2023.

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Clinical Review Criteria
Cervical Spine MRI

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Magnetic Resonance Imaging (220.2)
Local Coverage Determinations (LCD)	MRI and CT Scans of the Head and Neck (L35175) *Medical necessity review not required
Local Coverage Article (LCA)	Billing and Coding: MRI and CT Scans of the Head and Neck (A57215)

For Non-Medicare Members

Adapted from Washington State Department of Labor & Industries Final Imaging Guidelines: Cervical Spine MRI. Retrieved 9/3/2020 from https://lni.wa.gov/patient-care/treating-patients/treatment-guidelines-and-resources/_docs/CervicalSpineChecklist.pdf

**Note – most acute cervical radicular pain will resolve with time and conservative management. Bulging discs will retract away from the affected nerve root spontaneously in a high percentage of cases. Acute or chronic non-radicular or non-myelopathy neck pain may be associated with painful paresthesia's diffusely in one or both arms; MRI imaging is of low value for sensory symptoms alone.*

I. Acute cervical pain (onset within past 6 weeks)

A. Acute cervical radicular pain (radiating into one or both arms) without red flags – cervical spine MRI **not** indicated, medical management should be the initial approach

B. Acute cervical pain with radiating pain from the neck into arm **AND ONE or more** of the following red flag conditions present, where the result is likely to lead to emergent surgery: - cervical MRI may be indicated

Red Flags:

1. **Progressive (objective) neurological signs on repeat in-person examination** (i.e., progressive motor weakness present) *(MRI without contrast)*
2. **Evidence of spinal instability or spinal fracture on any other imaging test** (e.g., plain films or cervical spine CT) *(MRI without contrast)*
3. **Radiating pain from the neck with compelling clinical argument for one of the following:** *(MRI with or without contrast)*
   a. Malignancy
   b. Infection
   c. Immunosuppression
   d. Bone disc margin destruction on plain radiographs
   e. Trauma with neck pain, on anticoagulants

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4. **Evidence of neurologic signs suggestive of spinal cord involvement** (e.g., Bilateral "cape-like" sensory loss to suggest syrinx, myelopathy signs such as bowel or bladder changes, abnormally increased reflexes, positive Babinski sign, spastic gait ataxia) where the result is likely to lead to immediate surgery or similar intensive intervention

II. Subacute cervical pain (>6 weeks), no prior MRI for the same episode of cervical pain: *(MRI without contrast)*

A. Patient has had **at least 6** weeks medical/conservative treatment (must include **at least 4 weeks** of physical therapy, including an initial evaluation with PT and at least one follow up, within the last 3 months) for *current episode* of neck pain with no significant improvement (remote past history of physical therapy does not qualify)

AND

B. Clinical evaluation demonstrates **ONE or more** of the following:
   a. Abnormal reflexes or motor deficits in the C5, C6, C7, T1 nerve territory on one side
   b. Prior neck surgery and significant **new** neurological signs or symptoms, compared to maximal post-op recovery baseline, as defined in a. and b. above
   c. Evidence of spinal instability or spinal fracture on any other imaging test
   d. Complex congenital anomaly or deformity of the spine
   e. Strong suspicion for cervical spinal cord stenosis (e.g., myelopathy signs such as bowel or bladder changes, abnormally increased reflexes, positive Babinski sign, spastic gait ataxia)

OR

C. Patient's clinical presentation indicates need for urgent surgery or other intensive intervention as determined by a surgeon or interventional specialist, even without 6 weeks of medical/conservative treatment.

III. Chronic cervical pain

A. **Chronic cervical pain (> 3 months) with no prior MRI of cervical spine**: (MRI without contrast) for any of the criteria under subacute cervical spine pain (section II above)
   1. *Including* **at least 6** weeks medical/conservative treatment (must include **at least 4 weeks** of physical therapy, including an initial evaluation with PT and at least one follow up within the last 6 months) for *current episode* of neck pain with no significant improvement (remote past history of physical therapy does not qualify)

B. **Chronic or recurrent cervical pain (> 3 months) with prior MRI of cervical spine for the same episode of cervical pain with 1 or more of the following:** *(MRI without contrast)*
   1. *Should have* **at least 6** weeks medical/conservative treatment (must include **at least 4 weeks** of physical therapy, including an initial evaluation with PT and at least one follow up within the last 6 months) for *current episode* of neck pain with no significant improvement (remote past history of physical therapy does not qualify)
   2. Patient has not been determined to be a surgical candidate in the past:
      a. Documented significant objective worsening of neurological status on current in-person physical exam (e.g., documented sensory loss, motor weakness, abnormal reflexes in the C5, C6, C7, T1 nerve territory) compared to baseline *OR* electrodiagnostic testing confirming *new* radiculopathy *OR* myelopathy signs such as bowel or bladder changes, abnormally increased reflexes, positive Babinski sign, spastic gait ataxia *OR*
   3. Patient has been determined to be a definite candidate for cervical spine surgery by neurosurgery/orthopedics, (and **ONE** of the following):
      a. Progressive changes in objective neurological findings (see 1 above)
         OR
      b. If no objective neurological findings: the surgeon is requesting another MRI prior to surgery, and it has been at least 1 year since last cervical MRI
   4. Prior cervical spine surgery with **1 or more** of the **following** *(MRI without contrast)*:
      a. Objective and new or worsening neurological signs on physical exam compared with maximum fpost-op recovery baseline (e.g., documented sensory loss, motor weakness, abnormal reflexes in the C5, C6, C7, T1 nerve territory, or new radiculopathy on electrodiagnostic studies *OR* myelopathy signs such as bowel or bladder changes, abnormally increased reflexes, positive Babinski sign, spastic gait ataxia)
      OR
      b. Other imaging *OR* clinical findings suggest new adverse effects of surgery (e.g., hardware failure or **concern** for epidural scarring/arachnoiditis)

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These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage.
Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

IV. Suspect Cervical Multiple Sclerosis (MS) *(MRI with contrast)* if patient has been already evaluated by neurology:
A.

Effective until May 1, 2024	a. Approved for staging (along with MRI of brain) at time of initial presentation b. Known MS diagnosis (confirmed by neurology)—approved for annual surveillance along with Brain MRI
Effective May 1, 2024	a. Approved for staging (along with MRI of brain) at time of initial presentation b. Known MS diagnosis (confirmed by neurology): i. approved for annual surveillance along with Brain MRI ii. following clinical symptoms of a flare up, or iii. 3-6 months after radiologic evidence of a flare up, or iv. 3-6 months and/or 6-12 months after changing disease modifying agent

V. Interval follow up of known neurosurgical disease clinical indication for repeat imaging is documented (e.g., intermedullary or extramedullary tumors, bony spine tumors, syrinx, vascular malformation) when ordered by or in consultation with neurosurgery.

VI. Ankylosing Spondylitis (AS):

Effective until March 1, 2024	Send all cases to MD for review
Effective March 1, 2024	Advanced imaging of the spine for the indication of ankylosing spondylitis (AS) is considered medically necessary when **ONE** of the following are true: A. Suspected AS and **ALL** of the following criteria are met: 1. Radiographs of the affected area are not diagnostic 2. Inflammatory back pain which has been present for at least 3 months. Inflammatory back pain is defined as back pain with at least **FOUR (4)** of the following features: a. Patient is younger than age 40 b. Insidious (gradual) onset c. Improvement with exercise d. No improvement with rest e. Pain at night that improves on getting up 3. Advanced imaging is ordered by or in conjunction with a Rheumatologist B. Confirmed AS diagnosis and **ALL** of the following criteria are met: 1. Advanced imaging is ordered by the patient's managing Rheumatologist 2. Unclear disease activity after full clinical and laboratory evaluation 3. Progression on MRI will lead to a change of biologic drug or cessation of biologic therapy

If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

References

American College of Radiology (2008). ACR appropriateness criteria: chronic neck pain. Available at: http://www.acr.org/Quality-Safety/Appropriateness-Criteria/Diagnostic/MusculoskeletalImaging.

American College of Radiology (2009). ACR appropriateness criteria: suspected spine trauma. Available at: http://www.acr.org/Quality-Safety/Appropriateness-Criteria/Diagnostic/MusculoskeletalImaging.

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Bussieres AE, Peterson C, Taylor JAM. Diagnostic imaging guideline for musculoskeletal complaints in adults- an evidence-based approach—part 3: spinal disorders. J Manipulative Physiol Ther 2008; 31: 33-87.

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
72141	Magnetic resonance (e.g., proton) imaging, spinal canal and contents, cervical; without contrast material
72142	Magnetic resonance (e.g., proton) imaging, spinal canal and contents, cervical; with contrast material(s)
72156	Magnetic resonance (e.g., proton) imaging, spinal canal and contents, without contrast material, followed by contrast material(s) and further sequences; cervical

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed04/	Date Last Revised
09/18/2020	10/06/2020[MPC], 10/05/2021[MPC], 10/04/2022[MPC] , 10/03/2023[MPC]	12/09/2023

[MPC] Medical Policy Committee

Revision History	Description
10/06/2020	MPC approved to adopt new clinical criteria. Requires 60-day notice, effective date 2/1/2021.
04/01/2021	Added clarifying language to clinical criteria.
04/30/2021	Added clarifying language and formatting changes
10/04/2022	MPC approved to include quantifying number of 3 visits for physical therapy of subacute low back pain. 60-day notice required; effective March 1, 2023.
11/01/2022	MPC approved the minor change for MRI-Cervical Spine criteria to include language for MS patients.
04/04/2023	MPC approved to modify MRI criteria with 4 weeks of physical therapy (instead of 6 weeks) and updated indications for cervical spine imaging.
08/01/2023	MPC approved to modify existing criteria to indicate advanced imaging prior to a procedure is considered reasonable. Requires 60-day notice, Effective January 1, 2024.
10/03/2023	MPC approved updates to criteria allow Anklyosing Spondylitis (AS) indications. 60-notice required; effective March 1, 2024.
12/09/2023	MPC approved to medical necessity criteria cervical spine; allowing for a short-term imaging follow-up after radiologic signs of MS disease activity and more rapid imaging follow-up for up to one year following a change in therapy. 60-day notice required. Effective May 1, 2024.

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Clinical Review Criteria
Lumbar Spine MRI

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	Lumbar MRI (L37281) *Medical necessity review not required
Local Coverage Article (LCA)	Billing and Coding: Lumbar MRI (A57207)

For Non-Medicare Members

Adapted from Washington State Department of Labor & Industries Guidelines for Advanced Imaging Studies: Lumbar spine checklist. Retrieved 4/22/2020 from https://lni.wa.gov/patient-care/treating-patients/treatment-guidelines-and-resources/_docs/LBchecklist.pdf

Lumbar spine MRI is NOT indicated for the following:
Uncomplicated acute (<6 weeks) low back pain with or without suspected radiculopathy (no red flags) does not warrant the use of MRI, X-ray, CT, myelography or CT xylography, NUC Tc-99m bone scan with SPECT. Nonspecific lumbar disc abnormalities are commonly found in asymptomatic patients. (Chou, Qaseem et al. 2007) (American College of Radiology 2007)

**Note – most acute lumbar radicular pain will resolve with time and conservative management. Bulging discs will retract away from the affected nerve root spontaneously in a high percentage of cases. Most patients will respond to 6 weeks medical/conservative treatment including physical therapy.*

If advanced imaging is needed, lumbar spine MRI is the preferred imaging modality for the following circumstances unless contraindicated or not tolerated by the patient (i.e., due to presence of ferrous metal in body, or severe anxiety) or unavailable.

I. Acute low back pain (onset within past 6 weeks)

Lumbar spine MRI not indicated unless **ONE or more** of the following red flag conditions are present:

Red Flags:

1. **Progressive (objective) neurological signs on repeat in-person examination** (i.e. progressive motor weakness present) *(MRI without contrast)*
2. **Suspect Cauda Equina syndrome** *(MRI without contrast)* due to the following:
   - New onset bilateral neurologic signs and symptoms of cauda equina (e.g., saddle numbness with acute bladder or bowel dysfunction)

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*ACR appropriateness recommendation ranks MRI without contrast highest (rating = 9). MRI with and without contrast (rating = 8) depends on clinical circumstances. Other methods: Myelography and postmyelography CT (rating = 6), CT with and without contrast (rating = 5)-may be indicated if MRI is confusing or contraindicated, x-ray, NUC Tc-99m bone scan with SPECT and x-ray myelography are rated < 5.

3. **Strong clinical suspicion of spine infection** *(MRI with and without contrast)* and **TWO or more** of the following:
   - Fever
   - Immunosuppression (e.g., chronic steroid use, diabetes)
   - IV drug use
   - Known bacteremia
   - Elevated sedimentation rate/c-reactive protein
4. **History or strong clinical suspicion of cancer with new onset of low back pain and non-diagnostic plain films** and **TWO or more** of the following *(MRI with and without contrast)***:**
   - Unexplained weight loss
   - Failure of back pain to improve after one month
   - Age over 50

*ACP recommends plain radiography for unexplained weight loss, MRI or plain radiography if multiple risk factors present. ACR Guidelines for suspicion of cancer, infection or immunosuppression rate MRI without and with contrast highest (rating = 8). CT without contrast (rating = 6)-useful if MRI is contraindicated or unavailable. Other imaging methods: use of x-ray, NUC Tc-99m bone scan whole body with optional targeted SPECT, myelography and postmyelography CT (appropriateness rating < 6 for these).

5. **Suspected vertebral fracture in a patient with pain and non-diagnostic plain films** *(MRI without contrast) with **ONE** or more of the following:*
   - Low velocity trauma (e.g., fall from height or struck by object) OR
   - Osteoporosis OR
   - Age >70 years with other acute fracture(s)

*ACP Guideline recommends: if vertebral compression fracture is suspected due to history of osteoporosis, use of steroids, or age ≥ 70 plain radiography should be completed prior to MRI.
*For low velocity trauma, ACR Guidelines do not support use of NUC Tc-99m bone scan with SPECT, MRI with and without contrast, myelography and postmyelography CT, or x-ray myelography (appropriateness ratings < 5 for these)

II. Subacute Low back pain >6 weeks: *(MRI without contrast)*

A. Patient has had **at least 6 weeks** medical/conservative treatment (must include **at least 4 weeks** of physical therapy, including an initial evaluation with PT and at least one follow up, within the last 3 months) for *current episode* of back pain with no significant improvement (remote past history of physical therapy does not qualify)

AND

- **ONE or more** of the criteria under acute low back pain met (from section I above)

OR

- Suspected radiculopathy with **ALL of the following** documented in notes:
  - Lower extremity pain is > than back pain present in nerve root distribution (e.g., L5, S1, etc.)
    ONE or more of the following:
    - Positive supine straight leg raising test - radicular leg pain reproduced when the leg is extended >30° and <70° (pain reproduced only in the back is a negative test) or positive crossed straight leg raising test, **OR**
    - Motor weakness or sensory loss in a radicular distribution (must be in a specific radicular distribution), **OR**
    - EMG/NCS confirms acute radiculopathy consistent with the patient's symptoms

OR

- Strong clinical suspicion of lumbar spinal stenosis, with documentation of neurogenic claudication (bilateral or unilateral leg pain upon standing that is temporarily relieved by forward flexion or sitting)

OR

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- Patient's clinical presentation indicates need for urgent surgery or other intensive intervention as determined by a surgeon or interventional specialist, even without 6 weeks of conservative/medical treatment.

*ACP recommendation: consider EMG/NCS testing if symptoms > 1 month. For suspected radiculopathy, ACR Guidelines rate MRI without contrast as most appropriate. CT without contrast may be useful if MRI is not available or contraindicated. MRI with and without contrast may be indicated if noncontrast MRI is nondiagnostic or indeterminate. MRI is preferred over myelography and postmyelography CT but may be indicated if MRI is nondiagnostic. In some circumstances (facet arthropathy, stress fracture and spondylolysis) NUC Tc-99m bone scan with SPECT may be useful. Least appropriate x-ray (appropriateness rating 2).

III. Chronic low back pain

A. **Chronic low back pain (> 3 months) with no prior MRI of lumbar spine:** *(MRI without contrast)*
All patients should have **at least 6 weeks** of medical/conservative treatment (must include at least **4 weeks** of physical therapy, including an initial evaluation with PT and at least one follow up within the last 6 months) for *current episode* of back pain with no significant improvement (remote past history of physical therapy does not qualify **and must meet ONE of the following:**
- Any of the criteria under subacute low back pain (section II above)
- Lack of improvement accompanied by severe functional impairments
- Patients' clinical presentation indicates need for surgery or other invasive intervention as determined by a surgeon or interventional specialist.

B. **Chronic low back pain (> 3 months) with prior MRI of lumbar spine:** *(MRI without contrast)*
All patients should have **at least 6 weeks** medical/conservative treatment (must include at least **4 weeks** of physical therapy, including an initial evaluation with PT and at least one follow up therapy visit within the last 6 months) for *current episode* of back pain with no significant improvement (remote history of physical therapy does not qualify) **and must meet ONE of the following:**

1. Patient has not been determined to be a surgical candidate in the past
   - Documented objective worsening of neurological status on current physical exam (e.g. absence of reflexes, dermatomal sensory changes, radicular motor weakness, etc.) *OR* electrodiagnostic testing confirming new radiculopathy *OR*
2. Patient has been determined to be a definite candidate for spine surgery by neurosurgery/orthopedics, (and **ONE** of the following):
   - Progressive changes in objective neurological findings
   - If no objective neurological findings: the surgeon is requesting another MRI prior to surgery and it has been at least 1 year since last lumbar MRI

* ACR Guidelines rate MRI without contrast as most appropriate. CT without contrast may be useful if MRI is not available or contraindicated. MRI with and without contrast may be indicated if noncontrast MRI is nondiagnostic or indeterminate. MRI is preferred over myelography and postmyelography CT but may be indicated if MRI is nondiagnostic. In some circumstances (facet arthropathy, stress fracture and spondylolysis) NUC Tc-99m bone scan with SPECT may be useful. Least appropriate x-ray (appropriateness rating 2).

3. Prior lumbar surgery with **ONE or more** of the following *(MRI with and without contrast)*:
   - Objective and/or new or worsening neurological signs on physical exam (new absence of reflexes, dermatomal sensory changes, radicular motor weakness, or new radiculopathy on electrodiagnostic studies, etc.)
   - Plain radiography OR clinical findings suggest new adverse effects of surgery (e.g., hardware failure or concern for epidural scarring/arachnoiditis)
   - New changes to electrodiagnostic studies

*ACR appropriateness rates MRI with and without contrast highest (rating =8), CT without contrast(rating=6) may be indicated in postfusion patients or when MRI is contraindicated or indeterminate. Other methods rated lower: MRI without contrast (rating=6) as contrast is often necessary, myelography and postmyelography CT (rating= 5, x-ray (rating = 5)-flex/extension may be useful, NUC Tc-99m bone scan with SPECT (rating=5)-helps detect and localize pseudoarthrosis, x-ray myelography (rating = 2).

C. **Indication not listed: provide clinical justification**

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Patient with chronic pain not meeting the above criteria may be considered on a case by case basis. Indications here should be well documented. For example, while the vast majority of true radiculopathy cases would meet the criteria, specific syndromes (lateral stenosis, L1-L3 syndromes) may only meet some of these criteria. In these cases, clinical correlation should be clearly documented.

IV. Multiple Sclerosis (MS): There is no indication for Lumbar MRI for initial or subsequent evaluation of suspected or confirmed MS.

V. Ankylosing Spondylitis (AS):

Advanced imaging of the spine for the indication of ankylosing spondylitis (AS) is considered medically necessary when **ONE** of the following are true:

A. Suspected AS and **ALL** of the following criteria are met:
   1. Radiographs of the affected area are not diagnostic
   2. Inflammatory back pain which has been present for at least 3 months. Inflammatory back pain is defined as back pain with at least **FOUR (4)** of the following features:
      a. Patient is younger than age 40
      b. Insidious (gradual) onset
      c. Improvement with exercise
      d. No improvement with rest
      e. Pain at night that improves on getting up
   3. Advanced imaging is ordered by or in conjunction with a Rheumatologist

B. Confirmed AS diagnosis and **ALL** of the following criteria are met:
   1. Advanced imaging is ordered by the patient's managing Rheumatologist
   2. Unclear disease activity after full clinical and laboratory evaluation
   3. Progression on MRI will lead to a change of biologic drug or cessation of biologic therapy

References:

American College of Radiology (2008). ACR appropriateness criteria: low back pain. Available at: http://www.acr.org/SecondaryMainMenuCategories/quality_safety/app_criteria/pdf/ExpertPanelonNeurologicImaging/LowbackPainDoc7.aspx

Chou, R., A. Qaseem, et al. (2007). "Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society." Ann Intern Med 147(7): 478-91.

If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Summary of Recommendations

- Uncomplicated acute LBP and/or radiculopathy are benign, self-limited conditions that do not warrant any imaging studies.
- MRI of the lumbar spine should be considered at any point for those patients presenting with red flags raising suspicion for a serious underlying condition, such as cauda equina syndrome (CES), malignancy, or infection.
- In patients with a history of low-velocity trauma, osteoporosis, or chronic steroid use, initial evaluation with radiographs is recommended.
- In the absence of red flags, first-line treatment for chronic LBP remains conservative therapy with both pharmacologic and nonpharmacologic (eg, exercise, remaining active) therapy.

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- If there are persistent or progressive symptoms during or following 6 weeks of conservative management and the patient is a surgery or intervention candidate or diagnostic uncertainty remains, MRI of the lumbar spine has become the initial imaging modality of choice in evaluating complicated LBP.
- MRI is the imaging procedure of choice in patients suspected of cord compression or spinal cord injury.
- Patients with recurrent low back pain and history of prior surgical intervention should be evaluated with contrast-enhanced MRI.

Applicable Codes

Medicare – Medical Necessity review not required
Non-Medicare - Considered Medically Necessary when criteria in the applicable policy statements listed above are met

CPT® Codes	Description
72148	Magnetic resonance (eg, proton) imaging, spinal canal and contents, lumbar; without contrast material
72149	Magnetic resonance (eg, proton) imaging, spinal canal and contents, lumbar; with contrast material(s)
72158	Magnetic resonance (eg, proton) imaging, spinal canal and contents, without contrast material, followed by contrast material(s) and further sequences; lumbar

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed	Date Last Revised
05/05/2020	05/05/2020[MPC], 05/04/2021[MPC], 05/03/2022[MPC], 05/02/2023[MPC]	10/03/2023

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
05/05/2020	MPC approved to adopt new clinical criteria. Requires 60-day notice, effective date 9/1/2020.
04/30/2021	Added clarifying language and formatting changes
10/04/2022	MPC approved to include quantifying number of 3 visits for physical therapy of subacute low back pain. 60-day notice required.
04/04/2023	MPC approved to modify MRI criteria with 4 weeks of physical therapy (instead of 6 weeks)
08/08/2023	MPC approved to modify existing to indicate advanced imaging prior to a procedure is considered reasonable. Requires 60-day notice, effective 01/01/2024.
10/03/2023	MPC approved updates to criteria allow Anklyosing Spondylitis (AS) indications. 60-notice required; effective March 1, 2024.

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Clinical Review Criteria
Thoracic Spine MRI

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Magnetic Resonance Imaging (220.2)
Local Coverage Determinations (LCD)	None
Local Coverage Article (LCA)	None

For Non-Medicare Members

I. Acute thoracic back pain (onset within past 6 weeks)

Thoracic spine MRI not indicated unless **ONE or more** of the following red flag conditions are present:

Red Flags:

A. Objective neurological signs of thoracic myelopathy (leg weakness and incontinence with +/- spasticity) *(MRI without contrast)*

B. Progressive (objective) neurological signs of thoracic myelopathy (leg weakness and incontinence with +/- spasticity) on repeat examination during a course of conservative care (i.e., progressive motor weakness present) *(MRI without contrast)*

C. Strong clinical suspicion of spine infection with strong clinical concern for thoracic myelopathy or myelitis *(MRI with and without contrast)* and **TWO or more** of the following:
- Fever
- Immunosuppression (e.g., chronic steroid use, diabetes)
- IV drug use
- Known bacteremia
- Elevated sedimentation rate/c-reactive protein

D. History or strong clinical suspicion of cancer (by examination, lab and other ancillary testing) with new onset of thoracic back pain/myelopathy and non-diagnostic plain films and **TWO or more** of the following *(MRI with and without contrast)*:
- Unexplained weight loss
- Failure of back pain to improve after conservative management
- Back pain worse when supine is common in thoracic metastasis
- Age over 50

*ACP recommends plain radiography for unexplained weight loss, MRI or plain radiography if multiple risk factors present. ACR Guidelines for suspicion of cancer, infection or immunosuppression rate MRI without and with contrast

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highest (rating = 8). CT without contrast (rating = 6)-useful if MRI is contraindicated or unavailable. Other imaging methods: use of x-ray, NUC Tc-99m bone scan whole body with optional targeted SPECT, myelography and postmyelography CT (appropriateness rating < 6 for these).

E. Suspected vertebral fracture in a patient with pain and non-diagnostic plain films *(CT should be done first and MRI can be considered based on clinical findings/possible surgical intervention)*

- Low velocity trauma (e.g., fall from height or struck by object) OR
- Osteoporosis OR
- Age >70 years with other acute fracture(s)

*ACP Guideline recommends: if vertebral compression fracture is suspected due to history of osteoporosis, use of steroids, or age ≥ 70 plain radiography should be completed prior to MRI.
*For low velocity trauma, ACR Guidelines do not support use of NUC Tc-99m bone scan with SPECT, MRI with and without contrast, myelography and postmyelography CT, or x-ray myelography (appropriateness ratings < 5 for these)

II. Subacute Thoracic back pain >6 weeks (with no red flags above): *(MRI without contrast)*

A. Patient has had at least 6 weeks medical/conservative treatment (must include **at least 4 weeks** of physical therapy, including an initial evaluation with PT and at least one follow up, within the last 3 months) for current episode of back pain with no significant improvement (remote past history of physical therapy does not qualify); if diabetic should be well controlled

AND

- **ONE or more** of the criteria under acute thoracic back pain met (from section I above)
  OR
- Suspected thoracic radiculopathy (band of numbness, pain or sensitivity around midsection)
  OR
- Motor weakness or sensory loss in a spinal cord distribution (e.g., bilateral sensory loss from mid or low abdomen down, and/or leg weakness, and/or bowl or bladder incontinence)

III. Chronic thoracic back pain (> 3 months) with no prior MRI of thoracic spine (with no red flags above): *(MRI without contrast)*

A. All patients should have **at least 6 weeks** medical/conservative treatment (must include **at least 4 weeks** of physical therapy, including an initial evaluation with PT and at least one follow up within the last 6 months) for *current episode* of back pain with no significant improvement (remote past history of physical therapy does not qualify) **and must meet ONE of the following:**

- Any of the criteria under subacute thoracic back pain (section II above)

IV. Chronic thoracic back pain (> 3 months) with prior MRI of thoracic spine (with no red flags above): *(MRI without contrast)*:

A. All patients should have **at least 6 weeks** medical/conservative treatment (must include at least **4 weeks** of physical therapy, including an initial evaluation with PT and at least one follow up therapy within the last 6 months) for *current episode* of back pain with no significant improvement (remote past history of physical therapy does not qualify) **and must meet ONE of the following:**

- Any of the criteria under subacute thoracic back pain (section II above). If clinical exam is unchanged from prior, should not be repeated more than once every 12 months.

V. Suspect Thoracic Multiple Sclerosis (MS) *(MRI with contrast)* patient must have been already evaluated by neurology who specifically advises thoracic MRI:

A. Should not be part of initial staging unless there are specific findings attributable to the thoracic cord (e.g., MS “hug” or sensory loss beginning mid thorax)
B. Not routinely indicated for subsequent imaging for MS

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VI. Inflammatory or demyelinating process, suspected (e.g., transverse myelitis, spinal cord abscess, clinically isolated syndrome, conditions mimicking MS, other demyelinating disease), as indicated by **ONE or more** of the following (ordered with specific recommendation by neurology/neurosurgery):

- Ascending numbness or tingling (e.g., from foot to trunk)
- Brown-Sequard syndrome
- Autoimmune inflammatory disorders known to affect spinal cord (Sjogren syndrome, systemic lupus erythematosus, antiphospholipid syndrome)
- MS strongly suspected but MRI of brain and cervical spine nondiagnostic, after consultation with Neurology
- Signs or symptoms strongly indicative of myelopathy (leg weakness and incontinence with +/- spasticity) or myelitis (pain with weakness and incontinence and +/- spasticity)

VII.

A. Pediatric/Adolescent Scoliosis, as indicated by **ONE or more** of the following:

- Congenital scoliosis
- Early-onset scoliosis (age 9 years or younger)
- Neurofibromatosis
- Presurgical planning for adolescent idiopathic scoliosis to assess possible neural axis malformation, as indicated by **1 or more** of the following:
  - Abnormal neurologic findings on clinical examination
  - Age at first visit 10 years or younger
  - Kyphosis at curve apex
  - Left-sided thoracic curvature
  - Male gender
  - Pain, moderate to severe
  - Rapid curve progression (i.e., more than 1 degree per month)
  - Short segment curve (i.e., less than 6 vertebral segments)
  - Thoracic kyphosis 30 degrees or greater
  - Vertebral abnormalities (e.g., hemivertebrae, block vertebrae) detected on x-ray

B. Adult Scoliosis as indicated by **ONE or more** of the following:

- Abnormal neurologic findings on clinical examination
- Kyphosis at curve apex
- Pain, moderate to severe
- Rapid curve progression (i.e., more than 1 degree per month)
- Short segment curve (i.e., less than 6 vertebral segments)
- Thoracic kyphosis 30 degrees or greater
- Vertebral abnormalities (e.g., hemivertebrae, block vertebrae) detected on x-ray
- Presurgical planning

VIII. Spinal stenosis of thoracic spine, suspected, as indicated by **ALL** of the following):

- Patient being considered for invasive treatment
- Progressive or disabling symptoms of thoracic spine stenosis, as indicated by **ONE or more** of the following:
  - Hyperactive reflexes
  - Muscle weakness
  - Sensory loss
  - Spasticity

IX. Stereotactic spine radiotherapy treatment planning

X. Oncologic staging or restaging

XI. Syringomyelia in thoracic spine, suspected, as indicated by **ONE or more** of the following:

- Muscle wasting in appropriate thoracic spine dermatomes
- Sensory loss in appropriate thoracic spine dermatomes
- Weakness in appropriate thoracic spine dermatomes

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- Bowel/bladder dysfunction

XII. Tethered cord, suspected, as indicated by **ONE or more** of the following:
- Anorectal malformation
- Cutaneous manifestations of occult spina bifida (e.g., nevus, lipoma, tufts of hair, hemangioma, dimple overlying spine, asymmetric gluteal cleft, dermal sinus tract)
- Gait abnormality or difficulty
- Urinary dribbling or lack of bladder control
- Urodynamic tests abnormal

XIII. Ankylosing Spondylitis (AS):

Effective until March 1, 2024	Send all cases to MD for review
Effective March 1, 2024	Advanced imaging of the spine for the indication of ankylosing spondylitis (AS) is considered medically necessary when **ONE** of the following are true: A. Suspected AS and **ALL** of the following criteria are met: 1. Radiographs of the affected area are not diagnostic 2. Inflammatory back pain which has been present for at least 3 months. Inflammatory back pain is defined as back pain with at least **FOUR (4)** of the following features: a. Patient is younger than age 40 b. Insidious (gradual) onset c. Improvement with exercise d. No improvement with rest e. Pain at night that improves on getting up 3. Advanced imaging is ordered by or in conjunction with a Rheumatologist B. Confirmed AS diagnosis and **ALL** of the following criteria are met: 1. Advanced imaging is ordered by the patient's managing Rheumatologist 2. Unclear disease activity after full clinical and laboratory evaluation 3. Progression on MRI will lead to a change of biologic drug or cessation of biologic therapy

XIV. Indication not listed: provide clinical justification
- Indications here should be well documented.

For covered criteria:

If requesting this service (*or these services*), please send the following documentation to support medical necessity:
- Last 6 months of clinical notes from requesting provider &/or specialist

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References

The American College of Radiology (ACR), the American Society of Neuroradiology (ASNR),the Society of Computed Body Tomography and Magnetic Resonance (SCBT-MR), and the Society for Skeletal

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Radiology (SSR). (2020, October 13). *Search results*. American College of Radiology. Retrieved December 19, 2022, from https://www.acr.org/-/media/ACR/Files/Practice-Parameters/MR-Adult-Spine.pdf

Adapted from Washington State Department of Labor & Industries Final Imaging Guidelines: Thoracic Spine MRI. Retrieved 9/13/2022 from https://lni.wa.gov/patient-care/treating-patients/treatment-guidelines-and-resources/_docs/ThoracicSpineChecklist.pdf

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPCS Codes	Description
72146	MRI Thoracic without contrast
72147	MRI Thoracic with contrast
72157	MRI Thoracic without and with contrast

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed	Date Last Revised
12/06/2022	12/06/2022[MPC],	10/03/2023

[MPC] Medical Policy Committee

Revision History	Description
12/06/2022	MPC approved to adopt criteria for Thoracic MRI for non-Medicare members. Requires 60-day notice, effective date May 1, 2023.
04/04/2023	MPC approved to modify MRI criteria with 4 weeks of physical therapy (instead of 6 weeks)
05/05/2023	Added clarifying coverage indication language for oncologic staging
10/03/2023	MPC approved updates to criteria allow Anklyosing Spondylitis (AS) indications. 60-notice required; effective March 1, 2024.

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Clinical Review Criteria
Weight-Bearing MRI

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Magnetic Resonance Imaging (MRI) (220.2)
Local Coverage Determinations (LCD)	None

For Non-Medicare Members

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

If requesting review for this service, please send the following documentation:

- Last 6 months of clinical notes from requesting provider &/or specialist

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Background

Magnetic resonance imaging (MRI) uses magnetic fields and radiofrequency waves to provide images of internal organs and tissues. Among other applications, MRI is widely used to diagnose joint and musculoskeletal disorders especially injuries affecting the knee, shoulder, hip, elbow and wrist.

Conventional MRI may have limits for diagnosing certain conditions such as degenerative cervical spinal disorders in which symptoms are aggravated when patients are standing and relieved when patients are lying down. The closed cylindrical design of standard MRI systems requires patients to be imaged in a supine position. Thus, with conventional non-weight-bearing MRI, the conditions under which symptoms arise are often not reproduced. Biomechanical studies have found a decrease in spinal canal cross-sectional area (or dural sac) and spinal foraminal dimensions with weight-bearing (axial loading) and with flexion and extension. In some cases, MRI findings correlate with patient symptoms. Disk extrusion, disk sequestration and nerve root compression are infrequently seen in asymptomatic patients, leading to the common belief that nerve root compression seen on MRI is clinically relevant. MRI of patients in the supine position may not identify clinically relevant spinal canal and foraminal stenosis, or the degree of nerve root compression (Kumura et al., 2005; Weishaupt & Boxheimer, 2003).

Weight-bearing MRI is proposed as an alternative to conventional MRI imaging. There are two ways to image the weight-bearing spine. One approach is to simulate weight bearing using a special device with conventional MRI machines. A study of patients with symptoms of spinal stenosis (Hiwatashi et al., 2004) found that imaging with axially loaded MR imaging can yield information that results in different treatment decisions than standard MRI.

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The Hiwatashi study used a device, consisting of a harness/jacket with straps connected to a footplate that applies an axial load to the patient's spine during imaging in the supine position.

The other approach is to use a vertically open-configuration MRI that allows the patient to be imaged in a weight-bearing position. There are two FDA-approved devices:

- The Indomitable MRI scanner (Fonar) was approved by the FDA in October 2000 for imaging multiple planes of the head and body. It has an open design and the patient-scanning table can be moved to a variety of positions with the patient on it. Scanning positions include a vertical (upright) position, a horizontal (supine) position and an angled position (angles between -20o and 90o). Fonar, the manufacturer, claims that this is the only MRI system that can scan patients in flexion, extension, rotation and lateral bending (Fonar website; FDA website).
- The G-scan (Esaote) was approved by the FDA in August 2004; its use is limited to imaging the ankle, knee, hip, shoulder joint and spine. The scanning table can also be moved to a variety of positions with the patient on it. The table can be rotated to angles between supine (0o) to fully upright (90o). The system also includes specialized knee, hand/wrist, ankle/foot and shoulder coils (Esaote website; FDA website).

Weight-bearing MRI has not been previously reviewed by MTAC.
Assessment questions:

- Diagnostic accuracy: What is the evidence on the ability of upright MRI to accurately detect problems/pathology compared to conventional MRI?
- Diagnostic impact: What is evidence on whether findings from weight-bearing MRI contribute substantially to improved diagnosis compared to conventional MRI?
- Therapeutic impact: What is the evidence that more appropriate therapy is used after weight-bearing MRI compared to conventional MRI?

Medical Technology Assessment Committee (MTAC)

Weight-Bearing MRI

06/04/2007: MTAC REVIEW

Evidence Conclusion: There are no published studies on the diagnostic accuracy (sensitivity/specificity), diagnostic impact or therapeutic impact of upright MRI compared to conventional MRI. One study with the Fonar Upright MRI system (Perez et al., 2007 in press) compared the diagnostic yield of the new device compared to conventional MRI. There was no gold standard comparison; rather, weight-bearing MRI was compared to conventional MRI. 68 pathologies were identified in 89 symptomatic patients by one or both methods. The authors considered a technology to be "superior" if it identified a pathology not detected by the other method or indicated a herniation or spondylolisthesis that was larger in size. Upright MRI was found to be superior to recumbent MRI in 52 out of 68 pathologies identified, and recumbent MRI was found to be superior to upright MRI in 11 cases. The reports by the Washington State Labor and Industries Department and the Washington State Department of Health both also concluded that there was insufficient evidence on the diagnostic accuracy or utility of weight-bearing MRI.

Articles: Diagnostic accuracy: No studies were identified evaluated the sensitivity and specificity of weight-bearing MRI compared to conventional MRI, using an objective comparison. The empirical articles identified in the search generally involved obtaining spinal measurements with patients in various positions. For example, Hirasawa et al. (2007) examined 20 asymptomatic volunteers with the Fonar Indomitable MRI scanner in supine, sitting and standing positions. The primary outcome measures were differences in spinal measurements, specifically mean dural sac cross-sectional area and diameter. One study was identified that compared clinical diagnoses of patients imaged with weight-bearing MRI versus conventional MRI. This study (Ferreiro Perez et al., in press 2007) was critically appraised. See Evidence Table. Diagnostic accuracy: No studies were identified evaluated the sensitivity and specificity of weight-bearing MRI compared to conventional MRI, using an objective comparison. The empirical articles identified in the search generally involved obtaining spinal measurements with patients in various positions. For example, Hirasawa et al. (2007) examined 20 asymptomatic volunteers with the Fonar Indomitable MRI scanner in supine, sitting and standing positions. The primary outcome measures were differences in spinal measurements, specifically mean dural sac cross-sectional area and diameter. One study was identified that compared clinical diagnoses of patients imaged with weight-bearing MRI versus conventional MRI. This study (Ferreiro Perez et al., in press 2007) was critically appraised. See Evidence Table. Diagnostic impact: No studies were identified that evaluated whether findings from weight-bearing MRI contribute substantially to improved diagnosis compared to conventional MRI. Therapeutic impact: No studies were identified that reported quantitative data on whether more appropriate therapy was used after weight-bearing MRI than conventional MRI.

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The use of weight-bearing MRI does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Considered not medically necessary:

CPT® or HCPC Codes	Description
No specific codes	

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
06/26/2007	05/03/2011 MDCRPC, 08/02/2011 MDCRPC, 06/05/2012 MDCRPC, 04/02/2013 MDCRPC, 02/04/2014 MPC, 12/02/2014 MPC, 10/06/2015MPC, 08/02/2016MPC, 06/06/2017MPC, 04/03/2018MPC, 04/02/2019MPC, 04/07/2020MPC, 04/06/2021MPC, 04/05/2022MPC, 04/04/2023MPC	05/03/2011

MDCRPC Medical Director Clinical Review and Policy Committee
MPC Medical Policy Committee

Revision History	Description

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Clinical Review Criteria
Brain MRI

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Criteria

For Medicare Members

This policy does not apply to Medicare members.

For Non-Medicare Members

***Site of Care review also applies -** See the High-end imaging Site of Care Medical Policy

Magnetic resonance imaging (MRI) studies of the brain may be medically necessary when the following criteria are met:

I. **Evaluation of headache:**
Brain MRI is not indicated for any of the following headache diagnoses in the absence of focal neurological deficits: migraine, cluster headache, tension-type headache, or chronic stable headache**.**
MRI can be considered for 1 or more of the following –
   a. Chronic headache with a change in character/pattern (e.g., more frequent, increased severity, or duration) not explained after evaluation of common causes (e.g., medication overuse syndrome or cervicogenic headache) and failure to respond to standard medical management
   b. Suspected aneurysm rupture/leak or AVM. Typically described as a new onset (< 48 hours) of “worst headache in my life” or “thunderclap” headache. A thunderclap type headache is a sudden onset new headache reaching maximum intensity within 2-3 minutes, lasting more than 5 minutes.
   c. Prior history of stroke or intracranial bleed with sudden onset of severe headache
   d. New onset of headache and any of the following:
      i. Onset of headache before age 6 years
      ii. Onset of headache after age 50 years not explained after evaluation of common causes (e.g., medication overuse syndrome or cervicogenic headache)
      iii. A combination of acute, new, or fluctuating neurologic deficits such as unilateral sensory deficits, unilateral limb weakness, speech difficulties, visual loss, lack of coordination, gait disturbance, seizures, otherwise unexplained vomiting, otherwise unexplained acute hypertension, cranial nerve abnormality, mental status changes, or with papilledema or other signs of increased intracranial pressure
      iv. Clinical signs and symptoms strongly suggesting metastatic cancer as the cause of the headache
      v. Significantly immunocompromised patient (i.e., patient with HIV or immunosuppression)
      vi. Patients with risk factors for cerebral venous thrombosis:
         1. Pregnancy or post-partum
         2. Known history of active coagulation disorder (e.g., sickle cell crisis, or clinical signs of active coagulation disorder)
      vii. Fever or meningismus with suspected CNS cause
      viii. Reproducible headache immediately preceded by physical exertion, sexual activity, Valsalva maneuver, or positional change, e.g., leaning forward
   e. MRI can be considered in a **pediatric age (0-16 years old)** patient with worsening headache and **1 or more** of the following:
      i. Occipital location

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ii. Age < 6 years
iii. Repeatedly awakens child from sleep or is present upon awakening

II. **Acute, new, or fluctuating neurologic symptoms or deficits** such as **1 or more** of the following:
a. Ataxia or gait disturbance without other cause
b. Change in speech or language (e.g., dysarthria, aphasia)
c. Cranial nerve palsy (not otherwise explained (e.g., Bell's Palsy or diabetic CN III palsy)
d. Focal sensory /motor deficit suggesting brain or spinal cord cause (e.g., unilateral numbness or paresthesia's of face, arm and leg *OR* arm and leg)
e. Horner syndrome (unilateral miosis, ptosis, facial anhidrosis)
f. Papilledema
g. New visual disturbance (e.g., diplopia, visual field defect, nystagmus, visual loss)

III. **Evaluation of known or suspected seizure disorder and 1 or more** of the following:
a. New onset of a seizure (first focal seizure or first unprovoked generalized seizures)
b. Newly identified change in seizure activity/pattern not otherwise explained.
c. Medically refractory epilepsy
d. Preoperative evaluation when surgery being considered
e. Seizure in child younger than 2 years, excluding those with febrile seizures

IV. **Evaluation of movement disorders** – **Not indicated for **typical** Parkinson's Disease, essential tremor, primary dystonia, restless leg syndrome, or tics/spasms which can be duplicated at will*
a. Evaluation of suspected Parkinson's with atypical feature(s) or unresponsive to levodopa
b. Evaluation of new non-Parkinson symptoms in known Parkinson's disease complicating the evaluation of the current condition
c. Evaluation of other movement disorder to exclude a structural lesion (e.g., suspected Huntington disease, chorea, atypical parkinsonian syndromes, hemiballismus, secondary dystonia)
d. Prior to surgery or deep brain stimulation in patient with known Parkinson disease

V. **Evaluation of new or acutely worsened cognitive impairment with unclear cause (to rule out large frontal tumor or frontal stroke). Not indicated if the patient has a classic Alzheimer 's history of several years of progressive decline. CT may be sufficient if MRI cannot be done. Must meet ALL of the following:**
a. Change in mental status with a mental status score of either Mini-Mental State Exam (MMSE) or Montreal Cognitive Assessment (MoCA) of less than 26 or other similar mental status instruments showing at least mild cognitive impairment **AND**
b. A completed medication review and exclusion of medical causes (e.g., thyroid function testing, liver function testing, complete blood count, electrolytes, and B12) without cause found

VI. **Evaluation of known or suspected inflammatory disease or infection** (e.g., meningitis or abscess) for **1 of the following:**
a. Intracranial abscess or brain infection with acute altered mental status OR positive lab findings (such as elevated WBC's) OR follow up assessment during or after treatment completed
b. Meningitis with positive signs and symptoms (such as fever, headache, mental status changes, stiff neck) OR positive lab findings (such as abnormal lumbar puncture fluid exam)
c. Suspected encephalitis with a headache, altered mental status OR positive lab finding, (such as elevated WBC's)
d. Endocarditis with suspected septic emboli
e. Central nervous system (CNS) involvement in members with known or suspected vasculitis or autoimmune disease with positive lab findings

VII. **Evaluation of vertigo/dizziness** *All patients should have full neurologic examination, medication review, orthostatic vitals, and Dix-Hallpike test for peripheral vertigo prior to consideration of MRI.
MRI can be considered appropriate if **1 or more** of the following signs or symptoms suggestive of a CNS lesion:
a. Brainstem findings (e.g., dysarthria, Horner syndrome, double vision, vertical nystagmus) **OR**
b. Cerebellar findings (e.g., ataxia/incoordination of voluntary movements, intention tremor, disorder of equilibrium or gait, diminished muscle tone) **OR**
c. Focal neurologic findings (e.g., weakness, numbness, paresthesia's on one side of body) **OR**

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d. Acute or rapidly progressing unilateral hearing loss

VIII. **Evaluation of syncope, with 1 or more of the following:**
a. Concurrent bowel or bladder incontinence
b. Witnessed tonic-clonic seizure
c. Strong clinical suspicion of symptomatic third ventricular cyst

IX. **Precocious puberty** (central), as indicated by **ALL of the following**:
a. Clinical findings suggestive of central precocious puberty
b. Patient has been evaluated by pediatric endocrinologist

X. Global developmental delay or developmental delay with abnormal neurological examination (initial evaluation)

XI. Other indications for a brain MRI

Effective until May 1, 2024	a. Multiple sclerosis – known or strong clinical suspicion after discussion with neurology i. Frequency after diagnosis: annually to monitor for new lesions or following clinical flare up
Effective May 1, 2024	a. Multiple sclerosis – known or strong clinical suspicion after discussion with neurology. Frequency after diagnosis: i. annually to monitor for new lesions, or ii. following clinical symptoms of a flare up, or iii. 3-6 months after radiologic evidence of a flare up, or iv. iv. 3-6 months and/or 6-12 months after changing disease modifying agent

b. Trauma to the head with acute, new, or fluctuating neurologic findings
c. Brain tumor, mass, or metastasis – known or strong clinical suspicion based on history and physical exam
d. Routine surveillance of previously diagnosed brain tumor based on treatment plan from neuroscience specialty or oncology
e. Initial evaluation of stroke/TIA
f. Evaluation of known or suspected congenital abnormality with any acute, new, or fluctuating neurologic, motor, or mental status changes (hydrocephalus, craniosynostosis)
g. Evaluation of suspected acute subarachnoid hemorrhage (SAH) if CT scan is non-diagnostic
h. Evaluation of known or suspected cerebrospinal fluid (CSF) leakage
i. Follow-up of a recent brain hemorrhage to check for underlying tumor or AVM
j. Immunocompromised member (e.g., transplant recipients, HIV with CD4 < 200, primary immunodeficiency syndromes, hematologic malignancies) with focal neurologic symptoms, headaches, behavioral, cognitive, or personality changes
k. Pre-operative evaluation for brain/skull surgery, stereotactic radiosurgery
l. Post-operative/procedural evaluation - A follow-up study may be needed to help evaluate a member's progress after treatment, procedure, intervention or surgery. Documentation requires a medical reason that clearly indicates why additional imaging is needed for the type and area(s) requested
m. Suspected acoustic neuroma include IAC protocol (to ensure that imaging looks in detail at that part of the anatomy)
n. Anatomy or structural defect evaluation – e.g., when Chiari malformation is clinically suspected
o. Suspected intracranial vasculitis
p. Evaluation of neurological signs or symptoms in sickle cell disease
q. Unexplained acute unilateral hearing loss after other reasonable causes ruled out
r. Optic neuritis – consider orbit MRI in addition to brain MRI
s. Abnormal eye findings on physical or neurologic examination (e.g., papilledema, pathologic nystagmus, ocular nerve palsies, new onset anisocoria, visual field deficit)
t. Horner's syndrome with symptoms localizing the lesion to the central nervous system
u. Trigeminal neuralgia if medication is not effective or if atypical features/exam (e.g., bilateral, hearing loss, dizziness/vertigo, visual changes, sensory loss, numbness, pain >2 min, pain outside trigeminal nerve distribution, progression)
v. Bell's palsy - only if atypical signs, or no improvement at four months, or facial twitching/spasms prior to onset

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w. Psychological changes with neurological deficits on exam or after completion of a full neurological assessment by a neurologist that suggests a possible neurologic cause
x. Multiple cranial neuropathies.

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- Last 6 months of clinical notes from requesting provider &/or specialist

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Background

MRI can detect a variety of conditions of the brain such as cysts, tumors, bleeding, swelling, developmental and structural abnormalities, infections, inflammatory conditions, or problems with the blood vessels. It can determine if a shunt is working and detect damage to the brain caused by an injury or a stroke.

MRI of the brain can be useful in evaluating problems such as persistent headaches, dizziness, weakness, and blurry vision or seizures, and it can help to detect certain chronic diseases of the nervous system, such as multiple sclerosis.

In some cases, MRI can provide clear images of parts of the brain that can't be seen as well with an X-ray, CAT scan, or ultrasound, making it particularly valuable for diagnosing problems with the pituitary gland and brain stem.

Applicable Codes

Non-Medicare - Considered Medically Necessary when criteria in the applicable policy statements listed above are met
Medicare – Medical Necessity Review not required

CPT® or HCPCS Codes	Description
70551	Magnetic resonance (eg, proton) imaging, brain (including brain stem); without contrast material
70552	Magnetic resonance (eg, proton) imaging, brain (including brain stem); with contrast material(s)
70553	Magnetic resonance (eg, proton) imaging, brain (including brain stem); without contrast material, followed by contrast material(s) and further sequences

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Date Created	Date Reviewed	Date Last Revised
02/01/2022	02/01/2022[MPC], 02/07/2023[MPC]	12/09/2023

[MPC] Medical Policy Committee

Revision History	Description

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02/01/2022	MPC approved to adopt criteria for Brain MRI for non-Medicare members. Requires 60-day notice, effective date 07/01/2022.
12/09/2023	MPC approved to modify medical necessity criteria for brain MRI; allowing for a short-term imaging follow-up after radiologic signs of MS disease activity and more rapid imaging follow-up for up to one year following a change in therapy. Requires 60- day notice. Effective May 1, 2024

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Clinical Review Criteria
Knee Magnetic Resonance Imaging (MRI)

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Criteria

For Medicare Members

This policy does not apply to Medicare members.

For Non-Medicare Members

General principles:

- In general, MRIs are not appropriate for a knee with arthritis
- Require plain x-rays first
- MRI should only be done if surgical intervention is likely to be indicated *AND* there is documentation of concern for additional pathology

I. KPWA considers magnetic resonance imaging (MRI) studies of the knee medically necessary when *any* of the following criteria is met:

A. Joint anatomy or structural defect evaluation needed, as indicated by **1 or more** of the following:

- Loose body/mechanical symptoms in joint space, suspected and plain film negative
- Synovial pathology, as indicated by **1 or more** of the following:
  - Chronic synovitis secondary to hemarthrosis of hemophilia
  - Intra-articular venous malformation
  - Juvenile idiopathic arthritis with knee involvement, for assessment of joint involvement and treatment
  - Pigmented villonodular synovitis
  - Seronegative spondyloarthropathies (eg, ankylosing spondylitis, psoriatic arthritis) If recommended by Rheumatology
  - Synovial sarcoma
- Worrisome palpable mass, with normal findings on plain x-ray

B. Ligament tear, known or suspected, as indicated by **1 or more** of the following

1. Acute injury occurring with tearing or popping sound and with effusion on exam
2. Inability to bear weight after injury with negative x-rays and high suspicion for internal injury after one week of conservative treatment
3. Conservative treatment is not required prior to MRI if *any* of the following signs on physical exams are positive in comparison to the normal knee:
   - Anterior drawer test
   - Lachman test
   - Pivot shift test
   - Posterior drawer test
   - Posterior sag test

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- Valgus stress test
- Varus stress test

4. Postoperative assessment needed after ligament repair or reconstruction, if suspected graft failure/tear with symptoms of instability (i.e., giving way or buckling, particularly with sudden stops or rotational and cutting maneuvers)
5. Posttraumatic effusion with negative plain films
6. Symptoms of instability (i.e., giving way or buckling, particularly with sudden stops or rotational and cutting maneuvers) (with negative plain films)

C. Meniscus Tear/Injury:

Advanced imaging is considered medically necessary following nondiagnostic plain radiographs (and no significant arthritis on x-ray) in **ONE of the following** four scenarios:

1. Evaluation of *acute* knee pain after injury when **EITHER of the following** are present:
   A. Symptoms and exam findings of locking***
   B. Symptoms of catching, or instability with **one or more of the following** physical exam findings of meniscal tear:
      - Joint swelling or effusion
      - Positive McMurray, Thessaly or Apley test
      - Joint line tenderness
      - Inability to fully extend the knee
2. Evaluation of *chronic* knee pain in **ONE of the following** scenarios (if patient has no significant arthritis on x-ray):
   A. Symptoms and exam findings of locking***
   B. Symptoms of catching, or instability with and has had 4-6 weeks of conservative management, with **one or more of the following** physical exam findings of meniscal tear:
      - Joint swelling or effusion and no arthritis on x-ray
      - Positive McMurray, Thessaly or Apley test
      - Joint line tenderness
      - Inability to fully extend the knee
3. Effusion with acute injury or with subsequent episodes of minor injury or vigorous activity
4. Fractures with high association of meniscal tear (e.g., tibial plateau)

***Persistent true locking of the knee indicative of a torn meniscus or loose body. (True locking is defined as more than a momentary locking of the joint with the knee in a flexed position, as compared to the sensation of momentary “catching” that many individuals experience in extension.)

D. Osteomyelitis/Osteonecrosis

1. Suspected bone infection (i.e., osteomyelitis); *or*
2. Suspected osteochondritis dissecans or suspected osteonecrosis if the clinical picture, including x-rays, is not confirmatory.

E. Cancer or neoplasm evaluation or staging needed, as indicated by **1 or more** of the following:

Bone neoplasm (benign or malignant), as indicated by **1 or more** of the following:

- Abnormal finding on plain x-ray or bone scan
- Chondrosarcoma and **1 or more** of the following:
  - Initial staging
  - Monitoring response after treatment completed
  - Post-treatment surveillance for local tumor recurrence; intervals include **1 or more** of the following:
    - Low-grade and intercompartmental: every 6 to 12 months for 2 years, then annually as clinically indicated
  - High-grade (i.e., grade II or III), clear cell, or extra-compartmental: as clinically indicated
  - Current diagnosis or history of cancer located elsewhere and **BOTH** of the following:
    - Plain x-ray or bone scan findings indeterminate
    - Unexplained localized bony signs and symptoms (e.g., pain)
- Ewing sarcoma family of tumors and **1 or more** of the following:
  - Initial staging
  - Monitoring response after treatment completed

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- Post-treatment surveillance for local tumor recurrence; intervals include **1 or more** of the following:
  - Every 2 to 3 months for first 2 years, then decreasing frequency through year 5
  - Annually after 5 years

- Osteosarcoma and **1 or more** of the following:
  - Initial staging
  - Monitoring response after chemotherapy or radiation therapy
  - Post-treatment surveillance for local tumor recurrence; intervals include 1 or more of the following:
    - Every 3 months for 2 years
    - Every 4 months for year 3
    - Every 6 months for years 4 and 5
    - Annually after 5 years

II. KPWA considers knee MRI **experimental and investigational** for all other indications, including any of the following circumstances because its effectiveness for indications other than the ones listed above has not been established:
   A. If arthroscopy or ligament reconstruction is definitely planned and the MRI findings are unlikely to change the planned treatment; *or*
   B. If the clinical picture (i.e., history, physical examination, x-rays, etc.) is diagnostic with high degree of certainty of an isolated torn meniscus or loose body, or
   C. To diagnose or evaluate rheumatoid arthritis or degenerative joint disease.

If requesting this service (*or these services*), please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist
- Plain films/reports

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Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed

CPT® or HCPCS Codes	Description
73721	Magnetic resonance (eg, proton) imaging, any joint of lower extremity; without contrast material
73722	Magnetic resonance (eg, proton) imaging, any joint of lower extremity; with contrast material(s)
73723	Magnetic resonance (eg, proton) imaging, any joint of lower extremity; without contrast material(s), followed by contrast material(s) and further sequences

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed	Date Last Revised
12/03/2021	12/07/2021[MPC], 12/06/2022[MPC], 12/09/2023[MPC]	12/07/2021

[MPC] Medical Policy Committee

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Revision History	Description
12/07/2021	MPC approved to adopt criteria for Knee MRI for non-Medicare members. Requires 60-day notice, effective date 05/01/2022.

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Clinical Review Criteria
Magnetic Resonance Spectroscopy (MRS)

- ADHD
- Autism
- Cerebral Tumors
- Differentiating Tumors from Non-Tumors
- Epilepsy

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Magnetic Resonance Spectroscopy (220.2.1) **RETIRED** 06/08/2021 NCD Magnetic Resonance Spectroscopy (220.2.1) has been retired. These services still need to meet medical necessity as outlined in the NCD and will require review. NCDs are retired due to lack of evidence of current problems, or in some cases because the material is addressed by a National Coverage Decision (NCD), a coverage provision in a CMS interpretative manual or an article. Most NCDs are not retired because they are incorrect. Therefore, continue to use NCD 220.2.1.
Local Coverage Determinations (LCD)	None

For Non-Medicare Members

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

If requesting review for this service, please send the following documentation:

- Last 6 months of clinical notes from requesting provider &/or specialist

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Background

Magnetic resonance spectroscopy (MRS) is a non-invasive technique that provides chemical information on metabolites in tissues. It uses strong magnetic fields to generate an exchange of energy between external magnetic fields and protons within tissues. The energy exchange is transmitted back to the machine as a radiofrequency signal which is decoded by computer software. The software produces a waveform with peaks corresponding to the relative concentration of various chemicals. In addition, the specific chemicals that are present are identified--they appear at different locations on a horizontal axis. MRS utilizes the magnetic property of atomic nuclei. The proton is the most commonly studied nucleus. Proton (^{1}H) MRS defines approximately 15 brain metabolites. These include lipids, lactate, N-acetylaspartate (NAA), glutamate/glutamine (Glx), creatine (Cr), choline (Cho) and myinositol (mI) (Gulati et al., 2003; Lin et al., 2005; BlueCross BlueShield Association, 2005).

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A potential use of MRS is to diagnose conditions when other tests have been negative or inconclusive, or to refine existing diagnoses. For example, an increased Cho signal is believed to indicate the presence of cancerous cells. MRS can be used alone or in combination with magnetic resonance imaging (MRI) which produces anatomic images. In addition, MRS can be used to monitor metabolites to evaluate the effectiveness of therapy by seeing if levels change from elevated back to normal (Lin et al., 2005).

MRS has been used to study various neurologic diseases, including epilepsy, multiple sclerosis, HIV-related neurologic disorders and brain tumors, as well as cerebrovascular and metabolic diseases. One review article stated that MRS's most important use in neurology is quantifying neuronal loss and demonstrating reversible neuronal damage. (Rudkin & Arnold, 1999).

Other imaging tests used for epilepsy include EEG, MRI, FDG PET and CT scanning. ADHD and autism are diagnosed mainly by clinical evaluation. EEG and MRI are sometimes used to provide additional information on autism.

Cerebral Tumors
More than 190,000 people in the United States are diagnosed with primary or metastatic cerebral tumors annually. It is challenging to diagnose and treat cerebral tumors due to the similarity of these lesions to other types of pathologies on conventional imaging, the inaccessibility of the lesions and their proximity to complex brain structures. An accurate non-invasive method for diagnosing cerebral tumors is desirable, especially one that could replace biopsy which has a reported morbidity of 3-4% (AHRQ, 2003, Sibtain et al., 2007; National Brain Tumor Foundation).

Imaging procedures for diagnosing cerebral tumors include CT, MRI, SPECT and PET. CT uses x-rays and MRI uses non-ionizing radio frequency to acquire images. Both methods can generate multiple two-dimensional cross-sections of tissue as well as three-dimensional reconstructions and are generally used in conjunction with stereotactic biopsy. PET scans measure glucose activity which can be translated to a moving picture of the brain. SPECT imaging uses gamma rays to acquire multiple two-dimensional images from multiple angles, which can produce true three-dimensional information.

Magnetic resonance spectroscopy (MRS), a technique related to MRI, is also proposed for imaging cerebral tumors. MRS is a non-invasive technique that provides chemical information on metabolites in tissues. It uses strong magnetic fields to generate an exchange of energy between external magnetic fields and protons within tissues. The energy exchange is transmitted back to the machine as a radiofrequency signal which is decoded by computer software. The software produces a waveform with peaks corresponding to the relative concentration of various chemicals. In addition, the specific chemicals that are present are identified--they appear at different locations on a horizontal axis. MRS utilizes the magnetic property of atomic nuclei. The proton is the most commonly studied nucleus. Proton (1H) MRS defines approximately 15 brain metabolites. These include lipids, lactate, N-acetylaspartate (NAA), glutamate/glutamine (Glx), creatine (Cr), choline (Cho) and myinositol (mI). A chemical profile that may be characteristic of brain tumors includes an increase in Cho, and a reduction in Cr and NAA (Sibtain et al., 2007; Lin et al., 2005; BlueCross BlueShield Association, 2005).

Potential areas in which MRS may contribute diagnostic information include distinguishing abscesses from tumors, providing a more accurate way to determine the grade of primary tumors than conventional MRI, distinguishing single metastatic brain lesions from primary tumors, providing guidance for biopsy and gamma knife therapy, determining tumor recurrence and differentiating between radiation necrosis and tumor recurrence. MRS can be used alone, or in combination with MRI (AHRQ, 2003; Sibtain et al., 2007).

Several factors may limit the performance of MRS in identifying cerebral tumors. Sudden dramatic changes in the composition of tissue can cause inaccuracies in the magnetic fields. This is relevant for lesions adjacent to bone or air-filled structures such as the sinuses. Moreover, lesions that lie near areas of old infarcts or ischemic changes, or concurrent demyelinatin disease, can distort the chemical ratios used in interpretation. In addition, visual interpretation of spectra is difficult and requires special training (AHRQ, 2003; Sitbain et al., 2007).

Medical Technology Assessment Committee (MTAC)

Magnetic Resonance Spectroscopy (MRS)

12/05/2005: MTAC REVIEW

Evidence Conclusion: No published studies were identified on the accuracy of magnetic resonance spectroscopy for diagnosing ADHD or autism. One study was identified on the accuracy of MRS for lateralization

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of patients with medically refractory temporal lobe epilepsy. This study (Cendes et al., 1997) included 100 patients and used EEG as the gold standard. Lateralization based on MRS agreed with EEG findings in 87% of cases. Lateralization based on the results of MRS and MRI combined agreed with EEG findings in 86% of cases.
Articles: The ideal study of diagnostic accuracy would report the sensitivity and specificity of MRS and compare this to an independent blinded comparison to a "gold standard" diagnosis.
ADHD and autism None of the studies on ADHD, or ADHD and autism reported the sensitivity and specificity of MRS diagnosis compared to a "gold standard" such as clinical evaluation. The empirical studies reported on preliminary research using MRS to measure the concentrations of various chemicals in the brains of children with ADHD compared to healthy children. One of the articles included children with autism, in addition to children with ADHD and healthy controls. *Epilepsy* None of the studies on epilepsy reported the sensitivity and specificity of MRS diagnosis compared to a "gold standard". There were several studies examining the correlations between concentrations of chemicals identified by MRS and seizure duration, seizure severity or surgical outcome. One study compared chemical concentrations in patients with epilepsy and normal controls. These were all descriptive studies and were not evaluated further. One study was identified that compared the performance of MRI, MRS and the combination of the two in the lateralization of temporal lobe epilepsy (TLE). This article (Cendes et al., 1997) was critically appraised. No other studies on the diagnostic accuracy of MRS in patients with epilepsy were identified and no studies were identified on diagnostic or therapeutic impact.
The study critically appraised was: Cendes F, Caramanos Z, Andermann F et al. Proton magnetic resonance spectroscopic imaging and magnetic resonance imaging volumetry in the lateralization of temporal lobe epilepsy: A series of 100 patients. Ann Neurol 1997; 42: 737-746. See Evidence Table.

The use of Magnetic resonance spectroscopy (MRS) in diagnosing autism, ADHD and epilepsy does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

10/02/2006: MTAC REVIEW
Magnetic Resonance Spectroscopy (MRS)
Evidence Conclusion: No new published studies were identified on the accuracy of magnetic resonance spectroscopy for diagnosing ADHD, epilepsy or autism. No new studies were identified that validate specific chemical profiles that are diagnostic of particular conditions.
Articles: The ideal study of diagnostic accuracy would report the sensitivity and specificity of MRS and include an independent blinded comparison to a "gold standard" diagnosis. *ADHD and autism* - 2005 Review: None of the studies on ADHD, or ADHD and autism reported the sensitivity and specificity of MRS diagnosis compared to a "gold standard" such as clinical evaluation. The empirical studies reported on preliminary research using MRS to measure the concentrations of various chemicals in the brains of children with ADHD compared to healthy children. One of the articles included children with autism in addition to children with ADHD and healthy controls. 2006 Review: The newer studies were similar to those identified in the 2005 search. Studies reported on use of MRS to measure the concentrations of chemicals (i.e. Cho, CR and NAA) in children with autism or ADHD compared to healthy children. None of the studies reported the ability of MRS to diagnose autism or ADHD (i.e. sensitivity and specificity of MRS findings). *Epilepsy* - 2005 Review: None of the studies on epilepsy reported the sensitivity and specificity of MRS diagnosis compared to a "gold standard". Several studies examined the correlations between concentrations of chemicals identified by MRS and seizure duration, seizure severity or surgical outcome. One study compared chemical concentrations in patients with epilepsy and normal controls. These were all descriptive studies and were not evaluated further. One study compared the performance of MRI, MRS and the combination of the two in the lateralization of temporal lobe epilepsy (TLE). This article (Cendes et al., 1997) was critically appraised. 2006 Review: One meta-analysis was identified. This study (Willmann et al., in press, 2006) assessed the pre-operative value of MRS in identifying the epileptogenic zone (EZ) for epilepsy surgery. Preoperative evaluation of epilepsy patients is outside the scope of the current review and the study was thus not evaluated further.

The use of Magnetic resonance spectroscopy (MRS) in diagnosing autism, ADHD and epilepsy does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

12/03/2007: MTAC REVIEW
Magnetic Resonance Spectroscopy (MRS)
Evidence Conclusion: Three studies were reviewed that reported the sensitivity and specificity of MRS for distinguishing brain tumors from non-tumors, compared to a reference standard. All had relatively small sample sizes, especially as regards the number of patients without tumors, so estimates may not be reliable. One of the studies used combined MRS/MRI findings. Sensitivity ranged from 81% to 90% and specificity from 86% to 100%. The size of the studies was too small to draw conclusions about the accuracy of MRS for differentiating between brain tumors and any specific alternate condition such as radiation necrosis or abscess. There is a lack of

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evidence on the diagnostic accuracy of MRS alone compared to conventional imaging, or on MRS plus conventional imaging versus conventional imaging alone. Thus, it is difficult to draw conclusions about the ability of MRS to replace other diagnostic tests. Two studies addressed the impact of MRS on clinical decision-making. Both were case series; Lin et al., 1999 was limited in that it had only 15 patients, and Adamson et al. was retrospective. In the Adamson et al., study, MRS was seen as having a potential positive impact on treatment in 23/78 (29%) of cases. In 2 cases, MRS was seen as having a potential negative impact on treatment. For the remainder of the cases, MRS was viewed as neutral, or patients were lost to follow-up. In the Lin study, which only included 15 patients, MRS was used in place of biopsy in 7 cases, and MRS was correlated with clinical course in 6 cases. MRS did not correlate with clinical course in only 1 patient.

Articles: *Accuracy of MRS* the ideal study of diagnostic accuracy would report the sensitivity and specificity of MRS and include an independent blinded comparison to a "gold standard" diagnosis. Several studies met these criteria and were critically appraised. All had relatively small sample sizes. Rand et al., 1997 and McKnight et al., 2002 evaluated MRS alone and Gajewicz et al., 2003 evaluated MRS in combination with MRI. Rand SD, Prost P, Haughton V et al. Accuracy of single-voxel proton MR spectroscopy in distinguishing neoplastic from nonneoplastic brain lesions. AJRN 1997; 18: 1685-1704. See Evidence Table. McKnight TR, von dem Bussche BS, Vigneron DB. et al., Histopathological validation of a three-dimensional magnetic resonance spectroscopy index as a predictor of tumor presence. J Neurosurg 2002; 97: 794-802. See Evidence Table. Gajewicz W, Papierz W, Szymczak W et al. The use of proton MRS in the differential diagnosis of brain tumors and tumor-like processes. Med Sci Monit 2003; 9: MT97-105. See Evidence Table. Diagnostic impact (does MRS contributes substantially to improved diagnosis and/or replace other diagnostic tests or procedures). There were no studies comparing diagnosis with MRS to diagnosis with conventional imaging. Therapeutic impact of MRS (is more appropriate therapy is used after application of MRS than would be used if the test were not available). Two studies that evaluated the impact of MRS on clinical decision-making were identified and critically appraised: Adamson AJ, Rand SD, Prost RW et al. Focal brain lesions: Effect of single-voxel proton MR spectroscopic findings on treatment decisions. Radiol 1998; 209: 73-78. See Evidence Table**.** Lin A, Blum s, Mamelak AN. Efficacy of proton magnetic resonance spectroscopy in clinical decision making for patients with suspected malignant brain tumors. J Neuro-Oncol 1999; 45: 69-81. See Evidence Table.

The use of Magnetic resonance spectroscopy (MRS) in diagnosing cerebral tumors and differentiating tumors from non-tumors does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Applicable Codes

Considered Not Medically Necessary:

CPT® Codes	Description
76390	Magnetic resonance spectroscopy

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
12/23/2005	05/03/2011 MDCRPC, 08/02/2011 MDCRPC, 06/05/2012 MDCRPC, 04/02/2013 MDCRPC, 02/04/2014 MPC, 12/02/2014MPC, 10/06/2015MPC, 08/02/2016MPC, 06/06/2017MPC, 04/03/2018MPC, 04/02/2019MPC, 04/07/2020MPC, 04/06/2021MPC, 04/05/2022MPC, 04/04/2023MPC	11/18/2021

MDCRPC Medical Director Clinical Review and Policy Committee

MPC Medical Policy Committee

Revision History	Description
02/04/2020	MPC approved to remove MCG guideline A-0482 and to retain policy of non-coverage. Also added language that states, Clinical Review physician should consult with KP Neuroradiology on any requests received.
11/18/2021	Medicare Retired NCD (220.2.1) Magnetic Resonance Spectroscopy

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Clinical Review Criteria
Myocardial Perfusion Imaging

- Exercise Nuclear Stress Test
- Pharmacologic Nuclear Stress Test

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	Cardiovascular Stress Testing, Including Exercise and/or Pharmacological Stress and Stress Echocardiography (L36889) *In addition, LCD L36889 references:* Journal of the American College of Cardiology, Volume 53, Issue 23
Local Coverage Article (LCA)	Billing and Coding: Cardiovascular Stress Testing, Including Exercise and/or Pharmacological Stress and Stress Echocardiography (A57184)

For Non-Medicare Members

Service	Criteria Used
Exercise Nuclear Stress Test	Kaiser Permanente has elected to use the Myocardial Perfusion Imaging, Exercise Stress (KP-0078 02012024) MCG* for medical necessity determinations. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.
Pharmacologic Nuclear Stress Test	Kaiser Permanente has elected to use the Myocardial Perfusion Imaging, Pharmacologic Stress (KP-0079 02012024) MCG* for medical necessity determinations. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.

ASCVD Risk Estimator Plus (American College of Cardiology): please click here

***MCG manuals are proprietary and cannot be published and/or distributed**. However, on an individual member basis, Kaiser Permanente can share a copy of the specific criteria document used to make a utilization management decision. If one of your patients is being reviewed using these criteria, you may request a copy of the criteria by calling the Kaiser Permanente Clinical Review staff at 1-800-289-1363 or access the MCG Guideline Index using the link provided above.

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If requesting these services, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist

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Background

Myocardial perfusion exercise stress imaging, such as stress SPECT, involves intravenous injection of a radioactive tracer (eg, thallium, sestamibi, or tetrofosmin), which is taken up by myocardial cells and visualized by a digital gamma camera, thereby reflecting the distribution of blood perfusion throughout the myocardium. A defect in the image with exercise that is not present at rest usually indicates an area of myocardial ischemia. Myocardial perfusion imaging synchronized with ECG (eg, gated SPECT) can assess ventricular function, including ejection fraction, in addition to myocardial perfusion. Myocardial perfusion imaging has been noted by specialty societies to have the most clinical utility in patients who are at intermediate risk for coronary artery disease, in those requiring management or prognostic information, and in those with unexplained and persistent symptoms. Myocardial perfusion imaging systems that combine SPECT and CT technology (also known as "hybrid" systems) are now widely available. It has been noted that myocardial perfusion scans contribute at least 20% of the estimated annual collective radiation dose in the United States, although the lifetime cancer risk from a single myocardial perfusion imaging study is thought to be small. Best-practice methods to maximize diagnostic quality while minimizing radiation exposure have been proposed.

Pharmacologic stress myocardial perfusion imaging, such as pharmacologic stress SPECT, involves intravenous injection of a radioactive tracer (eg, thallium, sestamibi, or tetrofosmin), which is taken up by myocardial cells and visualized by a digital gamma camera, thereby reflecting the distribution of blood perfusion throughout the myocardium. Coronary hyperemia is induced by a vasodilator, such as adenosine, dipyridamole, or regadenoson, or an adrenergic agent such as dobutamine, in lieu of stress via exercise or in addition to submaximal exercise. A defect in the image with stress that is not present at rest usually indicates an area of myocardial ischemia. Myocardial perfusion imaging synchronized with ECG (eg, gated SPECT) can assess ventricular function, including ejection fraction, in addition to myocardial perfusion. Pharmacologic stress testing using the vasodilator agent's adenosine and dipyridamole is contraindicated in patients with severe reactive airway disease (eg, asthma or chronic obstructive pulmonary disease) because of provocation of bronchospasm; regadenoson or dobutamine may be substituted in this population.

Myocardial perfusion imaging has been noted by specialty societies to have the most clinical utility in patients who are at intermediate risk for coronary artery disease, in those requiring management or prognostic information, and in those with unexplained and persistent symptoms. Myocardial perfusion imaging systems that combine SPECT and CT technology (also known as "hybrid" systems) are now widely available. It has been noted that myocardial perfusion scans contribute at least 20% of the estimated annual collective radiation dose in the United States, although the lifetime cancer risk from a single myocardial perfusion imaging study is thought to be small. Best-practice methods to maximize diagnostic quality while minimizing radiation exposure have been proposed.

Applicable Codes

Myocardial Perfusion Imaging, Exercise or Pharmacologic Stress—

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
78451	Myocardial perfusion imaging, tomographic (SPECT) (including attenuation correction, qualitative or quantitative wall motion, ejection fraction by first pass or gated technique, additional quantification, when performed); single study, at rest or stress (exercise or pharmacologic)

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78452	Myocardial perfusion imaging, tomographic (SPECT) (including attenuation correction, qualitative or quantitative wall motion, ejection fraction by first pass or gated technique, additional quantification, when performed); multiple studies, at rest and/or stress (exercise or pharmacologic) and/or redistribution and/or rest reinjection
78453	Myocardial perfusion imaging, planar (including qualitative or quantitative wall motion, ejection fraction by first pass or gated technique, additional quantification, when performed); single study, at rest or stress (exercise or pharmacologic)
78454	Myocardial perfusion imaging, planar (including qualitative or quantitative wall motion, ejection fraction by first pass or gated technique, additional quantification, when performed); multiple studies, at rest and/or stress (exercise or pharmacologic) and/or redistribution and/or rest reinjection

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Date Created	Date Reviewed	Date Last Revised
01/05/2021	01/05/2021[MPC], 01/04/2022[MPC], 01/10/2023[MPC]	11/07/2023

[MPC] Medical Policy Committee

Revision History	Description
05/20/2021	Updated policy effective date to 7/1/2021. Medical necessity review requirement does not apply to Medicare.
02/16/2022	Updated applicable codes
08/24/2022	Added Cardiac Risk Calculator link
09/05/2023	MPC approved the updated changes to the hybrid criteria to improve the performance of the MPI criteria. Requires 60-day notice, effective February 1, 2024.
11/07/2023	MPC approved to initiate medical necessity review of MPI for Medicare Advantage members to align with 2024 CMS final rule. Requires expedited 60-day notice, effective February 1, 2024.

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KAISER PERMANENTE®

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Clinical Review Criteria
Myocardial Strain Imaging
- Speckle-tracking echocardiography

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article (LCA)	None
Kaiser Permanente Medical Policy	Due to the absence of an active NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Clinical Review Criteria, ***Myocardial Strain Imaging*** for medical necessity determinations. Refer to the Non-Medicare criteria below.

For Non-Medicare Members

Myocardial strain imaging is considered medically necessary:
- Prior to, during, or following exposure to oncology medications* that could result in cardiotoxicity

*Including but not limited to – doxorubicin (Adriamycin); trastuzumab (Herceptin, Kanjinti); pertuzumab (Perjeta); ado-trastuzumab emtansine (Kadcyla); fam-trastuzumab deruxtecan (Enhertu); mitoxantrone (Novantrone); liposomal doxorubicin (Doxil)

Myocardial strain imaging is considered experimental, investigational or unproven for all other indications.

If requesting this service, please send the following documentation to support medical necessity:
- Last 6 months of clinical notes from requesting provider &/or specialist

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Background

Technology Description

Myocardial strain imaging (MSI) involves a sophisticated analysis of images from echocardiography. Reflection of ultrasonic waves from myocardial tissue creates stable patterns of brighter and darker spots (speckles) that can

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serve as "fingerprints" to identify specific segments of the myocardial walls. Image processing computer software tracks the movement of these patterns to assess the severity of myocardial damage and abnormal heart function.

Quality of the Evidence
The body of evidence concerning diagnostic and prognostic use of MSI was large in size and overall low in quality. The overall low-quality rating for the body of evidence reflects individual study limitations, wide variability in the MSI parameters used for diagnosis or prognosis in DCM, and the absence of studies evaluating the clinical utility of MSI in patients with DCM. Overall quality was determined based on the balance of benefits and harms and was assessed taking into consideration the quality of individual studies; the precision, directness, and consistency of data; and the applicability of data to general practice.

Conclusion
The available studies have not provided sufficient evidence to evaluate diagnostic uses of MSI in DCM patients due to the small number and diverse applications of MSI in diagnostic studies. Although some prognostic studies found that certain MSI parameters had statistically significant correlations with health outcomes, results were not consistent across studies and the parameter that appeared most accurate for prognosis (early DSR) was measured in only 1 study. Furthermore, no studies of the clinical utility of MSI were identified to evaluate whether the diagnostic and prognostic information obtained from MSI can be used to improve patient management. MSI does not pose any safety concerns. Additional studies are needed to identify the optimal MSI parameters for diagnosis and prognosis in DCM patients and to demonstrate that guidance of care with MSI provides meaningful improvements in health outcomes for DCM patients.

Insights
- MSI can be used to measure many types of changes and rates of change in myocardial length, shape, and rotation in each of the 4 heart chambers. More research is needed to evaluate which of these measurements are most useful for all of the potential diagnostic and prognostic uses of MSI.

- Although the equipment needed to perform echocardiographic MSI is much less complicated than the equipment needed for cardiac magnetic resonance imaging (MRI), MSI may be less accurate and there is little evidence addressing the relative accuracy of these techniques. Only 1 study compared MSI with cardiac MRI; therefore, additional studies are needed to evaluate the relative accuracy of these techniques in patients with DCM.

- MSI may provide some useful diagnostic or prognostic information if cardiac MRI is not available or not feasible.

- Two studies that included exercise testing or cardiac stress testing obtained results that greatly differed from results of measurements obtained solely in resting patients, suggesting that additional MSI studies incorporating exercise and stress testing are needed.

Reference
Hayes. Hayes Health Technology Assessment. Myocardial Strain Imaging by Speckle-Tracking Echocardiography for Evaluation of Dilated Cardiomyopathy. Dallas, TX: Hayes; September 24, 2020. Retrieved January 7, 2022 from https://evidence.hayesinc.com/report/dir.myocardialstrain4712.

Applicable Codes

Considered Not Medically Necessary:

CPT® or HCPCS Codes	Description
93356	Myocardial strain imaging using speckle tracking-derived assessment of myocardial mechanics (List separately in addition to codes for echocardiography imaging)

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Date Created	Date Reviewed	Date Last Revised
01/18/2022	02/01/2022[MPC],02/07/2023[MPC]	

[MPC] Medical Policy Committee

Revision History	Description
02/01/2022	MPC approved to adopt criteria for Myocardial Strain Imaging. Requires 60-day notice, effective date 07/01/2022.

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KAISER PERMANENTE®

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Clinical Review Criteria

Nasal Cryoablation, Radiofrequency Ablation & Laser Treatments

- ClariFix® Cryotherapy for Chronic Rhinitis
- VivAer®
- RhinAer®

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article (LCA)	None
Kaiser Permanente Medical Policy	**Clarifix®, VivAer® & RhinAer®** Due to the absence of an active NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Clinical Review Criteria, "***Nasal Cryoablation, Radiofrequency Ablation & Laser Treatments***" for medical necessity determinations. Use the Non-Medicare criteria below.

For Non-Medicare Members

Non-Medicare

Service	Criteria
Nasal Cryoablation, Radiofrequency Ablation & Laser Treatments	
Cryoablation for allergic or nonallergic chronic rhinitis (e.g., Clarifix® device) (CPT 31243)	There is insufficient evidence in the published medical literature to show that this therapy is as safe as standard service/therapies and/or provides better long-term outcomes than current standard services/therapies.
Radiofrequency ablation for the treatment of airway obstruction (e.g., VivAer® Stylus device) (CPT 31242)	There is insufficient evidence in the published medical literature to show that this therapy is as safe as standard service/therapies and/or provides better long-term outcomes than current standard services/therapies
Radiofrequency ablation for allergic or nonallergic chronic rhinitis (e.g., RhinAer® Stylus device) (CPT 31242)	There is insufficient evidence in the published medical literature to show that this therapy is as safe as standard service/therapies and/or provides better long-term outcomes than current standard services/therapies.

If requesting review for this service, please send the following documentation:

- Last 6 months of clinical notes from requesting provider &/or specialist

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Background

Chronic rhinitis is long-term inflammatory condition of the nasal mucosa. Its etiology is not precisely understood, but it is thought to result from deregulation of the autonomic innervation of the nasal mucosa leading to increased vascular permeability, mucous secretion and edema. Rhinitis is generally classified as allergic and non-allergic rhinitis. Allergic rhinitis may be seasonal, perennial or both and is mainly characterized by sneezing, runny nose, stuffiness, and itchy watery eyes. The symptoms of non-allergic rhinitis include nasal obstruction, irritability, and hypersecretion (Kompelli 2018, Chang 2019, Krespi 2020).

The first-line treatment of chronic rhinitis involves avoiding known triggers and the use of over the counter or prescription medications including saline irrigation, topical steroids, topical or systemic adrenergic agents, antihistamine therapy, anticholinergic agents, and antileukotrienes. Medication use improves symptoms for the majority of patients, but needs constant daily use, and may not completely control symptoms in some patients (Kompelli 2018, Chang 2019, Krespi 2020).

Different procedural or operative interventions have been developed over the years for the treatment of patients with medically refractory rhinitis. Vidian neurectomy, first described in the early 1960s, aims at disrupting preganglionic parasympathetic innervation (autonomic supply) of the nasal mucosa. The surgery was found to be effective in reducing the symptoms of chronic rhinitis, but had its complications including severe bleeding from the sphenopalatine artery, numbness of the cheek and palate, and persistent dry eye symptoms due to the collateral disruption of the parasympathetic innervation of the lacrimal gland. In addition, the procedure must be performed in an operating room under general anesthesia. Resection of the postganglionic nerve fibers via the posterior nasal nerves (PNN) was proposed as an alternative for vidian neurectomy to avoid the dry eye complication. However, its use is limited by its technical complexity, lack of complete resolution of symptoms in some patients, and similar the vidian neurectomy, it must be performed in an operating room under general anesthesia (Huang 2017, Kompelli 2018, Chang 2019, Yan 2020).

Cryosurgical therapy for the treatment of chronic rhinitis was first proposed in the early 1970s and involves the placement of a cryoprobe in the nasal cavity against the posterior end of the inferior turbinate. Several cryoablation devices were developed over the years including Basco-Cryos, Krymed, Frigitronic, Cryospray, Cooper's cryo Unit, and SAmils Cryo. Cryotherapy for rhinitis, however. was not widely adopted due to its potential complications, lack of endoscopic visualization, non-ergonomic probe design, need for external cryogen reservoirs, and other associated challenges (Hwang 2017, Kompelli 2018, Yan 2020).

More recently a novel cryotherapy device (ClariFix™) was developed for cryosurgical ablation of the PNN region in an office setting and under local or mild sedation. The procedure involves the introduction of a cryosurgical ablation device under endoscopic visualization to deliver cryogen to the posterior middle meatus and freeze the posterior nerve (Yan,2020).

The ClariFix™ cryoablation device (Arrinex Inc, redwood City, CA, recently acquired by Stryker Corporation, Kalamazoo MI) is a hand-held, single-use, disposable cryosurgical device (cryoprobe) that uses nitrous oxide as the cryogen to freeze the mucosal tissue in a targeted fashion in the nasal cavity. The target tissue lies in the posterior aspect of the middle meatus adjacent to the sphenopalatine foramen and corresponding to the trajectory of the PNN as it emerges from the pterygopalatine fossa. The cryogen cartridge is inserted into the handle of the device immediately prior to the procedure. The Cryoprobe is then placed into contact with the target tissue via direct endoscopic visualization under local anesthesia with the patient seated upright or partially reclined. Once the Cryoprobe is in the desired position, the cryogen is released into the probe tip by the surgeon via a control dial. As cryogen flows into the Cryoprobe, the liquid partially evaporates and the inside of the Cryoprobe cools to -60 to -80°C; a freezing zone forms in the adjacent tissue destroying the unwanted tissue. The treatment is estimated to achieve
-20°C cryoablation at a depth of 3 millimeters. Nitrous oxide is fully contained within the Cryoprobe and does not come in direct contact with the tissue. Once the Cryoprobe has thawed it can be safely removed from the treatment area. The cryoprobe is activated for a single treatment of 30-60 seconds for each side. Additional

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treatment cycles can be initiated at the physician's discretion. The device is designed for singe patient use and is disposable. (Huang 2017, Chang 2019, FDA website).

The most common side effects associated with ClariFix cryotherapy are temporary increased congestion and transient pain or discomfort. Other reported adverse events include moderate or severe nasal dryness, nose bleeds, headache, ear blockage, dry eyes, watery eyes, oral numbness and sinusitis.

Hayes Conclusion

There is insufficient published evidence to evaluate the use of ClariFix for treatment of chronic rhinitis.

Reference

Cryotherapy Using ClariFix (Arrinex Inc.) for Treatment of Chronic Rhinitis. (2019, October 24). Retrieved July 10, 2020, from https://evidence.hayesinc.com/report/hss.clarifix4569

Medical Technology Assessment Committee (MTAC)

CRYOTHERAPY FOR THE TREATMENT OF CHRONIC RHINITIS USING THE CLARIFIX DEVICE

7/13/2020: MTAC REVIEW

The literature search did not identify any published randomized controlled trials, to date, that compared cryoablation therapy for chronic rhinitis using the ClariFix device versus any medical therapy, surgery, or a sham procedure. The published literature on ClariFix consisted of a small pilot study (Evidence table 1), and a prospective observational multicenter single-arm open-label study (Evidence table 2). The two studies were sponsored by the manufacturer and were subject to selection and observational bias.

Evidence Conclusion:

There is insufficient published evidence to date, to support Cryosurgery using ClariFix device for the treatment of chronic rhinitis.

The use of ClariFix® Cryotherapy for Chronic Rhinitis does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

TEMPERATURE-CONTROLLED RADIOFREQUENCY NEUROLYSIS of THE POSTERIOR NASAL NERVE FOR THE TREATMENT OF CHRONIC RHINITIS USING RHINAER SYSTEM

10/09/2023: MTAC REVIEW

Evidence Conclusion:

- The overall strength of the published evidence on the use of RhinAer device for the treatment of patients with symptomatic chronic rhinitis is low and insufficient to recommend its use for this indication.
- The published studies to date were industry funded and limited by their small number, small population sizes, short follow-up duration, study design, lack of RCTs with active comparators, use of subjective outcome measures, and lack of adjustments for confounding factors.
- More well-designed double-blinded randomized clinical trials directly comparing the RhinAer device therapy with other active surgical or non-surgical therapies with longer follow -up for both the active and control groups and are needed to provide higher quality evidence on the efficacy and safety the temperature-controlled radiofrequency device in the treatment of patients with chronic rhinitis.

Articles: The literature search identified one RCT, two prospective single arm studies and two systematic reviews with meta-analyses of the results of published studies. The RCT and a SR with MA were selected for critical appraisal.

The use of RhinAer for the treatment of Chronic Rhinitis does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

TEMPERATURE-CONTROLLED RADIOFREQUENCY TREATMENT OF NASAL AIRWAY OBSTRUCTION USING VIVAER SYSTEM

10/09/2023: MTAC REVIEW

Evidence Conclusion: The strength of the published evidence is low and insufficient to recommend the use of VivAer temperature-controlled radiofrequency device for remodeling the nasal valve in patients with nasal airway obstruction.

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The published studies to date are limited by their small number, small population sizes, short follow-up duration, study design, lack of RCTs with active comparators, use of subjective outcome measures, and lack of adjustments for confounding factors.

More well-designed double blinded randomized clinical trials comparing the VivAer device therapy to other active surgical or non-surgical therapies and using validated outcome measures are needed to provide higher quality evidence on the efficacy and safety the temperature-controlled radiofrequency device treatment of the nasal valve for patients with nasal airway obstruction.

Articles: PubMed and Cochrane database were searched through September 2023, for published studies evaluating the effectiveness and safety of temperature-controlled radiofrequency treatment of nasal airway obstruction using VivAer system. The search strategy used the terms*, airway obstruction, nasal valve, nasal valve collapse, radiofrequency device, temperature-controlled radiofrequency, treatment, VivAer,* and *minimally invasive surgery* with variations.

1. The search was limited to English language publications in peer-reviewed journals. Experimental studies, abstracts, case reports, case series with less than 25 patients, reviews, comments, and editorials were excluded. Preference was given to meta-analyses and randomized controlled trials reporting on clinical outcomes.
2. Reference lists of the retrieved articles were manually searched to for additional studies.
3. To identify ongoing clinical trials, a search of the National Institute of Health Clinical Trials website https://clinicaltrials.gov/ was conducted using the same methodology.

The use of VivAer for Nasal Obstruction does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Hayes Conclusion

VivAer (Aerin Medical Inc.) for Nasal Airway Remodeling to Treat Nasal Obstruction

A review of full-text clinical studies suggests minimal support for using the VivAer radiofrequency (RF) procedure for remodeling the nasal valve area when collapse of the nasal valve is associated with chronic nasal obstructive symptoms. This level of support reflects:

- Four clinical studies were identified, 3 of which were rated poor or very poor quality.
- Only 1 study compared VivAer with sham. No studies evaluated VivAer with another active treatment.
- Results were consistent across studies in direction and significance (both clinical and statistical) for patient-reported outcomes.
- The rate of clinical response exceeded 85%, and all studies reported improvements in symptom scores. VivAer also appears to improve nasal patency and may improve quality of life (QOL), especially as a result of improved sleep.
- VivAer appears to be safe, with most adverse effects (AEs) being mild, transient, and infrequently reported.
- The duration of effect was reported to last up to 4 years in 1 study. However, the follow-up duration of the sham-controlled part of the randomized controlled trial (RCT) was only 3 months.
- Only 1 study reported objective measures of nasal patency and airflow

RhinAer Procedure (Aerin Medical) for Treatment of Chronic Rhinitis

A review of full-text clinical studies suggests minimal support for using the RhinAer procedure to treat chronic rhinitis. This level of support reflects:

- 2 studies (1 poor quality, 1 fair quality) reported most patients had clinically significant nasal symptom relief after treatment
- 1 also reported more patients improved after RhinAer than sham
- No studies compared RhinAer with another treatment, so the current evidence does not inform whether its outcomes are better, worse, or the same as any other treatment.

Applicable Codes

Considered Not Medically Necessary - experimental, investigational, or unproven:

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CPT® or HCPCS Codes	Description
30117	Excision or destruction (eg, laser), intranasal lesion; internal approach
31242	Nasal/sinus endoscopy, surgical; with destruction by radiofrequency ablation, posterior nasal nerve
31423	Nasal/sinus endoscopy, surgical; with destruction by cryoablation, posterior nasal nerve
C9771	Nasal/sinus endoscopy, cryoablation nasal tissue(s) and/or nerve(s), unilateral or bilateral

ICD-10 Codes	Description
J30.0	Vasomotor rhinitis
J30.1-J30.9	Allergic rhinitis
J31.0	Chronic rhinitis
J31.1	Chronic nasopharyngitis
J34.89	Other specified disorders of nose and nasal sinuses
R09.81	Nasal congestion
R09.82	Postnasal drip

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Date Created	Date Reviewed	Date Last Revised
09/01/2020	09/01/2020 MPC, 09/07/2021 MPC, 09/06/2022MPC, 09/05/2023MPC	01/09/2024

MPC Medical Policy Committee

Revision History	Description
09/01/2020	MPC approved to endorse a non-coverage policy for ClariFix/cryotherapy for chronic rhinitis
09/05/2023	MPC approved the clinical criteria name change to Nasal Cryoablation, Radiofrequency Ablation & Laser Treatments. MPC approved to adopt non-coverage indications for Radiofrequency ablation for the treatment of airway obstruction (e.g., VivAer® Stylus device) and Radiofrequency ablation for allergic or nonallergic chronic rhinitis (e.g., RhinAer® Stylus device). Requires 60-day notice, effective February 1, 2024.
01/09/2024	Added MTAC reviews for RhinAer for the treatment of Chronic Rhinitis and VivAer for the treatment of Nasal Obstruction.
02/22/2024	Added new codes effective 1/1/2024 31242 & 31243.

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Clinical Review Criteria
Naturopathy

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Criteria

For Medicare Members

Naturopathy is not covered by Medicare and is considered a supplemental benefit. Please check member contract for specific coverage language.

For Non-Medicare Members

I. Authorizations for covered naturopathic treatments beyond three visits require prior approval by the health plan for those plans with alternative medicine benefits.

II. Clinical review criteria for naturopathy are as follows:
   A. The patient has an established, documented diagnosis of **ONE of the following**:
      1. Fibromyalgia (The patient has an established, documented diagnosis of fibromyalgia consistent with the 1990 American College of Rheumatology Criteria.)
      2. Chronic arthritis
      3. Chronic fatigue syndrome
      4. Premenstrual syndrome
      5. Irritable bowel syndrome
      6. Menopausal symptoms
      7. Headaches (persistent sinus, muscle tension, migraine)
      8. Chronic sinusitis, defined as persistent sinusitis
      9. Chronic serious otitis media, defined as persistent middle ear fluid for greater than three months
      10. Atopic dermatitis/chronic eczema
      11. Asthma that is mild to moderate in severity and not dependent on oral steroids
   B. Treatment progress reports submitted to the health plan after the second visit, or at intervals as specified in the referral, must demonstrate the benefit of treatment for continuation of care to be approved.

Review Services will consider each referral request on a case-by-case basis and will consider requests outside the above criteria based on, among other things, clear documentation of objective improvement by the licensed naturopathic physician or the patient's personal physician, as well as a detailed treatment plan.

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Background

Naturopathic medicine is a distinct profession of health care that has been in existence since the late nineteenth century. The philosophical approach includes the following principles:

- Utilization of therapies that first do no harm.
- Prevention of disease through healthy lifestyle and control of risk factors.
- Recognition and encouragement of the body's inherent healing abilities.

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- Treatment of the whole person – physical, emotional, mental, and spiritual.
- Patient education and cultivation of an attitude of personal responsibility for one's health.

Education standards for naturopathic medicine require at least three years of college level work followed by a four-year curriculum with over 4,000 hours of instruction at an accredited training institution (such as Bastyr University). In addition to conventional basic science courses, students receive training in botanical medicine, therapeutic nutrition, and various physical medicine modalities. Naturopathic physicians are licensed in the state of Washington and in ten other states.

Evidence and Source Documents

There is a small body of literature that supports some of the interventions that naturopaths provide.

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
Service Specialty: Naturopathy; TOS 320	

Date Created	Date Reviewed	Date Last Revised
11/15/2002	08/03/2010[MDCRPC], 06/07/2011[MDCRPC], 04/03/2012[MDCRPC], 02/05/2013[MDCRPC], 12/03/2013[MPC], 10/07/2014[MPC], 08/04/2015[MPC], 06/07/2016[MPC], 04/04/2017[MPC], 02/06/2018[MPC], 01/08/2019[MPC], 01/07/2020[MPC], 01/05/2021[MPC], 01/04/2022[MPC], 01/10/2023[MPC]	11/25/2002

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description

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Clinical Review Criteria
Negative Pressure Wound Therapy

- Pumps
- PICO (non-powered)
- SNAP (non-powered)
- Single Use Negative Pressure Wound Therapy (s-NPWT) for the Prevention of Surgical Site Infections (SSIs) in Closed Surgical Incisions

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	Negative Pressure Wound Therapy Pumps (L33821) for traditional NPWT covered under DME Wound Care (L37228) *Mentions disposable NPWT (dNPWT)*
Local Coverage Article	Negative Pressure Wound Therapy Pumps (A52511) for traditional NPWT covered under DME
MLN Matters Article	Separate Payment for Disposable Negative Pressure Wound Therapy Devices on Home Health Claims *For disposable NPWT provided by Home Health Agency*

For Non-Medicare Members

Service	Criteria
Initial Coverage—Traditional Negative Pressure Wound Therapy Pump (tNPWT)	Traditional Negative Pressure Wound Therapy Pumps (tNPWT) A traditional NPWT (tNPWT) pump and supplies are covered for wound edema, exudate management and stimulation of granulation for an initial 30-day course when the following main criteria are met: A. Ulcers and Wounds in the Home Setting: 1. The patient has a Stage III or IV pressure ulcer, neuropathic/diabetic ulcer, venous insufficiency or arterial ulcer, or a chronic ulcer of mixed etiology. These wounds should have exudate, size and depth to require this specialized therapy. A complete wound therapy program described by criterion i. and criteria ii., iii., or iv., as applicable depending on the type of wound, should have been tried for 30 days unless edema and/or exudate mandates NPWT. i. For all ulcers or wounds, the following components of a wound therapy program must include a minimum of all of the following general measures prior to application of NPWT: (a) Documentation in the patient's medical record of evaluation, care, and wound measurements by a licensed medical professional.

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(b) Consideration of the following risk factors is addressed in the documentation
(i) Risk for bleeding and hemorrhage
(ii) Active treatment with anticoagulants or platelet aggregation inhibitors
(iii) Presence of:
- Friable vessels and infected blood vessels
- Vascular anastomosis
- Infected wounds
- Osteomyelitis
- Exposed organs, vessels, nerves, tendons, and ligaments
- Sharp edges in the wound (i.e. bone fragments)
- Spinal cord injury (stimulation of sympathetic nervous system)
- Enteric fistulas

(c) Requirement for:
- MRI
- Hyperbaric chamber
- Defibrillation
- Size and weight
- Use of device near the vagus nerve
- Use of circumferential dressing application
- Mode of therapy – intermittent versus continuous negative pressure

(d) Application of dressings to maintain a moist wound environment.
(e) Debridement of necrotic tissue if present.
(f) Evaluation of and provision for adequate nutritional status.

ii. For Stage III or IV pressure ulcers:
(a) The patient has been appropriately turned and positioned.
(b) The patient's moisture and incontinence have been appropriately managed.

iii. For neuropathic/diabetic ulcers:
(a) The patient with diabetes has been on a comprehensive diabetic management program, **and**
(b) A foot ulcer has been appropriately off-loaded.

iv. For venous insufficiency ulcers:
(a) Compression bandages and/or garments have been consistently applied only after Ankle-Brachial Index has been done per guidelines, and
(b) Leg elevation with alternating ambulation has been encouraged.

B. Goal of therapy is clearly stated

C. Ulcers and Wounds Encountered in an Inpatient Setting:
1. An ulcer or wound (described in section A above) is encountered in the inpatient setting and, after wound treatments described under sections A-a through A-d have been tried or considered and ruled out, NPWT may be initiated.
2. The patient has complications of a surgically created wound (for example, dehiscence) or a traumatic wound (for example, pre-operative flap or graft) where there is documentation of the medical necessity for accelerated formation of granulation tissue which cannot be achieved by other available topical wound treatments (for example, other conditions of the patient that will not allow for healing times achievable with other topical wound treatments).
In either of the above situations, NPWT will be covered when treatment continuation is ordered beyond discharge to the home setting.

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	3. Skin-flaps or grafts approved as covered by the health plan in advance of the procedure. D. Contraindications for use: 1. The presence in the wound of necrotic tissue with eschar, if debridement has not been carried out 2. Untreated osteomyelitis within the vicinity of the wound 3. Possibility of malignant cells present in the wound 4. The presence of a fistula to an organ or body cavity within the vicinity of the wound 5. Exposed vascular in the wound 6. Exposed nerves in the wound 7. Exposed anastomotic site 8. Exposed organs 9. Recent lab value for albumin equal to or less than 2.5. 10. Pediatric patients (newborns, infants and children)
Initial Coverage—Disposable, single-use Negative Pressure Wound Therapy (i.e., SNAP, Prevena, V.A.C. VIA)	Disposable, single-use Negative Pressure Wound Therapy for **chronic wound and ulcers** A. The SNAP™ Therapy System (Acelity/KCI) may be used instead of traditional NPWT if **ALL** of the following criteria are met: B. Must complete the Kaiser Permanente initial coverage request form and fax it to the DME staff at 877-290-4632. C. These wounds should have exudate, size and depth to require this specialized therapy. A complete wound therapy program described by criterion 1.B.1.i and criteria 1.B.1.ii, 1.B.1.iii, or 1.B.1.iv, as applicable depending on the type of wound, should have been tried for 30 days. 1. Wound size < 13 cm x 13 cm 2. Wound drainage ≤ 180 mL/week (20mL/day) 3. Change dressing 2x/week at minimum; dispose of cartridge when full (typical cartridge holds 60 mL) D. Contraindications for use of disposable NPWT (SNAP) 1. Inadequately drained wounds 2. Necrotic tissue such as eschar or adherent slough 3. Exposed blood vessels, anastomotic sites, organs, tendons, or nerves 4. Wounds containing malignancy 5. Fistulas 6. Untreated osteomyelitis 7. Actively bleeding wounds Single Use Negative Pressure Wound Therapy (s-NPWT) may have a role in the prevention of surgical site infections for high-risk surgeries. However, in this setting Single Use Negative Pressure Wound Therapy (s-NPWT) is considered a surgical dressing and covered by the procedure billing code and is not separately reimbursable under the Prepayment Bill Review – Line item Deduction payment policy.
Continued Coverage (tNPWT/SNAP)	For wounds and ulcers described under sections 1 and 2 of Initial Coverage, once placed on any type of NPWT pump with supplies, for coverage to continue a licensed medical professional must do the following: 1) On a regular basis: A. Directly assess the wound(s) being treated with the NPWT pump B. Supervise or directly perform the NPWT dressing changes 2) On at least a weekly basis, document changes in the ulcer's dimensions and characteristics and the degree of granulation and management of exudate A. If using SNAP: If wound increases in size or is producing amounts of exudate above the parameters for SNAP, may need to evaluate the need for tNPWT or other wound management strategies.

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	3) Laboratory values at monthly intervals to show a contraindication does not exist 4) If these criteria are not fulfilled, continued coverage of the NPWT pump and supplies will be denied as not medically necessary
When Coverage Ends for tNPWT/SNAP	1) For wounds and ulcers described under sections A and B of Initial Coverage, an NPWT pump and supplies will be denied as not medically necessary with any of the following, whichever occurs earliest: A. Criteria for Continued Coverage cease to occur. B. In the judgment of the treating physician, adequate wound granulation has occurred to the degree that NPWT may be discontinued. C. Wound is not healing progressively 1. Progressive wound healing has failed to occur over the prior 30 days. There must be documented in the patient's medical records quantitative measurements of wound characteristics including wound length and width (surface area), or depth, serially observed and documented, over a specified time interval. The recorded wound measurements must be consistently and regularly updated and must have demonstrated progressive wound healing from week to week. 2. If using SNAP: If progressive wound healing has failed to occur, or wound increases in size or is producing amounts of exudate above the parameters for SNAP. D. NPWT should be ordered for a 30 day period of time as wounds are expected to change with this therapy. Once equipment or supplies are no longer being used for the patient, whether or not by the physician's order, the provided should be directly contacted and the delivery of further supplies stopped. Traditional NWPT Pumps must be returned to the provider for billing purposes and cleaning.
Supplies	**Supplies for tNPWT:** 1) Coverage for tNPWT is provided up to a maximum of 6 dressing kits (A6550) per wound per 30-day period unless there is documentation that the wound size requires more than one dressing kit for each dressing change. Dressings should be changed based on the patient's condition and the condition of the wound but normally not more frequently than 3 times a week. 2) Coverage for tNPWT is provided up to a maximum of 2 canister sets (A7000) per 30-day period unless there is documentation evidencing a large volume of drainage (greater than 90 ml of exudate per day). For high volume exudative wounds, a stationary pump with the largest capacity canister must be used. Excess utilization of canisters related to equipment failure (as opposed to excessive volume drainage) will be denied as not medically necessary. **Supplies for SNAP replacement:** 1) Coverage for SNAP is provided up to a maximum of 4 devices per 30-day period unless there is documented evidence of a larger volume of drainage requiring more frequent replacement. 2) The two codes of 97607 and 97608 should only be used when the provider is either initially applying an entirely new SNAP device or removing a SNAP device and replacing it with an entirely new one as clinically required. These codes may not be used if only a dressing change is performed for a SNAP system.
PICO	There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

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If requesting this service (*or these services*), please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, KAISER PERMANENTE will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Negative pressure wound therapy (NPWT) is a wound dressing system that was designed to promote wound healing through the use of subatmospheric pressure to the wound surface. NPWT systems include a vacuum pump, drainage tubing, and a dressing set. To place the device, the wound is covered or packed with a foam or gauze dressing and then secured using an adhesive film drape. A vacuum pump connected to the draining tube(s) in the wound dressing is used to apply pressure to the wound surface in the range of -50 to -125 mmHg. The precise mechanism through which NPWT aids the healing process is not fully understood; however, it has been suggested that NPWT may aid in the healing process through increasing local blood flow, increasing granulation tissue, reducing bacterial contamination, reducing wound area, reducing edema and exudate, and changes to the microenvironment (AHRQ 2009, Webster 2011).

Negative pressure therapy has been used in clinical applications for over five decades.
The concept of applying topical negative pressure in the management of wounds emerged in the late 1980s and is increasingly used for a wide variety of wounds. The technique is also known as vacuum assisted closure (VAC), negative pressure wound therapy (NPWT), vacuum sealing technique (VST), sealed surface wound suction (SSS), subatmospheric pressure therapy or dressing, foam suction dressing, and vacuum pack technique (VPT). The technology generally involves putting a dressing (foam or gauze) into the wound cavity, connecting it to a vacuum pump, and sealing the area with an adhesive film. The vacuum pump creates and maintains a subatmospheric pressure (intermittent or continuous) in the range of -50 to -125 mmHg. The default setting is -125 mmHg, and the pressure may be titrated up by 25 mmHg increments when there is excessive drainage or a large wound volume, or titrated down when the patient is elderly, nutritionally compromised, or has a risk of excessive bleeding. Dressings are usually changed every 48 hours, or every 12-24 hours if the wound is infected. The mechanism by which NPWT is believed to promote wound healing is unclear. In theory it may increase dermal perfusion, stimulate granulation tissue formation, reduce the edema and interstitial tissue fluid, reverse tissue expansion, and/or reduce bacterial colonization. It is also thought that the vacuum pressure may act as an effective skin graft splint over irregular surfaces. The therapy cannot be used as a replacement for surgical debridement, but as a complementary treatment. It is contraindicated for use in wounds with necrotic tissue, exposed vital structures, untreated osteomyelitis, unexplored fistulae and malignant wounds. Adverse effects include pain and damage to the skin around the wound (Braakenburg 2006, Bovill 2008, Wild 2008, Preston 2008).

Acute and chronic wounds and are a major cause of morbidity and impaired quality of life. They affect at least 1% of the population and represent a significant risk factor for hospitalization, amputation, sepsis, and even death. Wound healing is a complex series of events, broadly classified into inflammatory, proliferative, and remodeling phases. The healing process may be compromised by arterial or venous insufficiency which can prevent or delay healing and/or increase the risk of recurrent wound infections. The treatment of difficult-to-manage and chronic wounds remains a significant challenge to practitioners, a cause of pain and discomfort to the patients, and costly (Gregor 2008, Sadat 2008).

For centuries, gauze has been used in local wound care, mainly due to its low price and simplicity. In 1950s, a new concept, that wound healing is optimal when it is kept in a moist environment rather than air dried, was introduced. Since then, a large variety of occlusive or semi-occlusive dressings, topical applications, and other products were developed for the treatment of all kinds of wounds. Modern wound-healing agents include hydrocolloidal, alginates, hydrogels, hydrofiber, paraffin gauze dressings, as well as many other types of moist dressings and topical agents. The choice of the ideal regimen remains controversial due to the lack of good evidence from well conducted RCTs and depends mainly on the clinicians' preference (Chaby 2007, Gregor 2008, Ubbink 2009).

Skin grafts are used to promote healing in complex wounds with tissue loss. Successful skin grafting relies on the ability of the skin graft to integrate with the recipient wound bed. Bolstering the graft to the wound bed by applying

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a dressing along with positive pressure is used to improve integration with the wound bed and minimize seroma formation. NPWT is an alternative to standard bolstering techniques. It has been suggested that NPWT offers all of the advantage of standard bolstering in addition to other advantages such as active fluid removal and easier patient mobilization (Runkel 2011).

NPWT systems are FDA approved for use in patients with chronic, acute, traumatic, subacute and dehisced wounds, partial thickness burns, ulcers, flaps, and grafts. The device is contraindicated for use in wounds with exposed vital structures, devitalized tissue, malignant tissue, untreated osteomyelitis, or in patients with untreated coagulopathy or allergy to any component required for the procedure (AHRQ 2009). NPWT was reviewed by MTAC in 1999, 2003, and 2008 for the management of chronic wounds and did not meet MTAC evaluation criteria. It is being re-reviewed for a new indication.

Evidence Source Documents
Vacuum Assisted Closure for the Treatment of Wounds
Vacuum Assisted Closure in the Treatment of Non-Healing Wounds
Negative Pressure Wound Therapy in the Treatment of Skin Grafts and Flaps
SNAP & PICO Device

Medical Technology Assessment Committee (MTAC)

Vacuum Assisted Closure for the Treatment of Wounds

02/10/1999: MTAC REVIEW

Evidence Conclusion: The efficacy of the VST cannot be determined from the combination of these widely disparate studies/case series because of the widely heterogeneous samples, varying methods and application of the technique; small sample sizes, possible selection and observation bias, and the absence of comparison groups. In addition, there are a number of unresolved issues surrounding this technique, including but not limited to:

- which wounds are ideally suited for the application of this technique;
- the optimal conditions in which the technique can/should be applied;
- the ideal pressure required;
- ideal delivery of the negative pressure, e.g., by vacuum pump or bottle;
- when the wound dressing should be applied.

Further studies, preferably blinded, randomized control trials are warranted to determine the efficacy of this technique/device.

Articles: Articles were selected based on study type. There was one prospective clinical trial (Mullner et al, 1997), no meta-analyses or cohort studies, and a few case series. An evidence table for the clinical trial. No evidence tables were created for the case series, as the sample sizes were either too small, or the not described in sufficient detail. Case series were reviewed by abstract, and a brief summary of their findings is included. Mullner T, Mrkonjic L, Kwasny O, Vecsei V. The use of negative pressure to promote the healing of tissue defects: a clinical trial using the vacuum sealing technique. British Journal of Plastic Surgery 1997 Apr;50(3):194-9. See Evidence Table.

The use of Vacuum Assisted Closure for the treatment of wounds to promote healing does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Vacuum Assisted Closure in the Treatment of Non-Healing Wounds

08/13/2003: MTAC REVIEW

Evidence Conclusion: The best evidence on VAC consists of two RCTs, each with fewer than 30 patients. Both are limited by their small sample sizes which makes selection bias likely and results in low statistical power. The two studies had different findings. Ford found no significant differences in wound healing between VAC and gel. Joseph found a statistically significant greater reduction in wound volume, width and depth with VAC compared to traditional saline wet-to-moist (WM) dressings. Joseph had the stronger methodology—more complete follow-up and consistency between the unit of randomization and the unit of analysis. Although the Joseph RCT suggests that VAC may be superior to traditional WM dressings, additional research is needed with larger sample sizes and consideration of potential selection bias/confounding.

Articles: The search yielded 144 articles. Many of these were review articles, opinion pieces, dealt with technical aspects of wound closure techniques or were on related procedures. There were two small randomized controlled trials using the VAC system. No non-randomized comparative studies were identified. The two RCTs were critically appraised. Ford CN, Reinhard ER, Yeh D. et al. Interim analysis of a prospective, randomized trial of Vacuum-Assisted Closure versus the Healthpoint System in the management of pressure ulcers. *Ann Plast Surg*

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2002; 49: 55-61. See Evidence Table. Joseph E, Hamori CA, Bergman S. A prospective, randomized trial of vacuum-assisted closure versus standard therapy of chronic non-healing wounds. *Wounds* 2000; 12: 60-67. See Evidence Table.

The use of vacuum assisted closure in the treatment of non-healing wounds does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

04/06/2009: MTAC REVIEW

Vacuum Assisted Closure in the treatment of Non-Healing Wounds

Evidence Conclusion: There is a lack of high quality randomized controlled trials on the use of negative pressure therapy for wound healing. The best published clinical evidence consists of few RCTs with flawed methodology. The majority of the studies were small, had inadequate power to detect differences between treatment groups, were unblinded, and had little or no information on the baseline characteristics of the participants, or causes of dropouts. The trials mainly used surrogate outcomes as reduction in wound size and formation of granulation tissue, rather than complete healing of the ulcer. The largest published trial to date (Blume et al, 2008) randomized 341 patients with diabetic foot ulcers to receive negative pressure wound therapy (NPWT) or advanced moist wound therapy (AMWT). All participants in the two groups also underwent wound debridement and off-loading. The results of the trial showed a significantly higher rate of complete ulcer closure in the patients receiving NPWT vs. AMWTs. The study was randomized and controlled; however, it had several limitations including unblinding of the patients and physicians which is a potential source of bias as it could influence the patient motivation and the care provided. Patients were treated at home or in a hospital setting and there is no indication whether they were given the same care and therapy e.g. equal pressure relief, intermittent or continuous negative atmospheric pressure, debridement, antibiotics, and other potentially confounding factors. Moreover, the study had a high drop-out rate and was financially supported by the manufacturer of the device.
Conclusions: There is insufficient published evidence to date to determine whether topical negative pressure therapy is more effective than alternative wound dressings as regards rate of healing, pain management and quality of life. There is insufficient published evidence to date to determine that topical negative pressure therapy is safe to use in patients with acute or chronic wounds.
Articles: The search yielded over 300 articles on negative pressure wound therapy. Many were review articles, opinion pieces, dealt with technical aspects of wound closure techniques, or were unrelated to the current review. There were four systematic reviews with or without meta-analyses, four RCTs, and a number of case series published after the last MTAC review of the technology. Gregor et al's 2008 review included both randomized and non-randomized trials but pooled the results of each group of studies for only one surrogate outcome. In two Cochrane reviews (Ubbink 2008, Wasiak 2007), the authors could not pool the results in meta-analyses due to the small number of studies, poor reporting, heterogeneity in endpoints and comparator treatments. Another published meta-analysis (Sadat et al, 2008) included two small negative trials (total of 70 participants) on the use of VAC for various types of ulcers, and one positive larger trial (N= 162) on its use after diabetic foot amputation, which skewed the results of the meta-analysis. Only one RCT (Blume 2008) had clinically important outcomes, relatively large sample size, and generally valid methodology. Both the review with a meta-analysis as well as the RCT with generally valid methodology were selected for critical appraisal: Gregor S, Maegele M, Sauerland S, et al. Negative pressure wound therapy. A vacuum of evidence? Arch Surg 2008; 143:189-196. See Evidence Table.
Blume PA, Ayala J, Walters J, et al. Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers. A multicenter randomized controlled trial. Diabetes Care 2008;31: 631-636. See Evidence Table.

The use of vacuum assisted closure in the treatment of non-healing wounds does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Negative Pressure Wound Therapy in the Treatment of Skin Grafts and Flaps

12/19/2011: MTAC REVIEW

Evidence Conclusion: An RCT that included 60 subjects with acute traumatic injuries and skin loss evaluated the effectiveness of NPWT compared to dressings without NPWT. Results from this study suggest that NPWT may lead to less graft loss, less frequent regrafting, and reduced time from patient intervention to discharge compared to with dressings without NPWT (Llanos 2006).

	NPWT	Control	P-value
	Median (range)		
Loss of grafted area (cm^2)	0.0 (0-12)	4.5 (0-53)	0.001

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Percentage of graft loss	0.0 (0-62)	12.8 (0-76)	<0.001
Days from grafting to discharge	8 (7-13)	12 (7-23)	0.001
	Number (%)		
Need for 2nd coverage procedure	5 (16.7)	12 (40.0)	0.045

Conclusion: There is some evidence to support the use of NPWT as a splint or bolster for skin grafts.
Articles: NPWT for skin grafts or skin substitutes was reviewed in 2010 by NHS Quality Improvement Scotland (NHS QIS). This review found some evidence to support the use of NPWT for wounds caused by burns or trauma that require a skin graft as treatment and certain types of venous leg ulcers with split-thickness pinch skin graft. The recommendations from NHS QIS were based on evidence from two high-quality and two low-quality randomized controlled trials (RCTs) as well as several observational studies (NHS QIS 2010). Since the NHS QIS review, the literature search revealed two additional RCTs that evaluated the safety and efficacy of NPWT for skin grafts or skin substitutes. These studies were not selected for review due to methodological limitations (i.e., small sample size, high loss to follow-up, etc.) (Chio 2010, Petkar 2011). One of the high-quality trials evaluating the use of NPWT was not used for bolstering and therefore was not selected for review (Vuerstaek 2006). The other high-quality trial included in the NIH QIS was selected for review. The following study was selected for critical appraisal:
Llanos S, Danilla S, Barraza C, et al. Effectiveness of negative pressure closure in the integration of split thickness skin grafts. *Ann Surg.* 2006; 244:700-705. See Evidence Table.

The use of negative pressure wound therapy in the treatment of skin grafts and flaps does meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

SNAP & PICO Device

02/09/2015: MTAC REVIEW

Evidence Conclusion: First and foremost, it should be established that there is a lack of evidence to support the general use of NPWT. Previous MTAC critical appraisals have cited a lack of high-quality RCTs evaluating the use of NPWT for wound healing. To date, the best published clinical evidence consists of a few RCTs with flawed methodology due to limitations such as small sample size and inadequate power. Generally speaking, NPWT has been applied to a wide variety of wounds in varying locations, complexity and underlying pathology limiting the ability to make comparisons across studies. This limitation is demonstrated in a various systematic reviews with attempted meta-analyses that have failed to reach any definitive conclusions due to variable endpoints (Mendonca, Papini et al. 2006; Pham, Middleton et al. 2006; Sjögren, Malmsjö et al. 2006; Kanakaris, Thanasas et al. 2007; Wasiak and Cleland 2007; Bovill, Banwell et al. 2008; Group 2008; Noble-Bell and Forbes 2008; Ubbink, Westerbos et al. 2008; Ubbink, Westerbos et al. 2008; Dumville, Hinchliffe et al. 2013). *Effectiveness*: In 2011 and 2012, Armstrong and colleagues published an interim and final analysis with the overall aim of comparing NPWT with an ultraportable mechanically powered device with a traditional electrically powered device. Overall, the study enrolled 132 patients with lower-extremity diabetic and venous wounds. The primary outcome measurement was wound size reduction, however, data assessing the time for dressing change and user experience was also collected. The primary end point results indicated that the SNaP treated subjects were non-inferior to the VAC-treated patients at all follow-up points 4, 8, 12 and 16 weeks (p-value of 0.0054, 0.0047, <0.0001, and <0.0001, respectively). Exit surveys addressing quality of life (QoL) and activity were completed by 105 patients (79.5%) with the SNaP group consistently reporting less impact on activities such as sleep, mobility and socializing. Patient reporting of pain and discomfort associated with treatment, however, was similar in both groups with no statistical difference (Armstrong, Marston et al. 2011; Armstrong, Marston et al. 2012). [Evidence Table 1] *Safety:* In terms of safety, device related adverse events (AE) were similar in both groups with maceration being the most commonly reported complication. The investigators ultimately concluded that the treatment of wounds with a mechanically powered NPWT device resulted in similar wound healing outcomes as treatment with a traditional, electrically powered, NPWT device with less impact on the patient's quality of life. The evidence is limited by a variety of factors most notably, the use of an inadequate comparator. While NPWT is widely used, the current body of evidence is limited in supporting its effectiveness in promoting wound healing. Beyond that, limitations of the study's methodology include small sample size, as well as significant differences between groups in terms of wound size and age prior to treatment. Finally, it should be noted that the study was sponsored by Spiracur, Inc. the manufacturers of the SNaP® device. In addition, two of the investigators, Armstrong and Marston, have received research funding from both Spiracur and K.C.I. Conclusions: There is insufficient evidence to support the safety of the non-powered NPWT devices for treatment of patients with wounds. There is insufficient evidence to support the effectiveness of the non-powered NPWT devices for treatment of patients with wounds.

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Articles: The literature search revealed a variety of articles relating to the general use of NPWT. Only a few articles were directly related to the use of non-powered or non-electrically powered NPWT devices including a small pilot trial (n=30) of the effect of the PICO device on surgical wound healing in patients with Crohn's disease (Pellino, Sciaudone et al. 2014), a small case series (n=20) describing experience with the PICO device (Hudson, Adams et al. 2013), and a small retrospective case-control study (n=78) comparing the SNaP™ device to a variety of other wound therapies (Lerman, Oldenbrook et al. 2010). There were no randomized control trials (RCTs) identified that compared non-powered/electrical NPWT to conventional wound care. Two publications were revealed that presented the interim and final results of a small RCT comparing the SNaP device with a standard powered VAC (Armstrong, Marston et al. 2011; Armstrong, Marston et al. 2012). The following articles were selected for critical appraisal: Armstrong DG, Marston WA, Reyzelman AM et al. Comparison of negative pressure wound therapy with an ultraportable mechanically powered device vs. traditional electrically powered device for the treatment of chronic lower extremity ulcers: A multicenter randomized-controlled trial. Wound Rep Reg. 2011; 19(2):173-180. Evidence Table 1.Armstrong DG, Marston WA, Reyzelman AM et al. Comparative effectiveness of mechanically and electrically powered negative pressure wound therapy devices: a multicenter randomized controlled trial. 2012;20(3):332-341. Evidence Table 1

The use of SNAP & PICO device in the treatment of negative wound pressure therapy does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

10/14/2019: MTAC REVIEW
Evidence Conclusion:

- There is low-moderate quality evidence from a single open-label RCT suggesting that s-NPWT is superior to the traditional NPWT in treating venous leg ulcers (VLUs), or diabetic foot ulcers (DFUs) as regards reducing the wound area, and the ulcer depth and volume as well as time to complete closure in highly selected patients with chronic lower extremity ulcers.

- Low quality evidence from a sub-analysis of one open-label RCT suggests that SNaP may be superior to the traditional NPWT as regards wound size reduction and 50% wound closure when used in a highly selected group pf patients with venous leg ulcers.

- There is insufficient evidence to determine the safety of the single use NPWT in patients with lower extremity chronic wounds.

Articles: The literature search for studies on single use NPWT published after the last MTAC review of the technology, revealed one RCT that directly compared the efficacy of PICO versus traditional NPWT in the treatment of chronic ulcers in the lower extremities, and another RCT that compared a single use mechanically powered SNaP Wound Care System versus a traditional NPWT system for the management of venous leg ulcers. The rest of the published studies that evaluated the single use NPWT were either observational studies or RCTs that compared the devices versus conventional wound dressing (such as sterile gauze dressing, absorbent dressings, and silver-impregnated occlusive dressings). The results of these studies were pooled in five meta-analyses (MAs) identified by the search; three of which (Semsarzadeh et al, 2015, Watts et al, 2015, and De Vries et al, 2016) compared the outcomes of NPWT (t-NPWT and s-NPWT combined) versus conventional wound care. One MA (Strugala and Martin 2017); evaluated the effect of s-NPWT versus traditional dressing on the prevention of surgical site complications. and another (Singh et al, 2018) compared the effect of closed incision NPT (using PRAVENA system) also versus traditional dressing on reducing surgical site infections.

The following two RCTs that compared the single use NPWT versus the traditional NPWT were selected for critical appraised. None of the identified meta-analyses or the trials comparing the single use NPWT versus conventional/standard wound care was included as the aim of the current review is to compare the single use NPWT versus the traditional NPWT. See Evidence Table.

The use of SNAP & PICO device in the treatment of negative wound pressure therapy does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

tNPWT - Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

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HCPC Codes	Description
A6550	Wound care set, for negative pressure wound therapy electrical pump, includes all supplies and accessories
A7000	Canister, disposable, used with suction pump, each
E2402	Negative pressure wound therapy electrical pump, stationary or portable
K0743	Suction pump, home model, portable, for use on wounds
K0744	Absorptive wound dressing for use with suction pump, home model, portable, pad size 16 sq. in or less
K0745	Absorptive wound dressing for use with suction pump, home model, portable, pad size more than 16 sq. in but less than or equal to 48 sq. in
K0746	Absorptive wound dressing for use with suction pump, home model, portable, pad size greater than 48 sq. in

Disposable NPWT (including, but not limited to: SNAP, Prevena, V.A.C. VIA) - Considered Medically Necessary when criteria in the applicable policy statements listed above are met:
***not covered by Medicare**

CPT/HCPC Codes	Description
97607	Negative pressure wound therapy, (e.g., vacuum assisted drainage collection), utilizing disposable, non-durable medical equipment including provision of exudate management collection system, topical application(s), wound assessment, and instructions for ongoing care, per session; total wound(s) surface area less than or equal to 50 square centimeters
97608	Negative pressure wound therapy, (e.g., vacuum assisted drainage collection), utilizing disposable, non-durable medical equipment including provision of exudate management collection system, topical application(s), wound assessment, and instructions for ongoing care, per session; total wound(s) surface area greater than 50 square centimeters
A9272*	Wound suction, disposable, includes dressing, all accessories and components, any type, each

PICO - Considered Not Medically Necessary:
***not covered by Medicare**

CPT/HCPC Codes	Description
97607	Negative pressure wound therapy, (e.g., vacuum assisted drainage collection), utilizing disposable, non-durable medical equipment including provision of exudate management collection system, topical application(s), wound assessment, and instructions for ongoing care, per session; total wound(s) surface area less than or equal to 50 square centimeters
97608	Negative pressure wound therapy, (e.g., vacuum assisted drainage collection), utilizing disposable, non-durable medical equipment including provision of exudate management collection system, topical application(s), wound assessment, and instructions for ongoing care, per session; total wound(s) surface area greater than 50 square centimeters
A9272*	Wound suction, disposable, includes dressing, all accessories and components, any type, each

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check.**

CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Date Created	Date Reviewed	Date Last Revised
12/12/2000	06/01/2010 MDCRPC, 04/05/2011 MDCRPC, 01/03/2012 MDCRPC, 12/04/2012 MDCRPC, 10/01/2013MPC, 08/05/2014MPC, 06/02/2015MPC, 04/05/2016MPC, 02/07/2017MPC, 12/05/2017MPC, 10/02/2018MPC, 10/01/2019MPC, 10/06/2020MPC, 10/05/2021MPC, 10/04/2022MPC , 10/03/2023MPC, 02/13/2024MPC	07/11/2023

MDCRPC Medical Director Clinical Review and Policy Committee
MPC Medical Policy Committee

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Revision History	Description
10/26/2015	Changed codes for PICO and SNAP
06/02/2015	Codes Added
09/18/2017	Removed the requirement for Hemoglobin and Hematocrit
09/27/2017	Added LCA and MLN Matters Article
03/03/2020	MPC approved to adopt coverage policy for SNAP; Added October 2019 MTAC Review
04/07/2020	MPC approved to adopt new coverage criteria for SNAP
03/01/2022	MPC approved to adopt coverage criteria for dNPWT for SSI Prevention. 60-day notice required; effective 08/01/2022.
07/11/2023	MPC has approved to remove criteria for Single Use Negative Pressure Wound Therapy (s-NPWT) when applied in the operating room or apart from an encounter for the purpose of wound care. Requires 60-day notice effective 12/01/2023
07/24/2023	Updated initial duration for course of treatment to 30 days.

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KAISER PERMANENTE®

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Clinical Review Criteria
Neutron Beam Radiotherapy

- Soft Tissue Sarcoma
- Salivary Gland Tumors
- Locally Advanced Prostate Cancer

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article	None
Kaiser Permanente Medical Policy	Due to the absence of an active NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Clinical Review Criteria, "***Neutron Beam Radiotherapy***,***"*** for medical necessity determinations. Refer to the Non-Medicare criteria below.

For Non-Medicare Members

Kaiser Permanente considers neutron beam therapy medically necessary for the treatment of any of the following salivary gland tumors:

- Inoperable tumor; *or*
- Locally advanced tumor especially in persons with gross residual disease; *or*
- Unresectable tumor.

Kaiser Permanente considers neutron beam therapy experimental and investigational for all other indications including malignancies listed below (not an all-inclusive list) because its effectiveness for these indications has not been established:

1. Colon cancer
2. Dermatofibrosarcoma protuberans
3. Glioma
4. Kidney cancer
5. Laryngeal cancer
6. Lung cancer
7. Pancreatic cancer
8. Prostate cancer
9. Rectal cancer
10. Soft tissue sarcoma.

If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist

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The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Neutron radiotherapy is an alternative to conventional photon radiotherapy. Photon radiation is a type of low linear-energy-transfer (LET) radiation. After LET radiation, there is a relatively high chance that damaged tumor cells can repair themselves and continue to grow. In contrast, with neutrons, which are high LET radiation, damaged tumor cells are much less likely to resume growth. Because of the higher biological effectiveness of neutron radiotherapy, the required tumor dose with neutrons is about one-third the dose needed with photons and a lower total number of treatments is needed.

Neutrons were first used to treat patient tumors in 1938 using an early cyclotron. Research was discontinued due to World War II and began again in the 1960s in England. In the late 1970s, the National Cancer Institute awarded contracts for four modern cyclotrons in the U.S. According to a recent review article (Laramore, 1997), of the four centers, only the one at the University of Washington (UW) is still in operation. There are currently two other operating neutron radiotherapy centers in the country; the others are located at Harper-Grace Hospital in Detroit and the Fermi National Laboratory in Illinois. The UW built a new control system for its cyclotron, completed in July 1999. The UW materials state that the UW has the only facility with a computer-controlled, multi-leaf collimator for field shaping.

Neutron radiotherapy is believed to be most beneficial for malignant salivary gland tumors. The modern neutron facilities can deliver neutron radiation doses of approximately 20 Gy to the head and neck which corresponds to a proton dose of about 60-70 Gy-equivalent for normal tissues and approximately 160 Gy-equivalent for the tumor. In his review article, Laramore (1997) states that other than for salivary gland tumors, neutron radiotherapy has been shown to be most promising for sarcomas of soft tissue, bone and cartilage and locally advanced prostate cancer.

Evidence and Source Documents

Soft Tissue Sarcoma
Salivary Gland Tumors
Locally Advanced Prostate Cancer

Medical Technology Assessment Committee (MTAC)

Neutron Beam Radiotherapy for Soft Tissue Sarcoma

06/12/2002: MTAC REVIEW

Evidence Conclusion: There were only two case series that had sample sizes greater than n=10. The Schwartz study had n=73 (n=42 was treatment with curative intent) and was conducted at UW, where patients from Kaiser Permanente would be sent. The Schonekaes study, which was conducted in Germany, reports on two independent series of patients. Schwartz found a 68% local relapse-free 4-year survival rate and 66% overall 4-year survival rate in the 42 curative patients. Schonekaes found a 52% 5-year local recurrence-free survival rate and a 42.5% overall 5-year survival rate. In both studies, patients varied greatly in clinical characteristics, there was a lack of clear eligibility criteria, the intervention received was not consistent (e.g., dose of radiation). The Schwartz article did not have a control or comparison group. The efficacy of neutron radiotherapy for the treatment of soft-tissue sarcoma cannot be determined from these descriptive reports.

Articles: The search yielded 13 articles, many of which were review articles or opinion pieces. There were no randomized controlled trials or meta-analyses. There were four case series, two of which had sample sizes of ten or less. The two largest case series (n=73 and n=161) were critically appraised. Schwartz DL, Einck J, Bellon J, Laramore GE. Fast neutron radiotherapy for soft tissue and cartilaginous sarcomas at high risk for local recurrence. *Int J Radiation Oncology Biol Phys* 2001: 50: 449-456. See Evidence Table. Schonekaes K-G, Prott F-J, Micke O et al. Radiotherapy on adult patients with soft tissue sarcoma with fast neutrons or photons. *Anticancer Res* 1999; 19: 2355-2360. See Evidence Table.

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The use of neutron beam radiotherapy in the treatment of soft tissue sarcoma does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Neutron Beam Radiotherapy for Salivary Gland Tumors

06/12/2002: MTAC REVIEW

Evidence Conclusion: There was one small RCT (n=32 randomized, n=25 analyzed) comparing neutron radiotherapy to photon radiotherapy. This study (Griffin, 1988; Laramore, 1993) had methodological limitations but dramatic findings. At ten years, there was a statistically significant 39% absolute risk reduction for local/regional control favoring the neutron group. For survival, there was an absolute risk reduction of 37% at two years and 10% at ten years. Differences in survival rates were not statistically significant and the study may have been under powered. A case series from the UW with 128 patients was also reviewed. Actuarial local/regional control at five years was 59% and the 5-year survival rate was 39%. The evidence suggests that neutron radiotherapy is superior to traditional photon radiotherapy, but case series and one small, compromised RCT do not provide conclusive evidence.

Articles: The search yielded 34 articles, most of which were review articles, opinion pieces, dealt with technical aspects of the procedures or addressed other, similar treatments. There was one randomized controlled trial, published in 1993 and five newer case series with more than 50 patients. Some of the case series were from the same institution and there was overlap in the patients included in the articles. The RCT and the largest, most recent case series from the UW were reviewed. Laramore GE, Krall JM, Griffin TQ et al. Neutron versus photon irradiation for unresectable salivary gland tumors: Final report of an RTOG-MRC randomized clinical trial. *Int J Radiat Oncol Biol Phys* 1993; 27: 235-240. See Evidence Table. Douglas JG, Lee S, Laramore GE et al. Neutron radiotherapy for the treatment of locally advanced major salivary gland tumors. *Head Neck* 1999; 21: 255-263. See Evidence Table.

The use of neutron beam radiotherapy in the treatment of salivary gland tumors does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Neutron Beam Radiotherapy for Locally Advanced Prostate Cancer

06/12/2002: MTAC REVIEW

Evidence Conclusion: There were two RCTs; Laramore compared photon radiation to mixed photon-neutron radiotherapy and Russell compared photon radiation to neutron radiotherapy alone. Laramore found higher local/regional control and higher 5-year and 10-year survival rates in the neutron radiotherapy group. Russell found greater local/regional control but no difference in 5-year survival rates. It is possible that there could be a difference in effectiveness between mixed-beam and neutron-only radiotherapy, but this has not been studied. Neither study presented baseline demographic or clinical information, so the possibility of selection bias cannot be ruled out. The Laramore study has been criticized in the literature for the low rates of local/regional control and survival in the photon-treated group. The final reports on each of these RCTs were published in the early 1990s. No more recent studies were identified.

Articles: The search yielded 15 articles, many of which were review articles, dealt with technical aspects of the procedures or addressed other, similar treatments. There were two randomized controlled trials and one small case series on mixed-beam (mixed photon-neutron) treatment. The two RCTs were reviewed. Laramore GE, Krall JM, Thomas FJ et al. Fast neutron radiotherapy for locally advanced prostate cancer: Final report of Radiation Therapy Oncology Group Randomized Clinical Trial. *Am J Clin Oncol* 1993; 16: 164-67. See Evidence Table. Russell KJ, Caplan RJ, Laramore GE et al. Photon versus fast neutron external beam radiotherapy in the treatment of locally advanced prostate cancer: Results of a randomized prospective trial. *Int J Radiat Oncol Biol Phys* 1993; 28: 47-54. See Evidence Table.

The use of neutron beam radiotherapy in the treatment of locally advanced prostate cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
77423	High energy neutron radiation treatment delivery, 1 or more isocenter(s) with coplanar or non-coplanar geometry with blocking and/or wedge, and/or compensator(s)

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***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Date Created	Date Reviewed	Date Last Revised
6/12/2002	Initiated annual review because of Medicare criteria 04/05/2011 MDCRPC, 02/07/2012MDCRPC, 12/04/2012MDCRPC,10/01/2013MPC, 08/05/2014MPC, 06/02/2015MPC, 04/05/2016MPC, 02/07/2017MPC, 12/05/2017MPC, 10/02/2018MPC, 10/01/2019MPC, 10/06/2020MPC, 10/05/2021MPC , 10/04/2022MPC , 10/03/2023MPC	10/06/2020

MDCRPC Medical Director Clinical Review and Policy Committee
MPC Medical Policy Committee

Revision History	Description
05/26/2015	Added CPT codes
09/08/2015	Revised LCD L34151
12/05/2017	Adopted clinical criteria for Neutron Beam Therapy
10/06/2020	Removed unrelated SRS and SBRT LCD from Medicare, deferred to Kaiser Permanente criteria for Medicare

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Clinical Review Criteria
New and Emerging Medical Technologies and Procedures

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Criteria

For Medicare Members

Kaiser Permanente follows CMS coverage guidance when available per the CMS **Medicare Coverage Database** search tool. Where there is a conflict between this document and Medicare national and/or local coverage documentation, the Medicare source materials will apply. If there is no Medicare guidance, the information below applies.

For Non-Medicare Members

The following are new and emerging medical technologies which are considered to have unproven benefit because the current scientific evidence is not yet sufficient to establish the impact of these technologies on health outcomes:

CPT® Codes	Description
0499T	Cystourethroscopy, with mechanical dilation and urethral therapeutic drug delivery for urethral stricture or stenosis, including fluoroscopy, when performed
30469	Repair of nasal valve collapse with low energy, temperature-controlled (ie, radiofrequency) subcutaneous/submucosal remodeling
33370	Transcatheter placement and subsequent removal of cerebral embolic protection device(s), including arterial access, catheterization, imaging, and radiological supervision and interpretation, percutaneous (List separately in addition to code for primary procedure)
33900	Percutaneous pulmonary artery revascularization by stent placement, initial; normal native connections, unilateral
33901	Percutaneous pulmonary artery revascularization by stent placement, initial; normal native connections, bilateral
33902	Percutaneous pulmonary artery revascularization by stent placement, initial; abnormal connections, unilateral
33903	Percutaneous pulmonary artery revascularization by stent placement, initial; abnormal connections, bilateral
33904	Percutaneous pulmonary artery revascularization by stent placement, each additional vessel or separate lesion, normal or abnormal connections (List separately in addition to code for primary procedure)
36836	Percutaneous arteriovenous fistula creation, upper extremity, single access of both the peripheral artery and peripheral vein, including fistula maturation procedures (eg, transluminal balloon angioplasty, coil embolization) when performed, including all vascular access, imaging guidance and radiologic supervision and interpretation
36837	Percutaneous arteriovenous fistula creation, upper extremity, separate access sites of the peripheral artery and peripheral vein, including fistula maturation procedures (eg, transluminal balloon angioplasty, coil embolization) when performed, including all vascular access, imaging guidance and radiologic supervision and interpretation

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53451	Periurethral transperineal adjustable balloon continence device; bilateral insertion, including cystourethroscopy and imaging guidance
53452	Periurethral transperineal adjustable balloon continence device; unilateral insertion, including cystourethroscopy and imaging guidance
53453	Periurethral transperineal adjustable balloon continence device; removal, each balloon
53454	Periurethral transperineal adjustable balloon continence device; percutaneous adjustment of balloon(s) fluid volume
61736	Laser interstitial thermal therapy (LITT) of lesion, intracranial, including burr hole(s), with magnetic resonance imaging guidance, when performed; single trajectory for 1 simple lesion
61737	Laser interstitial thermal therapy (LITT) of lesion, intracranial, including burr hole(s), with magnetic resonance imaging guidance, when performed; multiple trajectories for multiple or complex lesion(s)
68841	Insertion of drug-eluting implant, including punctal dilation when performed, into lacrimal canaliculus, each
76883	Ultrasound, nerve(s) and accompanying structures throughout their entire anatomic course in one extremity, comprehensive, including real-time cine imaging with image documentation, per extremity
77089	Trabecular bone score (TBS), structural condition of the bone microarchitecture; using dual X-ray absorptiometry (DXA) or other imaging data on gray-scale variogram, calculation, with interpretation and report on fracture-risk
77090	Trabecular bone score (TBS), structural condition of the bone microarchitecture; technical preparation and transmission of data for analysis to be performed elsewhere
77091	Trabecular bone score (TBS), structural condition of the bone microarchitecture; technical calculation only
77092	Trabecular bone score (TBS), structural condition of the bone microarchitecture; interpretation and report on fracture-risk only by other qualified health care professional
81418	Drug metabolism (eg, pharmacogenomics) genomic sequence analysis panel, must include testing of at least 6 genes, including CYP2C19, CYP2D6, and CYP2D6 duplication/deletion analysis
81441	Inherited bone marrow failure syndromes (IBMFS) (eg, Fanconi anemia, dyskeratosis congenita, Diamond-Blackfan anemia, Shwachman-Diamond syndrome, GATA2 deficiency syndrome, congenital amegakaryocytic thrombocytopenia) sequence analysis panel, must include sequencing of at least 30 genes, including BRCA2, BRIP1, DKC1, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, GATA1, GATA2, MPL, NHP2, NOP10, PALB2, RAD51C, RPL11, RPL35A, RPL5, RPS10, RPS19, RPS24, RPS26, RPS7, SBDS, TERT, and TINF2
81451	Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NOTCH1, NPM1, NRAS), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis
81456	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis
81560	Transplantation medicine (allograft rejection, pediatric liver and small bowel), measurement of donor and third-party-induced CD154+T-cytotoxic memory cells, utilizing whole peripheral blood, algorithm reported as a rejection risk score
87154	Culture, typing; identification of blood pathogen and resistance typing, when performed, by nucleic acid (DNA or RNA) probe, multiplexed amplified probe technique including multiplex reverse transcription, when performed, per culture or isolate, 6 or more targets
92066	Orthoptic training; under supervision of a physician or other qualified health care professional
95919	Quantitative pupillometry with physician or other qualified health care professional interpretation and report, unilateral or bilateral
98975	Remote therapeutic monitoring (eg, therapy adherence, therapy response); initial set-up and patient education on use of equipment

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98976	Remote therapeutic monitoring (eg, therapy adherence, therapy response); device(s) supply with scheduled (eg, daily) recording(s) and/or programmed alert(s) transmission to monitor respiratory system, each 30 days
98977	Remote therapeutic monitoring (eg, therapy adherence, therapy response); device(s) supply with scheduled (eg, daily) recording(s) and/or programmed alert(s) transmission to monitor musculoskeletal system, each 30 days
98978	Remote therapeutic monitoring (eg, therapy adherence, therapy response); device(s) supply with scheduled (eg, daily) recording(s) and/or programmed alert(s) transmission to monitor cognitive behavioral therapy, each 30 days
98980	Remote therapeutic monitoring treatment management services, physician or other qualified health care professional time in a calendar month requiring at least one interactive communication with the patient or caregiver during the calendar month; first 20 minutes
98981	Remote therapeutic monitoring treatment management services, physician or other qualified health care professional time in a calendar month requiring at least one interactive communication with the patient or caregiver during the calendar month; each additional 20 minutes (List separately in addition to code for primary procedure)
0014M	Liver disease, analysis of 3 biomarkers (hyaluronic acid [HA], procollagen III amino terminal peptide [PIIINP], tissue inhibitor of metalloproteinase 1 [TIMP-1]), using immunoassays, utilizing serum, prognostic algorithm reported as a risk score and risk of liver fibrosis and liver-related clinical events within 5 years
0015M	Adrenal cortical tumor, biochemical assay of 25 steroid markers, utilizing 24-hour urine specimen and clinical parameters, prognostic algorithm reported as a clinical risk and integrated clinical steroid risk for adrenal cortical carcinoma, adenoma, or other adrenal malignancy
0016M	Oncology (bladder), mRNA, microarray gene expression profiling of 209 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as molecular subtype (luminal, luminal infiltrated, basal, basal claudin-low, neuroendocrine-like)
0163U	Oncology (colorectal) screening, biochemical enzyme-linked immunosorbent assay (ELISA) of 3 plasma or serum proteins (teratocarcinoma derived growth factor-1 [TDGF-1, Cripto-1], carcinoembryonic antigen [CEA], extracellular matrix protein [ECM]), with demographic data (age, gender, CRC-screening compliance) using a proprietary algorithm and reported as likelihood of CRC or advanced adenomas
0164U	Gastroenterology (irritable bowel syndrome [IBS]), immunoassay for anti-CdtB and anti-vinculin antibodies, utilizing plasma, algorithm for elevated or not elevated qualitative results
0165U	Peanut allergen-specific quantitative assessment of multiple epitopes using enzyme-linked immunosorbent assay (ELISA), blood, individual epitope results and probability of peanut allergy
0166U	Liver disease, 10 biochemical assays (a2-macroglobulin, haptoglobin, apolipoprotein A1, bilirubin, GGT, ALT, AST, triglycerides, cholesterol, fasting glucose) and biometric and demographic data, utilizing serum, algorithm reported as scores for fibrosis, necroinflammatory activity, and steatosis with a summary interpretation
0167U	Gonadotropin, chorionic (hCG), immunoassay with direct optical observation, blood
0168U	Fetal aneuploidy (trisomy 21, 18, and 13) DNA sequence analysis of selected regions using maternal plasma without fetal fraction cutoff, algorithm reported as a risk score for each trisomy
0169U	NUDT15 (nudix hydrolase 15) and TPMT (thiopurine S-methyltransferase) (eg, drug metabolism) gene analysis, common variants
0170U	Neurology (autism spectrum disorder [ASD]), RNA, next-generation sequencing, saliva, algorithmic analysis, and results reported as predictive probability of ASD diagnosis
0171U	Targeted genomic sequence analysis panel, acute myeloid leukemia, myelodysplastic syndrome, and myeloproliferative neoplasms, DNA analysis, 23 genes, interrogation for sequence variants, rearrangements and minimal residual disease, reported as presence/absence
0172U	Oncology (solid tumor as indicated by the label), somatic mutation analysis of BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) and analysis of homologous recombination deficiency pathways, DNA, formalin-fixed paraffin-embedded tissue, algorithm quantifying tumor genomic instability score
0173U	Psychiatry (ie, depression, anxiety), genomic analysis panel, includes variant analysis of 14 genes
0174U	Oncology (solid tumor), mass spectrometric 30 protein targets, formalin-fixed paraffin-embedded tissue, prognostic and predictive algorithm reported as likely, unlikely, or uncertain benefit of 39

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	chemotherapy and targeted therapeutic oncology agents
0175U	Psychiatry (eg, depression, anxiety), genomic analysis panel, variant analysis of 15 genes
0176U	Cytolethal distending toxin B (CdtB) and vinculin IgG antibodies by immunoassay (ie, ELISA)
0177U	Oncology (breast cancer), DNA, PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) gene analysis of 11 gene variants utilizing plasma, reported as PIK3CA gene mutation status
0178U	Peanut allergen-specific quantitative assessment of multiple epitopes using enzyme-linked immunosorbent assay (ELISA), blood, report of minimum eliciting exposure for a clinical reaction
0179U	Oncology (non-small cell lung cancer), cell-free DNA, targeted sequence analysis of 23 genes (single nucleotide variations, insertions and deletions, fusions without prior knowledge of partner/breakpoint, copy number variations), with report of significant mutation(s)
0180U	Red cell antigen (ABO blood group) genotyping (ABO), gene analysis Sanger/chain termination/conventional sequencing, ABO (ABO, alpha 1-3-N-acetylgalactosaminyltransferase and alpha 1-3-galactosyltransferase) gene, including subtyping, 7 exons
0181U	Red cell antigen (Colton blood group) genotyping (CO), gene analysis, AQP1 (aquaporin 1 [Colton blood group]) exon 1
0182U	Red cell antigen (Cromer blood group) genotyping (CROM), gene analysis, CD55 (CD55 molecule [Cromer blood group]) exons 1-10
0183U	Red cell antigen (Diego blood group) genotyping (DI), gene analysis, SLC4A1 (solute carrier family 4 member 1 [Diego blood group]) exon 19
0184U	Red cell antigen (Dombrock blood group) genotyping (DO), gene analysis, ART4 (ADP-ribosyltransferase 4 [Dombrock blood group]) exon 2
0185U	Red cell antigen (H blood group) genotyping (FUT1), gene analysis, FUT1 (fucosyltransferase 1 [H blood group]) exon 4
0186U	Red cell antigen (H blood group) genotyping (FUT2), gene analysis, FUT2 (fucosyltransferase 2) exon 2
0187U	Red cell antigen (Duffy blood group) genotyping (FY), gene analysis, ACKR1 (atypical chemokine receptor 1 [Duffy blood group]) exons 1-2
0188U	Red cell antigen (Gerbich blood group) genotyping (GE), gene analysis, GYPC (glycophorin C [Gerbich blood group]) exons 1-4
0189U	Red cell antigen (MNS blood group) genotyping (GYPA), gene analysis, GYPA (glycophorin A [MNS blood group]) introns 1, 5, exon 2
0190U	Red cell antigen (MNS blood group) genotyping (GYPB), gene analysis, GYPB (glycophorin B [MNS blood group]) introns 1, 5, pseudoexon 3
0191U	Red cell antigen (Indian blood group) genotyping (IN), gene analysis, CD44 (CD44 molecule [Indian blood group]) exons 2, 3, 6
0192U	Red cell antigen (Kidd blood group) genotyping (JK), gene analysis, SLC14A1 (solute carrier family 14 member 1 [Kidd blood group]) gene promoter, exon 9
0193U	Red cell antigen (JR blood group) genotyping (JR), gene analysis, ABCG2 (ATP binding cassette subfamily G member 2 [Junior blood group]) exons 2-26
0194U	Red cell antigen (Kell blood group) genotyping (KEL), gene analysis, KEL (Kell metallo-endopeptidase [Kell blood group]) exon 8
0195U	KLF1 (Kruppel-like factor 1), targeted sequencing (ie, exon 13)
0196U	Red cell antigen (Lutheran blood group) genotyping (LU), gene analysis, BCAM (basal cell adhesion molecule [Lutheran blood group]) exon 3
0197U	Red cell antigen (Landsteiner-Wiener blood group) genotyping (LW), gene analysis, ICAM4 (intercellular adhesion molecule 4 [Landsteiner-Wiener blood group]) exon 1
0198U	Red cell antigen (RH blood group) genotyping (RHD and RHCE), gene analysis Sanger/chain termination/conventional sequencing, RHD (Rh blood group D antigen) exons 1-10 and RHCE (Rh blood group CcEe antigens) exon 5
0199U	Red cell antigen (Scianna blood group) genotyping (SC), gene analysis, ERMAP (erythroblast membrane associated protein [Scianna blood group]) exons 4, 12
0200U	Red cell antigen (Kx blood group) genotyping (XK), gene analysis, XK (X-linked Kx blood group) exons 1-3
0201U	Red cell antigen (Yt blood group) genotyping (YT), gene analysis, ACHE (acetylcholinesterase [Cartwright blood group]) exon 2
0203U	Autoimmune (inflammatory bowel disease), mRNA, gene expression profiling by quantitative RT-PCR, 17 genes (15 target and 2 reference genes), whole blood, reported as a continuous risk

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	score and classification of inflammatory bowel disease aggressiveness
0204U	Oncology (thyroid), mRNA, gene expression analysis of 593 genes (including BRAF, RAS, RET, PAX8, and NTRK) for sequence variants and rearrangements, utilizing fine needle aspirate, reported as detected or not detected
0205U	Ophthalmology (age-related macular degeneration), analysis of 3 gene variants (2 CFH gene, 1 ARMS2 gene), using PCR and MALDI-TOF, buccal swab, reported as positive or negative for neovascular age-related macular-degeneration risk associated with zinc supplements
0206U	Neurology (Alzheimer disease); cell aggregation using morphometric imaging and protein kinase C-epsilon (PKCe) concentration in response to amylospheroid treatment by ELISA, cultured skin fibroblasts, each reported as positive or negative for Alzheimer disease
0207U	Neurology (Alzheimer disease); quantitative imaging of phosphorylated ERK1 and ERK2 in response to bradykinin treatment by in situ immunofluorescence, using cultured skin fibroblasts, reported as a probability index for Alzheimer disease (List separately in addition to code for primary procedure)
0209U	Cytogenomic constitutional (genome-wide) analysis, interrogation of genomic regions for copy number, structural changes and areas of homozygosity for chromosomal abnormalities
0210U	Syphilis test, non-treponemal antibody, immunoassay, quantitative (RPR)
0211U	Oncology (pan-tumor), DNA and RNA by next-generation sequencing, utilizing formalin-fixed paraffin-embedded tissue, interpretative report for single nucleotide variants, copy number alterations, tumor mutational burden, and microsatellite instability, with therapy association
0212U	Rare diseases (constitutional/heritable disorders), whole genome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, proband
0213U	Rare diseases (constitutional/heritable disorders), whole genome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, each comparator genome (eg, parent, sibling)
0214U	Rare diseases (constitutional/heritable disorders), whole exome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, proband
0215U	Rare diseases (constitutional/heritable disorders), whole exome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, each comparator exome (eg, parent, sibling)
0216U	Neurology (inherited ataxias), genomic DNA sequence analysis of 12 common genes including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants
0217U	Neurology (inherited ataxias), genomic DNA sequence analysis of 51 genes including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants
0218U	Neurology (muscular dystrophy), DMD gene sequence analysis, including small sequence changes, deletions, duplications, and variants in non-uniquely mappable regions, blood or saliva, identification and characterization of genetic variants
0219U	Infectious agent (human immunodeficiency virus), targeted viral next-generation sequence analysis (ie, protease [PR], reverse transcriptase [RT], integrase [INT]), algorithm reported as prediction of antiviral drug susceptibility
0220U	Oncology (breast cancer), image analysis with artificial intelligence assessment of 12 histologic and immunohistochemical features, reported as a recurrence score
0221U	Red cell antigen (ABO blood group) genotyping (ABO), gene analysis, next-generation sequencing, ABO (ABO, alpha 1-3-N-acetylgalactosaminyltransferase and alpha 1-3-galactosyltransferase) gene
0222U	Red cell antigen (RH blood group) genotyping (RHD and RHCE), gene analysis, next-generation sequencing, RH proximal promoter, exons 1-10, portions of introns 2-3
0243U	Obstetrics (preeclampsia), biochemical assay of placental-growth factor, time-resolved

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	fluorescence immunoassay, maternal serum, predictive algorithm reported as a risk score for preeclampsia
0244U	Oncology (solid organ), DNA, comprehensive genomic profiling, 257 genes, interrogation for single-nucleotide variants, insertions/deletions, copy number alterations, gene rearrangements, tumor-mutational burden and microsatellite instability, utilizing formalin-fixed paraffin-embedded tumor tissue
0246U	Red blood cell antigen typing, DNA, genotyping of at least 16 blood groups with phenotype prediction of at least 51 red blood cell antigens
0247U	Obstetrics (preterm birth), insulin-like growth factor-binding protein 4 (IBP4), sex hormone-binding globulin (SHBG), quantitative measurement by LC-MS/MS, utilizing maternal serum, combined with clinical data, reported as predictive-risk stratification for spontaneous preterm birth
0248U	Oncology (brain), spheroid cell culture in a 3D microenvironment, 12 drug panel, tumor-response prediction for each drug
0249U	Oncology (breast), semiquantitative analysis of 32 phosphoproteins and protein analytes, includes laser capture microdissection, with algorithmic analysis and interpretative report
0250U	Oncology (solid organ neoplasm), targeted genomic sequence DNA analysis of 505 genes, interrogation for somatic alterations (SNVs [single nucleotide variant], small insertions and deletions, one amplification, and four translocations), microsatellite instability and tumor-mutation burden
0251U	Hepcidin-25, enzyme-linked immunosorbent assay (ELISA), serum or plasma
0252U	Fetal aneuploidy short tandem-repeat comparative analysis, fetal DNA from products of conception, reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplications, mosaicism, and segmental aneuploidy
0253U	Reproductive medicine (endometrial receptivity analysis), RNA gene expression profile, 238 genes by next-generation sequencing, endometrial tissue, predictive algorithm reported as endometrial window of implantation (eg, pre-receptive, receptive, post-receptive)
0254U	Reproductive medicine (preimplantation genetic assessment), analysis of 24 chromosomes using embryonic DNA genomic sequence analysis for aneuploidy, and a mitochondrial DNA score in euploid embryos, results reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplications, mosaicism, and segmental aneuploidy, per embryo tested
0285U	Oncology, response to radiation, cell-free DNA, quantitative branched chain DNA amplification, plasma, reported as a radiation toxicity score
0287U	Oncology (thyroid), DNA and mRNA, next-generation sequencing analysis of 112 genes, fine needle aspirate or formalin-fixed paraffin-embedded (FFPE) tissue, algorithmic prediction of cancer recurrence, reported as a categorical risk result (low, intermediate, high)
0289U	Neurology (Alzheimer disease), mRNA, gene expression profiling by RNA sequencing of 24 genes, whole blood, algorithm reported as predictive risk score
0290U	Pain management, mRNA, gene expression profiling by RNA sequencing of 36 genes, whole blood, algorithm reported as predictive risk score
0291U	Psychiatry (mood disorders), mRNA, gene expression profiling by RNA sequencing of 144 genes, whole blood, algorithm reported as predictive risk score
0292U	Psychiatry (stress disorders), mRNA, gene expression profiling by RNA sequencing of 72 genes, whole blood, algorithm reported as predictive risk score
0293U	Psychiatry (suicidal ideation), mRNA, gene expression profiling by RNA sequencing of 54 genes, whole blood, algorithm reported as predictive risk score
0294U	Longevity and mortality risk, mRNA, gene expression profiling by RNA sequencing of 18 genes, whole blood, algorithm reported as predictive risk score
0295U	Oncology (breast ductal carcinoma in situ), protein expression profiling by immunohistochemistry of 7 proteins (COX2, FOXA1, HER2, Ki-67, p16, PR, SIAH2), with 4 clinicopathologic factors (size, age, margin status, palpability), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a recurrence risk score
0296U	Oncology (oral and/or oropharyngeal cancer), gene expression profiling by RNA sequencing at least 20 molecular features (eg, human and/or microbial mRNA), saliva, algorithm reported as positive or negative for signature associated with malignancy
0297U	Oncology (pan tumor), whole genome sequencing of paired malignant and normal DNA specimens, fresh or formalin-fixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and variant identification

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0298U	Oncology (pan tumor), whole transcriptome sequencing of paired malignant and normal RNA specimens, fresh or formalin-fixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and expression level and chimeric transcript identification
0299U	Oncology (pan tumor), whole genome optical genome mapping of paired malignant and normal DNA specimens, fresh frozen tissue, blood, or bone marrow, comparative structural variant identification
0300U	Oncology (pan tumor), whole genome sequencing and optical genome mapping of paired malignant and normal DNA specimens, fresh tissue, blood, or bone marrow, comparative sequence analyses and variant identification
0301U	Infectious agent detection by nucleic acid (DNA or RNA), Bartonella henselae and Bartonella quintana, droplet digital PCR (ddPCR);
0302U	Infectious agent detection by nucleic acid (DNA or RNA), Bartonella henselae and Bartonella quintana, droplet digital PCR (ddPCR); following liquid enhancement
0303U	Hematology, red blood cell (RBC) adhesion to endothelial/subendothelial adhesion molecules, functional assessment, whole blood, with algorithmic analysis and result reported as an RBC adhesion index; hypoxic
0304U	Hematology, red blood cell (RBC) adhesion to endothelial/subendothelial adhesion molecules, functional assessment, whole blood, with algorithmic analysis and result reported as an RBC adhesion index; normoxic
0305U	Hematology, red blood cell (RBC) functionality and deformity as a function of shear stress, whole blood, reported as a maximum elongation index
0306U	Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis, cell-free DNA, initial (baseline) assessment to determine a patient specific panel for future comparisons to evaluate for MRD
0307U	Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis of a patient-specific panel, cell-free DNA, subsequent assessment with comparison to previously analyzed patient specimens to evaluate for MRD
0308U	Cardiology (coronary artery disease [CAD]), analysis of 3 proteins (high sensitivity [hs] troponin, adiponectin, and kidney injury molecule-1 [KIM-1]) with 3 clinical parameters (age, sex, history of cardiac intervention), plasma, algorithm reported as a risk score for obstructive CAD
0309U	Cardiology (cardiovascular disease), analysis of 4 proteins (NT-proBNP, osteopontin, tissue inhibitor of metalloproteinase-1 [TIMP-1], and kidney injury molecule-1 [KIM-1]), plasma, algorithm reported as a risk score for major adverse cardiac event
0310U	Pediatrics (vasculitis, Kawasaki disease [KD]), analysis of 3 biomarkers (NT-proBNP, C-reactive protein, and T-uptake), plasma, algorithm reported as a risk score for KD
0311U	Infectious disease (bacterial), quantitative antimicrobial susceptibility reported as phenotypic minimum inhibitory concentration (MIC)–based antimicrobial susceptibility for each organisms identified
0312U	Autoimmune diseases (eg, systemic lupus erythematosus [SLE]), analysis of 8 IgG autoantibodies and 2 cell-bound complement activation products using enzyme-linked immunosorbent immunoassay (ELISA), flow cytometry and indirect immunofluorescence, serum, or plasma and whole blood, individual components reported along with an algorithmic SLE-likelihood assessment
0313U	Oncology (pancreas), DNA and mRNA next-generation sequencing analysis of 74 genes and analysis of CEA (CEACAM5) gene expression, pancreatic cyst fluid, algorithm reported as a categorical result (ie, negative, low probability of neoplasia or positive, high probability of neoplasia)
0315U	Oncology (cutaneous squamous cell carcinoma), mRNA gene expression profiling by RT-PCR of 40 genes (34 content and 6 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a categorical risk result (ie, Class 1, Class 2A, Class 2B)
0316U	Borrelia burgdorferi (Lyme disease), OspA protein evaluation, urine
0317U	Oncology (lung cancer), four-probe FISH (3q29, 3p22.1, 10q22.3, 10cen) assay, whole blood, predictive algorithm-generated evaluation reported as decreased or increased risk for lung cancer
0318U	Pediatrics (congenital epigenetic disorders), whole genome methylation analysis by microarray for 50 or more genes, blood
0319U	Nephrology (renal transplant), RNA expression by select transcriptome sequencing, using pretransplant peripheral blood, algorithm reported as a risk score for early acute rejection

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0320U	Nephrology (renal transplant), RNA expression by select transcriptome sequencing, using posttransplant peripheral blood, algorithm reported as a risk score for acute cellular rejection
0321U	Infectious agent detection by nucleic acid (DNA or RNA), genitourinary pathogens, identification of 20 bacterial and fungal organisms and identification of 16 associated antibiotic-resistance genes, multiplex amplified probe technique
0322U	Neurology (autism spectrum disorder [ASD]), quantitative measurements of 14 acyl carnitines and microbiome-derived metabolites, liquid chromatography with tandem mass spectrometry (LC-MS/MS), plasma, results reported as negative or positive for risk of metabolic subtypes associated with ASD
0323U	Infectious agent detection by nucleic acid (DNA and RNA), central nervous system pathogen, metagenomic next-generation sequencing, cerebrospinal fluid (CSF), identification of pathogenic bacteria, viruses, parasites, or fungi
0326U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of **83** or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden
0327U	Fetal aneuploidy (trisomy 13, 18, and 21), DNA sequence analysis of selected regions using maternal plasma, algorithm reported as a risk score for each trisomy, includes sex reporting, if performed
0328U	Drug assay, definitive, 120 or more drugs and metabolites, urine, quantitative liquid chromatography with tandem mass spectrometry (LC-MS/MS), includes specimen validity and algorithmic analysis describing drug or metabolite and presence or absence of risks for a significant patient-adverse event, per date of service
0329U	Oncology (neoplasia), exome and transcriptome sequence analysis for sequence variants, gene copy number amplifications and deletions, gene rearrangements, microsatellite instability and tumor mutational burden utilizing DNA and RNA from tumor with DNA from normal blood or saliva for subtraction, report of clinically significant mutation(s) with therapy associations
0330U	Infectious agent detection by nucleic acid (DNA or RNA), vaginal pathogen panel, identification of **27** organisms, amplified probe technique, vaginal swab
0331U	Oncology (hematolymphoid neoplasia), optical genome mapping for copy number alterations and gene rearrangements utilizing DNA from blood or bone marrow, report of clinically significant alterations
0333U	Oncology (liver), surveillance for hepatocellular carcinoma (HCC) in high-risk patients, analysis of methylation patterns on circulating cell-free DNA (cfDNA) plus measurement of serum of AFP/AFP-L3 and oncoprotein des-gamma-carboxy-prothrombin (DCP), algorithm reported as normal or abnormal result
0335U	Rare diseases (constitutional/heritable disorders), whole genome sequence analysis, including small sequence changes, copy number variants, deletions, duplications, mobile element insertions, uniparental disomy (UPD), inversions, aneuploidy, mitochondrial genome sequence analysis with heteroplasmy and large deletions, short tandem repeat (STR) gene expansions, fetal sample, identification and categorization of genetic variants
0336U	Rare diseases (constitutional/heritable disorders), whole genome sequence analysis, including small sequence changes, copy number variants, deletions, duplications, mobile element insertions, uniparental disomy (UPD), inversions, aneuploidy, mitochondrial genome sequence analysis with heteroplasmy and large deletions, short tandem repeat (STR) gene expansions, blood or saliva, identification and categorization of genetic variants, each comparator genome (eg, parent)
0337U	Oncology (plasma cell disorders and myeloma), circulating plasma cell immunologic selection, identification, morphological characterization, and enumeration of plasma cells based on differential CD138, CD38, CD19, and CD45 protein biomarker expression, peripheral blood
0338U	Oncology (solid tumor), circulating tumor cell selection, identification, morphological characterization, detection and enumeration based on differential EpCAM, cytokeratins 8, **18**, and **19**, and CD45 protein biomarkers, and quantification of HER2 protein biomarker-expressing cells, peripheral blood
0340U	Oncology (pan-cancer), analysis of minimal residual disease (MRD) from plasma, with assays personalized to each patient based on prior next-generation sequencing of the patient's tumor and germline DNA, reported as absence or presence of MRD, with disease-burden correlation, if appropriate

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0341U	Fetal aneuploidy DNA sequencing comparative analysis, fetal DNA from products of conception, reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplication, mosaicism, and segmental aneuploid
0343U	Oncology (prostate), exosome-based analysis of 442 small noncoding RNAs (sncRNAs) by quantitative reverse transcription polymerase chain reaction (RT-qPCR), urine, reported as molecular evidence of no-, low-, intermediate- or high-risk of prostate cancer
0326U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 83 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden
0332U	Oncology (pan-tumor), genetic profiling of 8 DNA-regulatory (epigenetic) markers by quantitative polymerase chain reaction (qPCR), whole blood, reported as a high or low probability of responding to immune checkpoint-inhibitor therapy
0334U	Oncology (solid organ), targeted genomic sequence analysis, formalin-fixed paraffin-embedded (FFPE) tumor tissue, DNA analysis, 84 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden
0344U	Hepatology (nonalcoholic fatty liver disease [NAFLD]), semiquantitative evaluation of **28** lipid markers by liquid chromatography with tandem mass spectrometry (LC-MS/MS), serum, reported as at-risk for nonalcoholic steatohepatitis (NASH) or not NASH
0346U	Beta amyloid, AB40 and AB42 by liquid chromatography with tandem mass spectrometry (LC-MS/MS), ratio, plasma
0347U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, **16** gene report, with variant analysis and reported phenotypes
0348U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, **25** gene report, with variant analysis and reported phenotypes
0349U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 27 gene report, with variant analysis, including reported phenotypes and impacted gene-drug interactions
0350U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, **27** gene report, with variant analysis and reported phenotypes
0351U	Infectious disease (bacterial or viral), biochemical assays, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), interferon gamma-induced protein-**10** (IP-**10**), and C-reactive protein, serum, algorithm reported as likelihood of bacterial infection
0352U	Infectious disease (bacterial vaginosis and vaginitis), multiplex amplified probe technique, for detection of bacterial vaginosis-associated bacteria (BVAB-2, Atopobium vaginae, and Megasphera type 1), algorithm reported as detected or not detected and separate detection of Candida species (C. albicans, C. tropicalis, C. parapsilosis, C. dubliniensis), Candida glabrata/Candida krusei, and trichomonas vaginalis, vaginal-fluid specimen, each result reported as detected or not detected
0353U	Infectious agent detection by nucleic acid (DNA), Chlamydia trachomatis and Neisseria gonorrhoeae, multiplex amplified probe technique, urine, vaginal, pharyngeal, or rectal, each pathogen reported as detected or not detected
0354U	Human papilloma virus (HPV), high-risk types (ie, **16**, **18**, **31**, **33**, **45**, **52** and **58**) qualitative mRNA expression of E6/E7 by quantitative polymerase chain reaction (qPCR)
0355U	APOL1 (apolipoprotein L1) (eg, chronic kidney disease), risk variants (G1, G2)
0356U	Oncology (oropharyngeal), evaluation of 17 DNA biomarkers using droplet digital PCR (ddPCR), cell-free DNA, algorithm reported as a prognostic risk score for cancer recurrence
0357U	Oncology (melanoma), artificial intelligence (AI)-enabled quantitative mass spectrometry analysis of 142 unique pairs of glycopeptide and product fragments, plasma, prognostic, and predictive algorithm reported as likely, unlikely, or uncertain benefit from immunotherapy agents
0358U	Neurology (mild cognitive impairment), analysis of B-amyloid 1-42 and 1-40, chemiluminescence enzyme immunoassay, cerebral spinal fluid, reported as positive, likely positive, or negative
0359U	Oncology (prostate cancer), analysis of all prostate-specific antigen (PSA) structural isoforms by phase separation and immunoassay, plasma, algorithm reports risk of cancer
0360U	Oncology (lung), enzyme-linked immunosorbent assay (ELISA) of 7 autoantibodies (p53, NY-ESO-1, CAGE, GBU4-5, SOX2, MAGE A4, and HuD), plasma, algorithm reported as a categorical result for risk of malignancy
0361U	Neurofilament light chain, digital immunoassay, plasma, quantitative

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0362U	Oncology (papillary thyroid cancer), gene-expression profiling via targeted hybrid capture–enrichment RNA sequencing of 82 content genes and 10 housekeeping genes, fine needle aspirate or formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as one of three molecular subtypes
0363U	Oncology (urothelial), mRNA, gene-expression profiling by real-time quantitative PCR of 5 genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm incorporates age, sex, smoking history, and macrohematuria frequency, reported as a risk score for having urothelial carcinoma
0365U	Oncology (bladder), analysis of 10 protein biomarkers (A1AT, ANG, APOE, CA9, IL8, MMP9, MMP10, PAI1, SDC1 and VEGFA) by immunoassays, urine, algorithm reported as a probability of bladder cancer
0366U	Oncology (bladder), analysis of 10 protein biomarkers (A1AT, ANG, APOE, CA9, IL8, MMP9, MMP10, PAI1, SDC1 and VEGFA) by immunoassays, urine, algorithm reported as a probability of recurrent bladder cancer
0367U	Oncology (bladder), analysis of 10 protein biomarkers (A1AT, ANG, APOE, CA9, IL8, MMP9, MMP10, PAI1, SDC1 and VEGFA) by immunoassays, urine, diagnostic algorithm reported as a risk score for probability of rapid recurrence of recurrent or persistent cancer following transurethral resection
0368U	Oncology (colorectal cancer), evaluation for mutations of APC, BRAF, CTNNB1, KRAS, NRAS, PIK3CA, SMAD4, and TP53, and methylation markers (MYO1G, KCNQ5, C9ORF50, FLI1, CLIP4, ZNF132 and TWIST1), multiplex quantitative polymerase chain reaction (qPCR), circulating cell-free DNA (cfDNA), plasma, report of risk score for advanced adenoma or colorectal cancer
0369U	Infectious agent detection by nucleic acid (DNA and RNA), gastrointestinal pathogens, 31 bacterial, viral, and parasitic organisms and identification of 21 associated antibiotic-resistance genes, multiplex amplified probe technique
0370U	Infectious agent detection by nucleic acid (DNA and RNA), surgical wound pathogens, 34 microorganisms and identification of 21 associated antibiotic-resistance genes, multiplex amplified probe technique, wound swab
0371U	Infectious agent detection by nucleic acid (DNA or RNA), genitourinary pathogen, semiquantitative identification, DNA from 16 bacterial organisms and 1 fungal organism, multiplex amplified probe technique via quantitative polymerase chain reaction (qPCR), urine
0372U	Infectious disease (genitourinary pathogens), antibiotic-resistance gene detection, multiplex amplified probe technique, urine, reported as an antimicrobial stewardship risk score
0373U	Infectious agent detection by nucleic acid (DNA and RNA), respiratory tract infection, 17 bacteria, 8 fungus, 13 virus, and 16 antibiotic-resistance genes, multiplex amplified probe technique, upper or lower respiratory specimen
0374U	Infectious agent detection by nucleic acid (DNA or RNA), genitourinary pathogens, identification of 21 bacterial and fungal organisms and identification of 21 associated antibiotic-resistance genes, multiplex amplified probe technique, urine
0375U	Oncology (ovarian), biochemical assays of 7 proteins (follicle stimulating hormone, human epididymis protein 4, apolipoprotein A-1, transferrin, beta-2 macroglobulin, prealbumin [ie, transthyretin], and cancer antigen 125), algorithm reported as ovarian cancer risk score
0376U	Oncology (prostate cancer), image analysis of at least 128 histologic features and clinical factors, prognostic algorithm determining the risk of distant metastases, and prostate cancer-specific mortality, includes predictive algorithm to androgen deprivation-therapy response, if appropriate
0377U	Cardiovascular disease, quantification of advanced serum or plasma lipoprotein profile, by nuclear magnetic resonance (NMR) spectrometry with report of a lipoprotein profile (including 23 variables)
0378U	RFC1 (replication factor C subunit 1), repeat expansion variant analysis by traditional and repeat-primed PCR, blood, saliva, or buccal swab
0380U	Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis, 20 gene variants and CYP2D6 deletion or duplication analysis with reported genotype and phenotype
0381U	Maple syrup urine disease monitoring by patient-collected blood card sample, quantitative measurement of allo-isoleucine, leucine, isoleucine, and valine, liquid chromatography with tandem mass spectrometry (LC-MS/MS)
0382U	Hyperphenylalaninemia monitoring by patient-collected blood card sample, quantitative

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	measurement of phenylalanine and tyrosine, liquid chromatography with tandem mass spectrometry (LC-MS/MS)
0383U	Tyrosinemia type I monitoring by patient-collected blood card sample, quantitative measurement of tyrosine, phenylalanine, methionine, succinylacetone, nitisinone, liquid chromatography with tandem mass spectrometry (LC-MS/MS)
0384U	Nephrology (chronic kidney disease), carboxymethyllysine, methylglyoxal hydroimidazolone, and carboxyethyl lysine by liquid chromatography with tandem mass spectrometry (LC-MS/MS) and HbA1c and estimated glomerular filtration rate (GFR), with risk score reported for predictive progression to high-stage kidney disease
0385U	Nephrology (chronic kidney disease), apolipoprotein A4 (ApoA4), CD5 antigen-like (CD5L), and insulin-like growth factor binding protein 3 (IGFBP3) by enzyme-linked immunoassay (ELISA), plasma, algorithm combining results with HDL, estimated glomerular filtration rate (GFR) and clinical data reported as a risk score for developing diabetic kidney disease
0386U	Gastroenterology (Barrett's esophagus), P16, RUNX3, HPP1, and FBN1 methylation analysis, prognostic and predictive algorithm reported as a risk score for progression to high-grade dysplasia or esophageal cancer
0443T	Real-time spectral analysis of prostate tissue by fluorescence spectroscopy, including imaging guidance (List separately in addition to code for primary procedure)
0594T	Osteotomy, humerus, with insertion of an externally controlled intramedullary lengthening device, including intraoperative imaging, initial and subsequent alignment assessments, computations of adjustment schedules, and management of the intramedullary lengthening device
0596T	Temporary female intraurethral valve-pump (ie, voiding prosthesis); initial insertion, including urethral measurement
0597T	Temporary female intraurethral valve-pump (ie, voiding prosthesis); replacement
0598T	Noncontact real-time fluorescence wound imaging, for bacterial presence, location, and load, per session; first anatomic site (eg, lower extremity)
0599T	Noncontact real-time fluorescence wound imaging, for bacterial presence, location, and load, per session; each additional anatomic site (eg, upper extremity) (List separately in addition to code for primary procedure)
0600T	Ablation, irreversible electroporation; 1 or more tumors per organ, including imaging guidance, when performed, percutaneous
0601T	Ablation, irreversible electroporation; 1 or more tumors, including fluoroscopic and ultrasound guidance, when performed, open
0602T	Glomerular filtration rate (GFR) measurement(s), transdermal, including sensor placement and administration of a single dose of fluorescent pyrazine agent
0603T	Glomerular filtration rate (GFR) monitoring, transdermal, including sensor placement and administration of more than one dose of fluorescent pyrazine agent, each 24 hours
0604T	Optical coherence tomography (OCT) of retina, remote, patient-initiated image capture and transmission to a remote surveillance center unilateral or bilateral; initial device provision, set-up and patient education on use of equipment
0605T	Optical coherence tomography (OCT) of retina, remote, patient-initiated image capture and transmission to a remote surveillance center unilateral or bilateral; remote surveillance center technical support, data analyses and reports, with a minimum of 8 daily recordings, each 30 days
0606T	Optical coherence tomography (OCT) of retina, remote, patient-initiated image capture and transmission to a remote surveillance center unilateral or bilateral; review, interpretation and report by the prescribing physician or other qualified health care professional of remote surveillance center data analyses, each 30 days
0607T	Remote monitoring of an external continuous pulmonary fluid monitoring system, including measurement of radiofrequency-derived pulmonary fluid levels, heart rate, respiration rate, activity, posture, and cardiovascular rhythm (eg, ECG data), transmitted to a remote 24-hour attended surveillance center; set-up and patient education on use of equipment
0608T	Remote monitoring of an external continuous pulmonary fluid monitoring system, including measurement of radiofrequency-derived pulmonary fluid levels, heart rate, respiration rate, activity, posture, and cardiovascular rhythm (eg, ECG data), transmitted to a remote 24-hour attended surveillance center; analysis of data received and transmission of reports to the physician or other qualified health care professional
0609T	Magnetic resonance spectroscopy, determination and localization of discogenic pain (cervical,

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	thoracic, or lumbar); acquisition of single voxel data, per disc, on biomarkers (ie, lactic acid, carbohydrate, alanine, laal, propionic acid, proteoglycan, and collagen) in at least 3 discs
0610T	Magnetic resonance spectroscopy, determination and localization of discogenic pain (cervical, thoracic, or lumbar); transmission of biomarker data for software analysis
0611T	Magnetic resonance spectroscopy, determination and localization of discogenic pain (cervical, thoracic, or lumbar); postprocessing for algorithmic analysis of biomarker data for determination of relative chemical differences between discs
0612T	Magnetic resonance spectroscopy, determination and localization of discogenic pain (cervical, thoracic, or lumbar); interpretation and report
0613T	Percutaneous transcatheter implantation of interatrial septal shunt device, including right and left heart catheterization, intracardiac echocardiography, and imaging guidance by the proceduralist, when performed
0615T	Eye-movement analysis without spatial calibration, with interpretation and report
0616T	Insertion of iris prosthesis, including suture fixation and repair or removal of iris, when performed; without removal of crystalline lens or intraocular lens, without insertion of intraocular lens
0617T	Insertion of iris prosthesis, including suture fixation and repair or removal of iris, when performed; with removal of crystalline lens and insertion of intraocular lens
0618T	Insertion of iris prosthesis, including suture fixation and repair or removal of iris, when performed; with secondary intraocular lens placement or intraocular lens exchange
0619T	Cystourethroscopy with transurethral anterior prostate commissurotomy and drug delivery, including transrectal ultrasound and fluoroscopy, when performed
0620T	Endovascular venous arterialization, tibial or peroneal vein, with transcatheter placement of intravascular stent graft(s) and closure by any method, including percutaneous or open vascular access, ultrasound guidance for vascular access when performed, all catheterization(s) and intraprocedural roadmapping and imaging guidance necessary to complete the intervention, all associated radiological supervision and interpretation, when performed
0621T	Trabeculostomy ab interno by laser
0622T	Trabeculostomy ab interno by laser; with use of ophthalmic endoscope
0623T	Automated quantification and characterization of coronary atherosclerotic plaque to assess severity of coronary disease, using data from coronary computed tomographic angiography; data preparation and transmission, computerized analysis of data, with review of computerized analysis output to reconcile discordant data, interpretation and report
0624T	Automated quantification and characterization of coronary atherosclerotic plaque to assess severity of coronary disease, using data from coronary computed tomographic angiography; data preparation and transmission
0625T	Automated quantification and characterization of coronary atherosclerotic plaque to assess severity of coronary disease, using data from coronary computed tomographic angiography; computerized analysis of data from coronary computed tomographic angiography
0626T	Automated quantification and characterization of coronary atherosclerotic plaque to assess severity of coronary disease, using data from coronary computed tomographic angiography; review of computerized analysis output to reconcile discordant data, interpretation and report
0627T	Percutaneous injection of allogeneic cellular and/or tissue-based product, intervertebral disc, unilateral or bilateral injection, with fluoroscopic guidance, lumbar; first level
0628T	Percutaneous injection of allogeneic cellular and/or tissue-based product, intervertebral disc, unilateral or bilateral injection, with fluoroscopic guidance, lumbar; each additional level (List separately in addition to code for primary procedure)
0629T	Percutaneous injection of allogeneic cellular and/or tissue-based product, intervertebral disc, unilateral or bilateral injection, with CT guidance, lumbar; first level
0630T	Percutaneous injection of allogeneic cellular and/or tissue-based product, intervertebral disc, unilateral or bilateral injection, with CT guidance, lumbar; each additional level (List separately in addition to code for primary procedure)
0631T	Transcutaneous visible light hyperspectral imaging measurement of oxyhemoglobin, deoxyhemoglobin, and tissue oxygenation, with interpretation and report, per extremity
0632T	Percutaneous transcatheter ultrasound ablation of nerves innervating the pulmonary arteries, including right heart catheterization, pulmonary artery angiography, and all imaging guidance
0633T	Computed tomography, breast, including 3D rendering, when performed, unilateral; without contrast material

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0634T	Computed tomography, breast, including 3D rendering, when performed, unilateral; with contrast material(s)
0635T	Computed tomography, breast, including 3D rendering, when performed, unilateral; without contrast, followed by contrast material(s)
0636T	Computed tomography, breast, including 3D rendering, when performed, bilateral; without contrast material(s)
0637T	Computed tomography, breast, including 3D rendering, when performed, bilateral; with contrast material(s)
0638T	Computed tomography, breast, including 3D rendering, when performed, bilateral; without contrast, followed by contrast material(s)
0639T	Wireless skin sensor thermal anisotropy measurement(s) and assessment of flow in cerebrospinal fluid shunt, including ultrasound guidance, when performed
0640T	Noncontact near-infrared spectroscopy studies of flap or wound (eg, for measurement of deoxyhemoglobin, oxyhemoglobin, and ratio of tissue oxygenation [StO2]); image acquisition, interpretation and report, each flap or wound
0641T	Noncontact near-infrared spectroscopy studies of flap or wound (eg, for measurement of deoxyhemoglobin, oxyhemoglobin, and ratio of tissue oxygenation [StO2]); image acquisition only, each flap or wound
0642T	Noncontact near-infrared spectroscopy studies of flap or wound (eg, for measurement of deoxyhemoglobin, oxyhemoglobin, and ratio of tissue oxygenation [StO2]); interpretation and report only, each flap or wound
0643T	Transcatheter left ventricular restoration device implantation including right and left heart catheterization and left ventriculography when performed, arterial approach
0644T	Transcatheter removal or debulking of intracardiac mass (eg, vegetations, thrombus) via suction (eg, vacuum, aspiration) device, percutaneous approach, with intraoperative reinfusion of aspirated blood, including imaging guidance, when performed
0645T	Transcatheter implantation of coronary sinus reduction device including vascular access and closure, right heart catheterization, venous angiography, coronary sinus angiography, imaging guidance, and supervision and interpretation, when performed
0646T	Transcatheter tricuspid valve implantation/replacement (TTVI) with prosthetic valve, percutaneous approach, including right heart catheterization, temporary pacemaker insertion, and selective right ventricular or right atrial angiography, when performed
0647T	Insertion of gastrostomy tube, percutaneous, with magnetic gastropexy, under ultrasound guidance, image documentation and report
0648T	Quantitative magnetic resonance for analysis of tissue composition (eg, fat, iron, water content), including multiparametric data acquisition, data preparation and transmission, interpretation and report, obtained without diagnostic MRI examination of the same anatomy (eg, organ, gland, tissue, target structure) during the same session
0649T	Quantitative magnetic resonance for analysis of tissue composition (eg, fat, iron, water content), including multiparametric data acquisition, data preparation and transmission, interpretation and report, obtained with diagnostic MRI examination of the same anatomy (eg, organ, gland, tissue, target structure) (List separately in addition to code for primary procedure)
0650T	Programming device evaluation (remote) of subcutaneous cardiac rhythm monitor system, with iterative adjustment of the implantable device to test the function of the device and select optimal permanently programmed values with analysis, review and report by a physician or other qualified health care professional
0651T	Magnetically controlled capsule endoscopy, esophagus through stomach, including intraprocedural positioning of capsule, with interpretation and report
0652T	Esophagogastroduodenoscopy, flexible, transnasal; diagnostic, including collection of specimen(s) by brushing or washing, when performed (separate procedure)
0653T	Esophagogastroduodenoscopy, flexible, transnasal; with biopsy, single or multiple
0654T	Esophagogastroduodenoscopy, flexible, transnasal; with insertion of intraluminal tube or catheter
0655T	Transperineal focal laser ablation of malignant prostate tissue, including transrectal imaging guidance, with MR-fused images or other enhanced ultrasound imaging
0656T	Vertebral body tethering, anterior; up to 7 vertebral segments
0657T	Vertebral body tethering, anterior; 8 or more vertebral segments
0658T	Electrical impedance spectroscopy of 1 or more skin lesions for automated melanoma risk score

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0659T	Transcatheter intracoronary infusion of supersaturated oxygen in conjunction with percutaneous coronary revascularization during acute myocardial infarction, including catheter placement, imaging guidance (eg, fluoroscopy), angiography, and radiologic supervision and interpretation
0660T	Implantation of anterior segment intraocular nonbiodegradable drug-eluting system, internal approach
0661T	Removal and reimplantation of anterior segment intraocular nonbiodegradable drug-eluting implant
0662T	Scalp cooling, mechanical; initial measurement and calibration of cap
0663T	Scalp cooling, mechanical; placement of device, monitoring, and removal of device (List separately in addition to code for primary procedure)
0664T	Donor hysterectomy (including cold preservation); open, from cadaver donor
0665T	Donor hysterectomy (including cold preservation); open, from living donor
0666T	Donor hysterectomy (including cold preservation); laparoscopic or robotic, from living donor
0667T	Donor hysterectomy (including cold preservation); recipient uterus allograft transplantation from cadaver or living donor
0668T	Backbench standard preparation of cadaver or living donor uterine allograft prior to transplantation, including dissection and removal of surrounding soft tissues and preparation of uterine vein(s) and uterine artery(ies), as necessary
0669T	Backbench reconstruction of cadaver or living donor uterus allograft prior to transplantation; venous anastomosis, each
0670T	Backbench reconstruction of cadaver or living donor uterus allograft prior to transplantation; arterial anastomosis, each
0672T	Endovaginal cryogen-cooled, monopolar radiofrequency remodeling of the tissues surrounding the female bladder neck and proximal urethra for urinary incontinence
0673T	Ablation, benign thyroid nodule(s), percutaneous, laser, including imaging guidance
0674T	Laparoscopic insertion of new or replacement of permanent implantable synchronized diaphragmatic stimulation system for augmentation of cardiac function, including an implantable pulse generator and diaphragmatic lead(s)
0675T	Laparoscopic insertion of new or replacement of diaphragmatic lead(s), permanent implantable synchronized diaphragmatic stimulation system for augmentation of cardiac function, including connection to an existing pulse generator; first lead
0676T	Laparoscopic insertion of new or replacement of diaphragmatic lead(s), permanent implantable synchronized diaphragmatic stimulation system for augmentation of cardiac function, including connection to an existing pulse generator; each additional lead (List separately in addition to code for primary procedure)
0677T	Laparoscopic repositioning of diaphragmatic lead(s), permanent implantable synchronized diaphragmatic stimulation system for augmentation of cardiac function, including connection to an existing pulse generator; first repositioned lead
0678T	Laparoscopic repositioning of diaphragmatic lead(s), permanent implantable synchronized diaphragmatic stimulation system for augmentation of cardiac function, including connection to an existing pulse generator; each additional repositioned lead (List separately in addition to code for primary procedure)
0679T	Laparoscopic removal of diaphragmatic lead(s), permanent implantable synchronized diaphragmatic stimulation system for augmentation of cardiac function
0680T	Insertion or replacement of pulse generator only, permanent implantable synchronized diaphragmatic stimulation system for augmentation of cardiac function, with connection to existing lead(s)
0681T	Relocation of pulse generator only, permanent implantable synchronized diaphragmatic stimulation system for augmentation of cardiac function, with connection to existing dual leads
0682T	Removal of pulse generator only, permanent implantable synchronized diaphragmatic stimulation system for augmentation of cardiac function
0683T	Programming device evaluation (in-person) with iterative adjustment of the implantable device to test the function of the device and select optimal permanent programmed values with analysis, review and report by a physician or other qualified health care professional, permanent implantable synchronized diaphragmatic stimulation system for augmentation of cardiac function
0684T	Peri-procedural device evaluation (in-person) and programming of device system parameters before or after a surgery, procedure, or test with analysis, review, and report by a physician or other qualified health care professional, permanent implantable synchronized diaphragmatic

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	stimulation system for augmentation of cardiac function
0685T	Interrogation device evaluation (in-person) with analysis, review and report by a physician or other qualified health care professional, including connection, recording and disconnection per patient encounter, permanent implantable synchronized diaphragmatic stimulation system for augmentation of cardiac function
0686T	Histotripsy (ie, non-thermal ablation via acoustic energy delivery) of malignant hepatocellular tissue, including image guidance
0687T	Treatment of amblyopia using an online digital program; device supply, educational set-up, and initial session
0688T	Treatment of amblyopia using an online digital program; assessment of patient performance and program data by physician or other qualified health care professional, with report, per calendar month
0689T	Quantitative ultrasound tissue characterization (non-elastographic), including interpretation and report, obtained without diagnostic ultrasound examination of the same anatomy (eg, organ, gland, tissue, target structure)
0690T	Quantitative ultrasound tissue characterization (non-elastographic), including interpretation and report, obtained with diagnostic ultrasound examination of the same anatomy (eg, organ, gland, tissue, target structure) (List separately in addition to code for primary procedure)
0691T	Automated analysis of an existing computed tomography study for vertebral fracture(s), including assessment of bone density when performed, data preparation, interpretation, and report
0693T	Comprehensive full body computer-based markerless 3D kinematic and kinetic motion analysis and report
0694T	3-dimensional volumetric imaging and reconstruction of breast or axillary lymph node tissue, each excised specimen, 3-dimensional automatic specimen reorientation, interpretation and report, real-time intraoperative
0695T	Body surface-activation mapping of pacemaker or pacing cardioverter-defibrillator lead(s) to optimize electrical synchrony, cardiac resynchronization therapy device, including connection, recording, disconnection, review, and report; at time of implant or replacement
0696T	Body surface-activation mapping of pacemaker or pacing cardioverter-defibrillator lead(s) to optimize electrical synchrony, cardiac resynchronization therapy device, including connection, recording, disconnection, review, and report; at time of follow-up interrogation or programming device evaluation
0697T	Quantitative magnetic resonance for analysis of tissue composition (eg, fat, iron, water content), including multiparametric data acquisition, data preparation and transmission, interpretation and report, obtained without diagnostic MRI examination of the same anatomy (eg, organ, gland, tissue, target structure) during the same session; multiple organs
0698T	Quantitative magnetic resonance for analysis of tissue composition (eg, fat, iron, water content), including multiparametric data acquisition, data preparation and transmission, interpretation and report, obtained with diagnostic MRI examination of the same anatomy (eg, organ, gland, tissue, target structure); multiple organs (List separately in addition to code for primary procedure)
0699T	Injection, posterior chamber of eye, medication
0700T	Molecular fluorescent imaging of suspicious nevus; first lesion
0701T	Molecular fluorescent imaging of suspicious nevus; each additional lesion (List separately in addition to code for primary procedure)
0704T	Remote treatment of amblyopia using an eye tracking device; device supply with initial set-up and patient education on use of equipment
0705T	Remote treatment of amblyopia using an eye tracking device; surveillance center technical support including data transmission with analysis, with a minimum of 18 training hours, each 30 days
0706T	Remote treatment of amblyopia using an eye tracking device; interpretation and report by physician or other qualified health care professional, per calendar month
0707T	Injection(s), bone substitute material (eg, calcium phosphate) into subchondral bone defect (ie, bone marrow lesion, bone bruise, stress injury, microtrabecular fracture), including imaging guidance and arthroscopic assistance for joint visualization
0708T	Intradermal cancer immunotherapy; preparation and initial injection
0709T	Intradermal cancer immunotherapy; each additional injection (List separately in addition to code for primary procedure)
0710T	Noninvasive arterial plaque analysis using software processing of data from non-coronary

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	computerized tomography angiography; including data preparation and transmission, quantification of the structure and composition of the vessel wall and assessment for lipid-rich necrotic core plaque to assess atherosclerotic plaque stability, data review, interpretation and report
0711T	Noninvasive arterial plaque analysis using software processing of data from non-coronary computerized tomography angiography; data preparation and transmission
0712T	Noninvasive arterial plaque analysis using software processing of data from non-coronary computerized tomography angiography; quantification of the structure and composition of the vessel wall and assessment for lipid-rich necrotic core plaque to assess atherosclerotic plaque stability
0713T	Noninvasive arterial plaque analysis using software processing of data from non-coronary computerized tomography angiography; data review, interpretation and report
0714T	Transperineal laser ablation of benign prostatic hyperplasia, including imaging guidance
0715T	Percutaneous transluminal coronary lithotripsy (List separately in addition to code for primary procedure)
0716T	Cardiac acoustic waveform recording with automated analysis and generation of coronary artery disease risk score
0717T	Autologous adipose-derived regenerative cell (ADRC) therapy for partial thickness rotator cuff tear; adipose tissue harvesting, isolation and preparation of harvested cells, including incubation with cell dissociation enzymes, filtration, washing and concentration of ADRCs
0718T	Autologous adipose-derived regenerative cell (ADRC) therapy for partial thickness rotator cuff tear; injection into supraspinatus tendon including ultrasound guidance, unilateral
0719T	Posterior vertebral joint replacement, including bilateral facetectomy, laminectomy, and radical discectomy, including imaging guidance, lumbar spine, single segment
0720T	Percutaneous electrical nerve field stimulation, cranial nerves, without implantation
0721T	Quantitative computed tomography (CT) tissue characterization, including interpretation and report, obtained without concurrent CT examination of any structure contained in previously acquired diagnostic imaging
0722T	Quantitative computed tomography (CT) tissue characterization, including interpretation and report, obtained with concurrent CT examination of any structure contained in the concurrently acquired diagnostic imaging dataset (List separately in addition to code for primary procedure)
0723T	Quantitative magnetic resonance cholangiopancreatography (QMRCP) including data preparation and transmission, interpretation and report, obtained without diagnostic magnetic resonance imaging (MRI) examination of the same anatomy (eg, organ, gland, tissue, target structure) during the same session
0724T	Quantitative magnetic resonance cholangiopancreatography (QMRCP) including data preparation and transmission, interpretation and report, obtained with diagnostic magnetic resonance imaging (MRI) examination of the same anatomy (eg, organ, gland, tissue, target structure) (List separately in addition to code for primary procedure)
0725T	Vestibular device implantation, unilateral
0726T	Removal of implanted vestibular device, unilateral
0727T	Removal and replacement of implanted vestibular device, unilateral
0728T	Diagnostic analysis of vestibular implant, unilateral; with initial programming
0729T	Diagnostic analysis of vestibular implant, unilateral; with subsequent programming
0730T	Trabeculotomy by laser, including optical coherence tomography (OCT) guidance
0731T	Augmentative AI-based facial phenotype analysis with report
0732T	Immunotherapy administration with electroporation, intramuscular
0733T	Remote real-time, motion capture-based neurorehabilitative therapy ordered by a physician or other qualified health care professional; supply and technical support, per 30 days
0734T	Remote real-time, motion capture-based neurorehabilitative therapy ordered by a physician or other qualified health care professional; treatment management services by a physician or other qualified health care professional, per calendar month
0735T	Preparation of tumor cavity, with placement of a radiation therapy applicator for intraoperative radiation therapy (IORT) concurrent with primary craniotomy (List separately in addition to code for primary procedure)
0736T	Colonic lavage, 35 or more liters of water, gravity-fed, with induced defecation, including insertion of rectal catheter
0737T	Xenograft implantation into the articular surface

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0738T	Treatment planning for magnetic field induction ablation of malignant prostate tissue, using data from previously performed magnetic resonance imaging (MRI) examination
0739T	Ablation of malignant prostate tissue by magnetic field induction, including all intraprocedural, transperineal needle/catheter placement for nanoparticle installation and intraprocedural temperature monitoring, thermal dosimetry, bladder irrigation, and magnetic field nanoparticle activation
0740T	Remote autonomous algorithm-based recommendation system for insulin dose calculation and titration; initial set-up and patient education
0741T	Remote autonomous algorithm-based recommendation system for insulin dose calculation and titration; provision of software, data collection, transmission, and storage, each 30 days
0742T	Absolute quantitation of myocardial blood flow (AQMBF), single-photon emission computed tomography (SPECT), with exercise or pharmacologic stress, and at rest, when performed (List separately in addition to code for primary procedure)
0743T	Bone strength and fracture risk using finite element analysis of functional data and bone-mineral density, with concurrent vertebral fracture assessment, utilizing data from a computed tomography scan, retrieval and transmission of the scan data, measurement of bone strength and bone mineral density and classification of any vertebral fractures, with overall fracture risk assessment, interpretation and report
0744T	Insertion of bioprosthetic valve, open, femoral vein, including duplex ultrasound imaging guidance, when performed, including autogenous or nonautogenous patch graft (eg, polyester, ePTFE, bovine pericardium), when performed
0745T	Cardiac focal ablation utilizing radiation therapy for arrhythmia; noninvasive arrhythmia localization and mapping of arrhythmia site (nidus), derived from anatomical image data (eg, CT, MRI, or myocardial perfusion scan) and electrical data (eg, 12-lead ECG data), and identification of areas of avoidance
0746T	Cardiac focal ablation utilizing radiation therapy for arrhythmia; conversion of arrhythmia localization and mapping of arrhythmia site (nidus) into a multidimensional radiation treatment plan
0747T	Cardiac focal ablation utilizing radiation therapy for arrhythmia; delivery of radiation therapy, arrhythmia
0748T	Injections of stem cell product into perianal perifistular soft tissue, including fistula preparation (eg, removal of setons, fistula curettage, closure of internal openings)
0749T	Bone strength and fracture-risk assessment using digital X-ray radiogrammetry-bone mineral density (DXR-BMD) analysis of bone mineral density (BMD) utilizing data from a digital X ray, retrieval and transmission of digital X ray data, assessment of bone strength and fracture-risk and BMD, interpretation and report;
0750T	Bone strength and fracture-risk assessment using digital X-ray radiogrammetry-bone mineral density (DXR-BMD) analysis of bone mineral density (BMD) utilizing data from a digital X ray, retrieval and transmission of digital X ray data, assessment of bone strength and fracture-risk and BMD, interpretation and report; with single-view digital X-ray examination of the hand taken for the purpose of DXR-BMD
0751T	Digitization of glass microscope slides for level II, surgical pathology, gross and microscopic examination (List separately in addition to code for primary procedure)
0752T	Digitization of glass microscope slides for level III, surgical pathology, gross and microscopic examination (List separately in addition to code for primary procedure)
0753T	Digitization of glass microscope slides for level IV, surgical pathology, gross and microscopic examination (List separately in addition to code for primary procedure)
0754T	Digitization of glass microscope slides for level V, surgical pathology, gross and microscopic examination (List separately in addition to code for primary procedure)
0755T	Digitization of glass microscope slide for level VI, surgical pathology, gross and microscopic examination (List separately in addition to code for primary procedure)
0756T	Digitization of glass microscope slides for special stain, including interpretation and report, group I, for microorganisms (eg, acid fast, methenamine silver) (List separately in addition to code for primary procedure)
0757T	Digitization of glass microscope slides for special stain, including interpretation and report, group II, all other (eg, iron, trichrome), except stain for microorganisms, stains for enzyme constituents, or immunocytochemistry and immunohistochemistry (List separately in addition to code for primary procedure)
0758T	Digitization of glass microscope slides for special stain, including interpretation and report,

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	histochemical stain on frozen tissue block (List separately in addition to code for primary procedure)
0759T	Digitization of glass microscope slides for special stain, including interpretation and report, group III, for enzyme constituents (List separately in addition to code for primary procedure)
0760T	Digitization of glass microscope slides for immunohistochemistry or immunocytochemistry, per specimen, initial single antibody stain procedure (List separately in addition to code for primary procedure)
0761T	Digitization of glass microscope slides for immunohistochemistry or immunocytochemistry, per specimen, each additional single antibody stain procedure (List separately in addition to code for primary procedure)
0762T	Digitization of glass microscope slides for immunohistochemistry or immunocytochemistry, per specimen, each multiplex antibody stain procedure (List separately in addition to code for primary procedure)
0763T	Digitization of glass microscope slides for morphometric analysis, tumor immunohistochemistry (eg, Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen, each single antibody stain procedure, manual (List separately in addition to code for primary procedure)
0764T	Assistive algorithmic electrocardiogram risk-based assessment for cardiac dysfunction (eg, low-ejection fraction, pulmonary hypertension, hypertrophic cardiomyopathy); related to concurrently performed electrocardiogram (List separately in addition to code for primary procedure)
0765T	Assistive algorithmic electrocardiogram risk-based assessment for cardiac dysfunction (eg, low-ejection fraction, pulmonary hypertension, hypertrophic cardiomyopathy); related to previously performed electrocardiogram
0766T	Transcutaneous magnetic stimulation by focused low-frequency electromagnetic pulse, peripheral nerve, initial treatment, with identification and marking of the treatment location, including noninvasive electroneurographic localization (nerve conduction localization), when performed; first nerve
0767T	Transcutaneous magnetic stimulation by focused low-frequency electromagnetic pulse, peripheral nerve, initial treatment, with identification and marking of the treatment location, including noninvasive electroneurographic localization (nerve conduction localization), when performed; each additional nerve (List separately in addition to code for primary procedure)
0768T	Transcutaneous magnetic stimulation by focused low-frequency electromagnetic pulse, peripheral nerve, subsequent treatment, including noninvasive electroneurographic localization (nerve conduction localization), when performed; first nerve
0769T	Transcutaneous magnetic stimulation by focused low-frequency electromagnetic pulse, peripheral nerve, subsequent treatment, including noninvasive electroneurographic localization (nerve conduction localization), when performed; each additional nerve (List separately in addition to code for primary procedure)
0770T	Virtual reality technology to assist therapy (List separately in addition to code for primary procedure)
0771T	Virtual reality (VR) procedural dissociation services provided by the same physician or other qualified health care professional performing the diagnostic or therapeutic service that the VR procedural dissociation supports, requiring the presence of an independent, trained observer to assist in the monitoring of the patient's level of dissociation or consciousness and physiological status; initial 15 minutes of intraservice time, patient age 5 years or older
0772T	Virtual reality (VR) procedural dissociation services provided by the same physician or other qualified health care professional performing the diagnostic or therapeutic service that the VR procedural dissociation supports, requiring the presence of an independent, trained observer to assist in the monitoring of the patient's level of dissociation or consciousness and physiological status; each additional 15 minutes intraservice time (List separately in addition to code for primary service)
0773T	Virtual reality (VR) procedural dissociation services provided by a physician or other qualified health care professional other than the physician or other qualified health care professional performing the diagnostic or therapeutic service that the VR procedural dissociation supports; initial 15 minutes of intraservice time, patient age 5 years or older
0774T	Virtual reality (VR) procedural dissociation services provided by a physician or other qualified health care professional other than the physician or other qualified health care professional performing the diagnostic or therapeutic service that the VR procedural dissociation supports; each additional 15 minutes intraservice time (List separately in addition to code for primary

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	service)
0776T	Therapeutic induction of intra-brain hypothermia, including placement of a mechanical temperature-controlled cooling device to the neck over carotids and head, including monitoring (eg, vital signs and sport concussion assessment tool 5 [SCAT5]), 30 minutes of treatment
0777T	Real-time pressure-sensing epidural guidance system (List separately in addition to code for primary procedure)
0778T	Surface mechanomyography (sMMG) with concurrent application of inertial measurement unit (IMU) sensors for measurement of multi-joint range of motion, posture, gait, and muscle function
0779T	Gastrointestinal myoelectrical activity study, stomach through colon, with interpretation and report
0781T	Bronchoscopy, rigid or flexible, with insertion of esophageal protection device and circumferential radiofrequency destruction of the pulmonary nerves, including fluoroscopic guidance when performed; bilateral mainstem bronchi
0782T	Bronchoscopy, rigid or flexible, with insertion of esophageal protection device and circumferential radiofrequency destruction of the pulmonary nerves, including fluoroscopic guidance when performed; unilateral mainstem bronchus
0783T	Transcutaneous auricular neurostimulation, set-up, calibration, and patient education on use of equipment
90880	Hypnotherapy
90584	Dengue vaccine, quadrivalent, live, 2 dose schedule, for subcutaneous use
0791T	Motor-cognitive, semi-immersive virtual reality–facilitated gait training, each 15 minutes (List separately in addition to code for primary procedure)
0792T	Application of silver diamine fluoride 38%, by a physician or other qualified health care professional
0793T	Percutaneous transcatheter thermal ablation of nerves innervating the pulmonary arteries, including right heart catheterization, pulmonary artery angiography, and all imaging guidance
0794T	Patient-specific, assistive, rules-based algorithm for ranking pharmaco-oncologic treatment options based on the patient's tumor-specific cancer marker information obtained from prior molecular pathology, immunohistochemical, or other pathology results which have been previously interpreted and reported separately
0795T	Transcatheter insertion of permanent dual-chamber leadless pacemaker, including imaging guidance (eg, fluoroscopy, venous ultrasound, right atrial angiography, right ventriculography, femoral venography) and device evaluation (eg, interrogation or programming), when performed; complete system (ie, right atrial and right ventricular pacemaker components)
0796T	Transcatheter insertion of permanent dual-chamber leadless pacemaker, including imaging guidance (eg, fluoroscopy, venous ultrasound, right atrial angiography, right ventriculography, femoral venography) and device evaluation (eg, interrogation or programming), when performed; right atrial pacemaker component (when an existing right ventricular single leadless pacemaker exists to create a dual-chamber leadless pacemaker system)
0797T	Transcatheter insertion of permanent dual-chamber leadless pacemaker, including imaging guidance (eg, fluoroscopy, venous ultrasound, right atrial angiography, right ventriculography, femoral venography) and device evaluation (eg, interrogation or programming), when performed; right ventricular pacemaker component (when part of a dual-chamber leadless pacemaker system)
0798T	Transcatheter removal of permanent dual-chamber leadless pacemaker, including imaging guidance (eg, fluoroscopy, venous ultrasound, right atrial angiography, right ventriculography, femoral venography), when performed; complete system (ie, right atrial and right ventricular pacemaker components)
0799T	Transcatheter removal of permanent dual-chamber leadless pacemaker, including imaging guidance (eg, fluoroscopy, venous ultrasound, right atrial angiography, right ventriculography, femoral venography), when performed; right atrial pacemaker component
0800T	Transcatheter removal of permanent dual-chamber leadless pacemaker, including imaging guidance (eg, fluoroscopy, venous ultrasound, right atrial angiography, right ventriculography, femoral venography), when performed; right ventricular pacemaker component (when part of a dual-chamber leadless pacemaker system)
0801T	Transcatheter removal and replacement of permanent dual-chamber leadless pacemaker, including imaging guidance (eg, fluoroscopy, venous ultrasound, right atrial angiography, right ventriculography, femoral venography) and device evaluation (eg, interrogation or programming), when performed; dual-chamber system (ie, right atrial and right ventricular

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	pacemaker components)
0802T	Transcatheter removal and replacement of permanent dual-chamber leadless pacemaker, including imaging guidance (eg, fluoroscopy, venous ultrasound, right atrial angiography, right ventriculography, femoral venography) and device evaluation (eg, interrogation or programming), when performed; right atrial pacemaker component
0803T	Transcatheter removal and replacement of permanent dual-chamber leadless pacemaker, including imaging guidance (eg, fluoroscopy, venous ultrasound, right atrial angiography, right ventriculography, femoral venography) and device evaluation (eg, interrogation or programming), when performed; right ventricular pacemaker component (when part of a dual-chamber leadless pacemaker system)
0804T	Programming device evaluation (in person) with iterative adjustment of implantable device to test the function of device and to select optimal permanent programmed values, with analysis, review, and report, by a physician or other qualified health care professional, leadless pacemaker system in dual cardiac chambers
0805T	Transcatheter superior and inferior vena cava prosthetic valve implantation (ie, caval valve implantation [CAVI]); percutaneous femoral vein approach
0806T	Transcatheter superior and inferior vena cava prosthetic valve implantation (ie, caval valve implantation [CAVI]); open femoral vein approach
0807T	Pulmonary tissue ventilation analysis using software-based processing of data from separately captured cinefluorograph images; in combination with previously acquired computed tomography (CT) images, including data preparation and transmission, quantification of pulmonary tissue ventilation, data review, interpretation and report
0808T	Pulmonary tissue ventilation analysis using software-based processing of data from separately captured cinefluorograph images; in combination with computed tomography (CT) images taken for the purpose of pulmonary tissue ventilation analysis, including data preparation and transmission, quantification of pulmonary tissue ventilation, data review, interpretation and report
0809T	Arthrodesis, sacroiliac joint, percutaneous or minimally invasive (indirect visualization), with image guidance, placement of transfixing device(s) and intraarticular implant(s), including allograft or synthetic device(s)
0810T	Subretinal injection of a pharmacologic agent, including vitrectomy and 1 or more retinotomies
0387U	Oncology (melanoma), autophagy and beclin 1 regulator 1 (AMBRA1) and loricrin (AMLo) by immunohistochemistry, formalin-fixed paraffin-embedded (FFPE) tissue, report for risk of progression
0388U	Oncology (non-small cell lung cancer), next-generation sequencing with identification of single nucleotide variants, copy number variants, insertions and deletions, and structural variants in 37 cancer-related genes, plasma, with report for alteration detection
0389U	Pediatric febrile illness (Kawasaki disease [KD]), interferon alpha-inducible protein 27 (IFI27) and mast cell-expressed membrane protein 1 (MCEMP1), RNA, using reverse transcription polymerase chain reaction (RT-qPCR), blood, reported as a risk score for KD
0390U	Obstetrics (preeclampsia), kinase insert domain receptor (KDR), Endoglin (ENG), and retinol-binding protein 4 (RBP4), by immunoassay, serum, algorithm reported as a risk score
0391U	Oncology (solid tumor), DNA and RNA by next-generation sequencing, utilizing formalin-fixed paraffin-embedded (FFPE) tissue, 437 genes, interpretive report for single nucleotide variants, splice-site variants, insertions/deletions, copy number alterations, gene fusions, tumor mutational burden, and microsatellite instability, with algorithm quantifying immunotherapy response score
0392U	Drug metabolism (depression, anxiety, attention deficit hyperactivity disorder [ADHD]), gene-drug interactions, variant analysis of 16 genes, including deletion/duplication analysis of CYP2D6, reported as impact of gene-drug interaction for each drug
0393U	Neurology (eg, Parkinson disease, dementia with Lewy bodies), cerebrospinal fluid (CSF), detection of misfolded a-synuclein protein by seed amplification assay, qualitative
0394U	Perfluoroalkyl substances (PFAS) (eg, perfluorooctanoic acid, perfluorooctane sulfonic acid), 16 PFAS compounds by liquid chromatography with tandem mass spectrometry (LC-MS/MS), plasma or serum, quantitative
0395U	Oncology (lung), multi-omics (microbial DNA by shotgun next-generation sequencing and carcinoembryonic antigen and osteopontin by immunoassay), plasma, algorithm reported as malignancy risk for lung nodules in early-stage disease
0396U	Obstetrics (pre-implantation genetic testing), evaluation of 300000 DNA single-nucleotide polymorphisms (SNPs) by microarray, embryonic tissue, algorithm reported as a probability for

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	single-gene germline conditions
0397U	Oncology (non-small cell lung cancer), cell-free DNA from plasma, targeted sequence analysis of at least 109 genes, including sequence variants, substitutions, insertions, deletions, select rearrangements, and copy number variations
0398U	Gastroenterology (Barrett esophagus), P16, RUNX3, HPP1, and FBN1 DNA methylation analysis using PCR, formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as risk score for progression to high-grade dysplasia or cancer
0399U	Neurology (cerebral folate deficiency), serum, detection of anti-human folate receptor IgG-binding antibody and blocking autoantibodies by enzyme-linked immunoassay (ELISA), qualitative, and blocking autoantibodies, using a functional blocking assay for IgG or IgM, quantitative, reported as positive or not detected
0400U	Obstetrics (expanded carrier screening), 145 genes by nextgeneration sequencing, fragment analysis and multiplex ligationdependent probe amplification, DNA, reported as carrier positive or negative
0401U	Cardiology (coronary heart disease [CAD]), 9 genes (12 variants), targeted variant genotyping, blood, saliva, or buccal swab, algorithm reported as a genetic risk score for a coronary event
0388U	Oncology (non-small cell lung cancer), next-generation sequencing with identification of single nucleotide variants, copy number variants, insertions and deletions, and structural variants in 37 cancer-related genes, plasma, with report for alteration detection
0391U	Oncology (solid tumor), DNA and RNA by next-generation sequencing, utilizing formalin-fixed paraffin-embedded (FFPE) tissue, 437 genes, interpretive report for single nucleotide variants, splice-site variants, insertions/deletions, copy number alterations, gene fusions, tumor mutational burden, and microsatellite instability, with algorithm quantifying immunotherapy response score
HCPC Codes	**Description**
A4341	Indwelling intraurethral drainage device with valve, patient inserted, replacement only, each
A4342	Accessories for patient inserted indwelling intraurethral drainage device with valve, replacement only, each
A4560	Neuromuscular electrical stimulator (NMES), disposable, replacement only
A4596	Cranial electrotherapy stimulation (CES) system supplies and accessories, per month
A7049	Expiratory positive airway pressure intranasal resistance valve
A9291	Prescription digital behavioral therapy, fda cleared, per course of treatment
C1747	Endoscope, single-use (i.e., disposable), urinary tract, imaging/illumination device (insertable)
C1761	Catheter, transluminal intravascular lithotripsy, coronary
C1832	Autograft suspension, including cell processing and application, and all system components
C1833	Monitor, cardiac, including intracardiac lead and all system components (implantable)
C7550	Cystourethroscopy, with biopsy(ies) with adjunctive blue light cystoscopy with fluorescent imaging agent
C7554	Cystourethroscopy with adjunctive blue light cystoscopy with fluorescent imaging agent
C9759	Transcatheter intraoperative blood vessel microinfusion(s) (e.g., intraluminal, vascular wall and/or perivascular) therapy, any vessel, including radiological supervision and interpretation, when performed
C9760	Non-randomized, non-blinded procedure for NYHA class II, III, IV heart failure; transcatheter implantation of interatrial shunt, including right and left heart catheterization, transeptal puncture, transesophageal echocardiography (TEE)/intracardiac echocardiography (ICE), and all imaging with or without guidance (e.g., ultrasound, fluoroscopy), performed in an approved investigational device exemption (IDE) study
C9761	Cystourethroscopy, with ureteroscopy and/or pyeloscopy, with lithotripsy, and ureteral catheterization for steerable vacuum aspiration of the kidney, collecting system, ureter, bladder, and urethra if applicable (must use a steerable ureteral catheter)
C9762	Cardiac magnetic resonance imaging for morphology and function, quantification of segmental dysfunction; with strain imaging
C9763	Cardiac magnetic resonance imaging for morphology and function, quantification of segmental dysfunction; with stress imaging
C9764	Revascularization, endovascular, open or percutaneous, lower extremity artery(ies), except tibial/peroneal; with intravascular lithotripsy, includes angioplasty within the same vessel(s), when performed

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C9765	Revascularization, endovascular, open or percutaneous, lower extremity artery(ies), except tibial/peroneal; with intravascular lithotripsy, and transluminal stent placement(s), includes angioplasty within the same vessel(s), when performed
C9766	Revascularization, endovascular, open or percutaneous, lower extremity artery(ies), except tibial/peroneal; with intravascular lithotripsy and atherectomy, includes angioplasty within the same vessel(s), when performed
C9767	Revascularization, endovascular, open or percutaneous, lower extremity artery(ies), except tibial/peroneal; with intravascular lithotripsy and transluminal stent placement(s), and atherectomy, includes angioplasty within the same vessel(s), when performed
C9768	Endoscopic ultrasound-guided direct measurement of hepatic portosystemic pressure gradient by any method (list separately in addition to code for primary procedure)
C9769	Cystourethroscopy, with insertion of temporary prostatic implant/stent with fixation/anchor and incisional struts
C9772	Revascularization, endovascular, open or percutaneous, tibial/peroneal artery(ies), with intravascular lithotripsy, includes angioplasty within the same vessel (s), when performed
C9773	Revascularization, endovascular, open or percutaneous, tibial/peroneal artery(ies); with intravascular lithotripsy, and transluminal stent placement(s), includes angioplasty within the same vessel(s), when performed
C9774	Revascularization, endovascular, open or percutaneous, tibial/peroneal artery(ies); with intravascular lithotripsy and atherectomy, includes angioplasty within the same vessel (s), when performed
C9775	Revascularization, endovascular, open or percutaneous, tibial/peroneal artery(ies); with intravascular lithotripsy and transluminal stent placement(s), and atherectomy, includes angioplasty within the same vessel (s), when performed
C9776	Intraoperative near-infrared fluorescence imaging of major extra-hepatic bile duct(s) (e.g., cystic duct, common bile duct and common hepatic duct) with intravenous administration of indocyanine green (ICG) (list separately in addition to code for primary procedure)
C9777	Esophageal mucosal integrity testing by electrical impedance, transoral (list separately in addition to code for primary procedure)
C9778	Colpopexy, vaginal; minimally invasive extraperitoneal approach (sacrospinous)
C9781	Arthroscopy, shoulder, surgical; with implantation of subacromial spacer (e.g., balloon), includes debridement (e.g., limited or extensive), subacromial decompression, acromioplasty, and biceps tenodesis when performed
E0677	Nonpneumatic sequential compression garment, trunk
E1905	Virtual reality cognitive behavioral therapy device (CBT), including preprogrammed therapy software
K1009	Speech volume modulation system, any type, including all components and accessories
K1028	Power source and control electronics unit for oral device/appliance for neuromuscular electrical stimulation of the tongue muscle, controlled by phone application
K1029	Oral device/appliance for neuromuscular electrical stimulation of the tongue muscle, used in conjunction with the power source and control electronics unit, controlled by phone application, 90-day supply
K1031	Non-pneumatic compression controller without calibrated gradient pressure
K1032	Non-pneumatic sequential compression garment, full leg
K1033	Non-pneumatic sequential compression garment, half leg
K1035	Molecular diagnostic test reader, nonprescription self-administered and self-collected use, FDA approved, authorized or cleared
S1091	Stent, noncoronary, temporary, with delivery system (Propel)
V2525	Contact lens, hydrophilic, dual focus, per lens
C9150	Xenon xe-129 hyperpolarized gas, diagnostic, per study dose
C9786	Echocardiography image post processing for computer aided detection of heart failure with preserved ejection fraction, including interpretation and report
C9787	Gastric electrophysiology mapping with simultaneous patient symptom profiling

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
7/7/2020	07/07/2020[MPC] ,07/06/2021[MPC], 07/05/2022[MPC], 07/11/2023[MPC]	07/25/2023

[MPC] Medical Policy Committee

Revision History	Description
07/07/2020	Created document including new codes from 04/2020 and 07/2020.
01/01/2021	Added new codes from 10/2020 and 01/2021.
07/06/2021	Updating applicable coding, including new codes released 04/01/21 and 07/01/2021.
06/15/2022	Updated codes for remote therapeutic monitoring
10/24/2022	Updated applicable codes, including new codes released 01/01/22 and 04/01/22.
11/10/2022	Updated applicable codes including new code from 7/1/2022
03/03/2023	Updated applicable codes new codes from 10/01/2022. Including CPT codes 0332U, 0333U, 0334U, 0335U, 0336U, 0337U, 0338U, 0340U, 0341U, 0343U, 0344U, 0346U, 0347U, 0348U, 0349U, 0350U, 0351U, 0352U, 0353U, 0354U. Including HCPC codes A4596, C1834
03/06/2023	Updated applicable codes new codes from 07/01/2022, Including CPT codes 0323U, 0324U, 0325U, 0326U, 0327U, 0328U, 0329U, 0330U, 0331U, 0714T, 0715T, 0716T, 0717T, 0718T, 0719T, 0720T, 0721T, 0722T, 0723T, 0724T, 0725T, 0726T, 0727T, 0728T, 0729T, 0730T, 0731T, 0732T, 0733T, 0734T, 0735T, 0736T, 0737T, 90584
07/25/2023	Updated new applicable codes from 01/01/2023 and 04/01/2023
03/18/2024	Removed codes K1018 & K1019

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KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Next Generation Sequencing for Advanced Cancer (somatic/tissue testing)

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Next Generation Sequencing (NGS) (90.2)
Local Coverage Determinations (LCD)	9/30/2015 - Noridian retired LCD for Genetic Testing (L24308). These services still need to meet medical necessity as outlined in the LCD and will require review. LCDs are retired due to lack of evidence of current problems, or in some cases because the material is addressed by a National Coverage Decision (NCD), a coverage provision in a CMS interpretative manual or an LCD. Most LCDs are not retired because they are incorrect. The criteria should be still referenced when making an initial decision. However, if the decision is appealed, the retired LCD cannot be specifically referenced. Maximus instead looks for “medical judgment” which could be based on our commercial criteria or literature search. MolDX: Plasma-Based Genomic Profiling in Solid Tumors (L39232) (Guardant360®) MolDX: Inivata, InVisionFirst, Liquid Biopsy for Patients with Lung Cancer (37899) MolDX: Next-Generation Sequencing Lab-Developed Tests for Myeloid Malignancies and Suspected Myeloid Malignancies (L38125) MolDX: Phenotypic Biomarker Detection in Circulating Tumor Cells (L38645) MolDX: Prognostic and Predictive Molecular Classifiers for Bladder Cancer (L38649)
Local Coverage Article (LCA)	MolDX: Plasma-Based Genomic Profiling in Solid Tumors (A58975) (Guardant 360®) Billing and Coding: MolDX: Targeted and Comprehensive Genomic Profile Testing in Cancer (A56518)

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Decision Memo	Decision Memo for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG-00450R) ***FDA-approved tests*** *(not all-inclusive)* FoundationFocus™ CDxBRCA Assay (Foundation Medicine, Inc.) FoundationOne CDx (Foundation Medicine, Inc.) FoundationOne Liquid CDx (Foundation Medicine, Inc.) Guardant360® CDx (Guardant Health, Inc.) Oncomine™ Dx Target Test (Thermo Fisher Scientific, Inc.) Praxis™ Extended RAS Panel (Illumina, Inc.) MSK-IMPACT™ (Memorial Sloan Kettering Cancer Center's (MSK) IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets))

For Non-Medicare Members

I. Next Generation Sequencing can **only be covered for the following solid cancer types:**
1. Stage III or IV non-small cell lung cancer
2. stage IV pancreatic carcinoma
3. stage IV colon carcinoma
4. stage IV prostate
5. stage IV ovarian
6. stage IV endometrial
7. stage IV biliary
8. stage IV gastric
9. stage IV esophageal (adeno and squamous) gastroesophageal
10. stage IV breast (ER or PR positive)

II. In addition, the member must meet **ALL of the following**:
1. The individual is a candidate for a targeted therapy associated with a specific tumor biomarker or disease site
2. Results of testing will directly impact clinical decision making
3. The testing method is considered to be scientifically valid and proven to have clinical utility based on prospective evidence
4. **EITHER** of the following:
   - Identification of the specific biomarker or risk assessment using a Gene Expression Classifier (GEC)/Next Generation Sequencing is required in order to initiate a related therapy and the therapy has been validated by the National Comprehensive Cancer Network™ (NCCN Guidelines™) as a category 1, 2A, or 2B recommendation for the individual's tumor type or disease site **OR**
   - Identification of the specific biomarker or use of a GEC/Next Generation Sequencing has been demonstrated in published peer-reviewed literature to improve diagnosis, management or clinical outcomes for the individual's condition being addressed

III. The following panels meet Kaiser Permanente coverage criteria in regard to actionable mutations —any of these three labs can be used:
- CellNetix SymGene Panel
- Oncoplex (University of Washington)
- Caris Life Sciences

NOTE: If the submission is for a different vendor, it will be redirected to one of the above preferred labs under section III for HMO. For POS and PPO, a similar narrow panel limited to the genes above can be considered on a case-by-case basis if labs A-D are unacceptable.

IV. Molecular testing for hematology-oncology indications is **considered experimental, investigational or unproven in the following situations:**
- there is insufficient evidence to support molecular testing for the specific tumor type or disease site
- the requested gene(s) or biomarker(s) are correlated with a known therapy, but that therapy has not been validated for the specific tumor type or disease site

Individual or targeted gene testing can be covered for specific, actionable mutations for cancer types that panel testing is not covered.

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Please see the list of ***non-covered*** genetic panels on the KPWA criteria page – Genetic Panel Testing. This includes, but is not limited to:

- FoundationOne
- Guardant360

Repeat testing is non-covered.

If requesting this these services, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist

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Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

Symgene 79 NGS Cancer Panel:

CPT® or HCPC Codes	Description
88374 (x2)	Morphometric analysis, in situ hybridization (quantitative or semi-quantitative), using computer-assisted technology, per specimen; each multiplex probe stain procedure
81445	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
88381	Microdissection (ie, sample preparation of microscopically identified target); manual
G0452	Molecular pathology procedure; physician interpretation and report

Symgene Focus- Targeted NGS Cancer Panel (Lung):

CPT® or HCPC Codes	Description
81445	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
88374 (x2)	Morphometric analysis, in situ hybridization (quantitative or semi-quantitative), using computer-assisted technology, per specimen; each multiplex probe stain procedure
88360	Morphometric analysis, tumor immunohistochemistry (eg, Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen, each single antibody stain procedure; manual
88381	Microdissection (ie, sample preparation of microscopically identified target); manual
G0452	Molecular pathology procedure; physician interpretation and report

Symgene Focus- Targeted NGS Cancer Panel (Colon):

CPT® or HCPC Codes	Description
81445	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS,

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	NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
88381	Microdissection (ie, sample preparation of microscopically identified target); manual
G0452	Molecular pathology procedure; physician interpretation and report

Caris Life Sciences

CPT® or HCPC Codes	Description
81479	Unlisted molecular pathology procedure

Oncoplex (University of Washington)

CPT® or HCPC Codes	Description
81445	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed

FoundationOne® (Foundation Medicine) –
Medicare: Considered Medically Necessary when criteria in the applicable policy statements listed above are met
Non-Medicare: Considered Not Medically Necessary, use preferred vendors above

CPT® or HCPC Codes	Description
0239U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations *FoundationOne® Liquid CDx*
0037U	Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden *FoundationOne CDx™*

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
08/04/2020	08/04/2020 MPC, 08/03/2021 MPC, 08/02/2022MPC, 09/06/2022MPC, 08/01/2023MPC	11/13/2023

MPC Medical Policy Committee

Revision History	Description
08/04/2020	MPC approved to adopt new clinical criteria. Requires 60-day notice, effective date 01/01/2021.
11/13/2020	Added codes from CellNetix
09/06/2022	MPC approved to expand solid cancer types to include: stage IV prostate, stage IV ovarian , stage IV endometrial , stage IV biliary , stage IV gastric, stage IV esophageal (adeno and squamous) gastroesophageal, stage IV breast (ER or PR positive). Also approved Caris and Oncoplex as contracted lab vendors. 60-day notice required; effective 2/1/2023.

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10/26/2022	Refiled 60 day notice. Adjusted effective dates for advanced cancers to 1/1/23 per RCW 48.43.810
01/24/2023	Added Applicable codes for FoundationOne® NGS testing
11/13/2023	Updated Medicare coverage article link
02/22/2024	Updated Medicare coverage article links

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KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Recombinant Activated Factor VII (NovoSeven®)

- Glanzmann's Disease
- Hemophilia
- Post-Partum Hemorrhage
- Cardiac Surgery Hemorrhage

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Criteria

For Non-Medicare Members

Kaiser Permanente has elected to use the Coagulation Factor VIIa – (NovoSeven) (KP-0452) MCG* for medical necessity determinations. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.

***MCG Manuals are proprietary and cannot be published and/or distributed.** However, on an individual member basis, Kaiser Permanente can share a copy of the specific criteria document used to make a utilization management decision. If one of your patients is being reviewed using these criteria, you may request a copy of the criteria by calling the Kaiser Permanente Clinical Review staff at 1-800-289-1363 or access the MCG Guideline Index using the link provided above.

If requesting this service, please send the following documentation to support medical necessity:

- Last 12 months of clinical notes from requesting provider &/or specialist (hematology, primary care physician)

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Background

Glanzmann's disease (aka Glanzmann's thrombasthenia) is a platelet disorder characterized by a deficiency in the platelet membrane glycoproteins (GP) IIb-IIIa. It is one of several hereditary platelet disorders typified by normal platelet numbers and a prolonged bleeding time. NovoSeven® may also be appropriate for use with patients who have other bleeding disorders such as Glanzmann's thrombasthenia or Bernard-Soulier's thrombasthenia.

NovoSeven® (manufactured by Novo Nordisk, Denmark) is a product containing recombinant coagulation Factor VII. It has been used to prevent bleeding and treat hemorrhage during surgery in patients with hemophilia A with a Factor VIII inhibitor, hemophilia B with a Factor IX inhibitor and acquired deficiencies in Factors VIII or IX.

NovoSeven® has been approved by the FDA as a biological product.

People with hemophilia A (approximately 85% of hemophilia patients) lack the blood clotting protein, factor VIII and people with hemophilia B lack factor IX. The severity of the condition varies, depending on the amount of clotting factor in the blood. About 70% of individuals with hemophilia A have less than 1 percent of the normal amount of clotting factor and are considered to have severe disease. Treatment of hemophilia A or B consists of replacement of the deficient factor.

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Approximately 20-50% of severe hemophilia A patients and 1.5-3% of hemophilia B patients (Kulkarni, 2001) develop antibodies called inhibitors that block the activity of the replacement clotting factor. Management of hemophilia patients with inhibitors is challenging. Injection of high quantities of clotting factors is sometimes effective at neutralizing the inhibitors and allowing sufficient quantities of the factors to circulate. Another treatment is injection of porcine factor VIII, which is often sufficiently different from human factor VIII to go unrecognized by inhibitors. However, many patients have cross-reactive antibodies to Porcine FVIII concentrates. Removing the antibody from the plasma (plasmapheresis), in combination with injections of clotting factor, is sometimes used.

Another approach to treatment is the use of bypassing agents, treatments that induce hemostasis independent of the presence of factors VIII and IV. Prothrombin complex concentrates (PCCs) and activated prothrombin complex concentrates (aPCC) were developed in the 1970s. They are derived from human plasma and contain the vitamin K-dependent coagulation proteins.

Recombinant activated Factor VII (rFVIIa) or NovoSeven is also a bypassing agent. This product is derived from cultured baby hamster kidney cells using recombinant DNA technology. Because it does not any human serum or proteins, NovoSeven has a low risk of infecting patients with human viruses that could be present in plasma-derived products. NovoSeven has a relatively short half-life and injections must be given frequently. The initial recommended dose is 90 ug/kg every two hours until cessation of bleeding. PCCs and aPCCs have been associated with thromboembolic side effects and it is also possible that there is a risk of thrombosis with NovoSeven (Kulkarni, 2001).

NovoSeven (manufactured by Novo Nordisk, Denmark) has been available in the European Union since 1996. In 1999, NovoSeven was approved by the FDA for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to factors VIII or IX. It is available in the US through Novo Nordisk Pharmaceuticals, New Jersey.

Major bleeding is a common and potentially serious complication in high-risk **cardiovascular surgeries** and is a well-known risk factor for postoperative morbidity and mortality. Excessive blood loss frequently requires the transfusion of allogenic blood, blood products, and surgical re-exploration when appropriate. Re-exploration may not reveal a surgically repairable source of bleeding in up to 50% of cases. Both massive blood transfusion and re-exploration are associated with longer intensive care and hospital stay, wound infection, higher morbidity, and reduced survival rates. The high risk of bleeding and its consequences have prompted cardiac surgeons to explore the off-label use of recombinant factor VIIa as an alternative haemostatic agent for postoperative bleeding (Murphy 2007, Zangrillo 2009, Goksedef 2010, Chapman 2011).

Recombinant factor VIIa (rFVIIa; NovoSeven®, NovoNordisk, Copenhagen, Denmark) is a recombinant DNA preparation of activated blood coagulation factor VII. It is an engineered preparation of factor VIIa produced in cultured baby hamster kidney cells and is nearly identical to plasma-derived factor VIIa in structure and function. At the pharmacological level, it is to some degree different from the natural FVIIa (nFVIIa). Its pharmacologic action induces thrombin generation on locally activated platelets and contributes to the formation of a stabilized clot at the site of vessel injury. NovoSeven received market approval by the US Food and Drug Administration (FDA) in 1999 for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX respectively. In 2005, it was further approved by the FDA for the treatment of bleeding episodes and for the prevention of bleeding in surgical interventions or invasive procedures in patients with acquired hemophilia. NovoSeven is licensed in Europe for the treatment of congenital factor VII deficiency and Glanzmann's thrombasthenia refractory to platelet administration (Ratko 2004, Al-Ruzzeh 2008, Gill 2009, Zangrillo 2009, Logan 2011, Goksedef 2012, Guzette 2012).

Over the last decade, rFVIIa (NovoSeven) has been increasingly used off-label for a wide range of disorders including life threatening bleeding after body and brain trauma, intracranial hemorrhage, major abdominal surgeries, drug-induced coagulopathy, platelet disorders, intraoperative or postoperative hemorrhage, and a number of other conditions. The vast majority of adults and pediatric patients who have received rFVIIa received it for an off-label indication. It is also being used off-label for pediatric and adult cardiac surgery. However, its use in these patients is controversial and widely debated due to the concern about its safety especially for the potential increase the risk of thromboembolic events. Cardiac surgery patients are already at high risk of myocardial ischemia, arterial and venous thrombosis before, during, and after the surgery due to either or both the underlining pathology and the surgery performed with cardiopulmonary bypass or cross clamping. The reported mortality and complication rate among cardiac surgery patients receiving rFVIIa ranged from 19-40%. The issue of the appropriate dosing is also a major concern (Ratko 2004, Al-Ruzzeh 2008, Gelsomino 2008, Gill 2009, Zangrillo 2009, Logan 2011, Goksedef 2012, Guzette 2012).

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Medical Technology Assessment Committee (MTAC)

NovoSeven®

10/10/2001: MTAC REVIEW

Evidence Conclusion: There is insufficient published scientific evidence on which to base conclusions about the effect of NovoSeven® on health outcomes in people with Glanzmann's disease.

Articles: The search yielded 7 articles. Two were review articles, two were case studies (report on only one patient) and three were case series, each of which included five or fewer patients with Glanzmann's disease. Due to the small sizes of the case series, no evidence tables created.

The use of NovoSeven® in the treatment of Glanzmann's disease does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

NovoSeven®

12/10/2003: MTAC REVIEW

Evidence Conclusion: There are no studies comparing NovoSeven to another treatment for hemophilia patients with inhibitors. A comparison to the alternative bypass agents, prothrombin complex concentrates (PCCs) or activated prothombin complex concentrates (aPCC), might be feasible. In the Scharrer study, 7 (25%) of the patients had failed PCCs/aPCCs, but neither of the other two studies attempted to select patients who had failed treatment with another bypass agent. Non-comparative clinical data suggests that NovoSeven is effective at achieving hemostasis in 80-90% of bleeding episodes. There are data on both in-home and surgical use of NovoSeven. There was a low rate of thrombosis associated with treatment in the published data.

Articles: The search yielded 71 articles, many of which were reviews, opinion pieces, overviews or dealt with technical aspects of the treatment. There were no randomized or non-randomized studies with hemophilia patients with inhibitors that compared NovoSeven to an alternate treatment. One randomized controlled trial was identified with hemophilia patients, but this compared two doses of NovoSeven. The remaining empirical studies were case series. The RCT was critically appraised, not for comparative data, but because it was a reasonably well-designed study with the target population. In addition, two of the largest case series using NovoSeven to treat hemophilia patients with inhibitors were critically appraised. The articles reviewed are as follows: Shapiro AD, Gilchrist S, Hoots WK. Prospective, randomized trial of two doses of rFVIIa (NovoSeven) in hemophilia patients with inhibitors undergoing surgery. *Thromb Haemost* 1998; 80: 773-778. See Evidence Table. Key NS Aledort LM, Beardsley D. Home treatment of mild to moderate bleeding episodes using recombinant factor VIIa (NovoSeven) in hemophiliacs with inhibitors. *Thromb Haemost* 1998; 80: 912-918. See Evidence Table. Scharrer I et al. Recombinant factor VIIa for patients with inhibitors to factor VIII or IX or factor II deficiency. *Hemophilia* 1999; 5: 253-259. See Evidence Table.

The use of NovoSeven® in the treatment of Hemophilia does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

NovoSeven®

02/11/2013: MTAC REVIEW

Evidence Conclusion: There is a lack of published high-quality studies on the off-label use of rFVIIa in cardiac surgery. To date only two RCTs evaluated the use of rFVIIa in adult cardiac surgery; one was a very small pilot study with 20 patients that assessed the prophylactic use of the therapy, and the other was conducted among 172 patients (Gill 2009, evidence table 3) to evaluate the effectiveness and safety of rFVIIa in 172 patients bleeding after cardiac surgery requiring cardiopulmonary bypass. Both trials lacked statistical power to detect significant differences between the study groups. The rest of the published studies were observational with or without matched comparison groups. A number of these observational studies compared outcomes of patients receiving rFVIIa to matched groups using propensity score (PS) analysis. This method is used to adjust for selection bias in observational studies of causal effect, when RCTs are unfeasible, unethical, or too costly to conduct. PS matching adjusts for observed variables and can only decrease but not eliminate the selection bias. It may also reduce the study's external validity as only a subset of the treated patients is used in the analysis. The majority of the published studies were conducted over a long period of time; the administration of rFVIIa was based on the guidelines of each institution, but was ultimately made by at the discretion of the operating team, and may have evolved throughout the study period as the experience with using the therapy increased (Anderson 2012). There were no consistent well-defined and measurable endpoints to evaluate the efficacy of the therapy. In addition, the published studies followed different protocols for the threshold for using rFVIIa and its dose. This ranged from prophylactic use as a haemostatic agent in the operating room, to a rescue therapy for

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patients with refractory bleeding. Rescue therapy is defined as situations in which rFVII is used when patients continue to bleed excessively despite having received maximal standard haemostatic therapy, the definition of which varied between institutions (Guzette 2012).The dosage of rFVIIa ranged between studies from 9-192 µg/kg, and was used either repeatedly or a in a single dose.The results of the RCTs and the four comparative observational studies on the use of rFVIIa in adult cardiac surgery were pooled in three meta-analyses (Zangrillo 2009, Ponschab 2011, and Yank 2011). The pooled results of the two more recent meta-analyses comprising a total 470 patients, showed no significant effect of rFVIIa on reducing mortality compared to usual care, but a statistically significant increase in the occurrence of stroke (calculated number needed to harm of 26). The meta-analyses showed a lower but statistically insignificant rate of re-exploration and a trend towards the lower blood loss and need for transfusion with the use of rFVIIa. Gill and colleagues' RCT found a statistically significant lower rate of re-operation rates and need for blood transfusion, and a statistically insignificant increase in serious adverse events in the adult cardiac surgery patients who received rFVIIa. In conclusion, the available evidence suggests that rFVIIa use in adult cardiac surgery patients may result in an increased risk of stroke and lower re-exploration rate without a significant mortality benefit. Larger randomized controlled trials with sufficient power are needed to verify the results of the meta-analyses and clearly assess the benefits and risks of the off-label use of rFVIIa in cardiac surgery patients.

Articles: The literature search for studies on the use of rFVIIa (NovoSeven) for adults undergoing cardiac surgery revealed two meta-analyses, two randomized controlled trials, and a number of observational prospective and retrospective studies with or without comparison groups. The search also identified an updated Cochrane review and other meta-analyses and systematic reviews that included trials on the use of rFVII for any off-label indication including cardiac surgery. Among these, there was one review (Yank 2011) prepared for the agency for Healthcare Research and Quality (AHRQ) that included a meta-analysis of studies on the use of the rFVIIa for adult cardiac surgery. The two meta-analyses on the use of rFVIIa or cardiac surgery patients were conducted by the same group of authors, but the more recent analysis included an additional RCT and focused on the rates of thromboembolic events associated with the use of rFVIIa. Two meta-analyses of trials using rFVII for adult patients undergoing cardiac surgery as well as the most recent RCT among cardiac surgery patients were selected for critical appraisal. Zangrillo A, Mizzi A, Biondi-Zoccai G, et al. Recombinant activated factor VII in cardiac surgery: a meta-analysis. J Cardiothoracic Vasc Anesth. 2009.23:34-40. Evidence Table. Ponschab M, Landoni G, Biondi-Zoccai G, etal. Recombinant activated factor VII increases stroke in cardiac surgery: a meta-analysis. J Cardiothoracic Vasc Anesth. 2011.25:804-810. Evidence Table.Gill Ravi, Herbertson M, Vuylsteke A, et al. Safety and efficacy of recombinant activated factor VII A randomized placebo-controlled trial in the setting of bleeding after cardiac surgery. Circulation 2009; 120:21-27. Evidence Table.

The use of NovoSeven® in the prevention of cardiac surgery bleeding does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
J7189	Factor VIIa (antihemophilic factor, recombinant), (NovoSeven RT), 1 mcg

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed	Date Last Revised
10/10/2001	10/10/2001, 12/10/2003, Reinstitute criteria set on 03/05/2013[MDCRPC] 03/05/2013[MDCRPC], 01/07/2014[MDCRPC], 11/04/2014 [MPC], 09/01/2015[MPC], 06/07/2016[MPC], 04/04/2017[MPC], 02/06/2018[MPC], 01/08/2019[MPC], 01/07/2020[MPC], 01/05/2021[MPC], 01/04/2022[MPC], 01/10/2023[MPC], 03/12/2024[MPC]	03/05/2013

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MDCRPC Medical Director Clinical Review and Policy Committee
MPC Medical Policy Committee

Revision History	Description

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KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Observation Level of Care

NOTICE: Kaiser Foundation Health Plan of Washington and Kaiser Foundation Health Plan of Washington Options, Inc. (Kaiser Permanente) provide these Clinical Review Criteria for internal use by their members and health care providers. The Clinical Review Criteria only apply to Kaiser Foundation Health Plan of Washington and Kaiser Foundation Health Plan of Washington Options, Inc. Use of the Clinical Review Criteria or any Kaiser Permanente entity name, logo, trade name, trademark, or service mark for marketing or publicity purposes, including on any website, or in any press release or promotional material, is strictly prohibited.

Kaiser Permanente Clinical Review Criteria are developed to assist in administering plan benefits. These criteria neither offer medical advice nor guarantee coverage. Kaiser Permanente reserves the exclusive right to modify, revoke, suspend or change any or all of these Clinical Review Criteria, at Kaiser Permanente's sole discretion, at any time, with or without notice. **Member contracts differ in health plan benefits. Always consult the patient's Evidence of Coverage or call Kaiser Permanente Member Services at 1-888-901-4636 (TTY 711), Monday through Friday, 8 a.m. to 5 p.m. to determine coverage for a specific medical service.**

PURPOSE

To provide a regional standard for appropriate utilization of observation care that ensures consistent application of the outpatient and acute care benefits for Kaiser Permanente of Washington members regardless of where care is delivered.

POLICY

A. Observation care will be utilized, when in the judgment of the admitting physician, the patient's presenting medical condition requires services which are reasonable and necessary to evaluate a patient's condition or determine the need for a possible inpatient admission.

   Observation care is a set of specific, clinically appropriate services, not a location. Therefore, a patient can be in observation status regardless of where the services are performed, i.e. critical care unit, emergency room, recovery room, telemetry, or on a medical floor. MCG Care Guidelines and the CMS "Two Midnight Rule" may serve as guidance for the attending physician in determining the appropriate use of observation care. (See MCG white paper on "Observation Care 101", by Bill Rifkin, M.D.) Observation services are defined by Centers for Medicare and Medicaid (CMS). See definition on following page.

B. CMS Manual- "When a physician orders observation care, the patient's status is that of an outpatient. The purpose of observation care is to determine the need for further treatment or for inpatient admission. Thus, a patient receiving observation care may improve and be released or be admitted as an inpatient. A physician's order must specify, "admit to observation" or "observation status" and signed electronically.

   Conversion to inpatient status must meet medical necessity for admission and be documented at the time of conversion from observation to inpatient status. A physician's order must specify, "admit to inpatient status" and be signed electronically.

   Medical records may be evaluated by Kaiser Permanente of Washington to determine the consistency between the physician order (physician intent), the services actually provided (inpatient or outpatient), and the medical necessity of those services, including the medical appropriateness of the inpatient or observation stay.

C. A patient in observation care may improve and be released or be admitted as an inpatient. In most instances a placement in observation care a will result in a disposition being implemented within 48 hours-either to discharge or continued hospitalization under inpatient status.

D. If a patient is retained in observation care for 48 hours without being admitted as an inpatient, further observation services may be denied as not reasonable and necessary for the diagnosis or treatment of illness or injury.

E. Conversion from observation status to inpatient status must meet medical necessity

Date Sent: 3/29/24 1002
These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage.
Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

F. Medicare does not consider use of observation as a convenience of the patient, the patient's family, or a physician to be appropriate. For example, a decision to keep the patient overnight due to transportation issues or because the procedure could not be scheduled in a timely manner would not qualify.

DEFINITIONS

Medicare CMS definition:

Observation care is a well-defined set of specific, clinically appropriate services, which include ongoing short term treatment, assessment, and reassessment before a decision can be made regarding whether patients will require further treatment as hospital inpatients or if they are able to be discharged from the hospital.

Observation services are commonly ordered for patients who present to the emergency department and who then require a significant period of treatment or monitoring in order to make a decision concerning their admission or discharge.

Observation services are covered only when provided by the order of a physician or another individual authorized by State licensure law and hospital staff bylaws to admit patients to the hospital or to order outpatient tests. In the majority of cases, the decision whether to discharge a patient from the hospital following resolution of the reason for the observation care or to admit the patient as an inpatient can be made in less than 48 hours, usually in less than 24 hours.

In only rare and exceptional cases do reasonable and necessary outpatient observation care span more than 48 hours. For coverage requirements, see the Medicare Benefit Policy manual, Chapter 6.

Medicare Outpatient Observation Notice (MOON):

The MOON informs all Medicare beneficiaries when they are an outpatient receiving observation services and are not an inpatient of the hospital or critical access hospital (CAH).

Beneficiary Notices Initiative (BNI)

RESPONSIBILITIES

TIMELINESS

A. MOON - The MOON must be delivered to beneficiaries in Original Medicare (fee-for-service) and Medicare Advantage plans. Enrollees who receive observation services as outpatients for more than 24 hours will be issued a MOON by the facility. The hospital or CAH must provide the MOON no later than 36 hours after observation services as an outpatient begin.

B. If the attending physician intends to place or retain a patient in observation care longer than 48 hours for:
   1. a non-medical reason,
   2. or the patient and/or family are unable or unwilling to make other arrangements for care

   A coverage determination should be requested of the Health Plan to determine if the stay is approved or denied.

PROCESS

Primary Responsibility	Actions
Facility or CAH	1. Must deliver verbal & written MOON no later than 36 hours after observation services as an outpatient begin.
KP Physician (Kaiser Permanente of Washington) and Contracted MD) (Attending/Admitting Physician)	1. Utilizing clinical judgment and CMS 2 Midnight Rule, admits the patient to observation status. (see MCG white paper "Observation Care 101" by Bill Rifkin, M.D.) 2. The KP Physician's order must specify, "admit to observation" and be electronically signed. 3. The history and physical must clearly document the medical intent of the use of observation care and be supported by the patient's presenting medical condition (severity of illness) and plan for observation/treatment (intensity of service). 4. Medical necessity for admission must be met and documented at the time of

Primary Responsibility	Actions
	conversion from observation to inpatient status. 5. The KP Physician may change admission status prior to discharge. The patient must be informed before they are transferred or discharged from the hospital if their status is Observation care only for Medicare patients. 6. The KP Physician may convert a patient from inpatient status to observation status. This will cancel the inpatient admission prior to discharge if the physician determines: a. that the inpatient admission is unnecessary b. or the original order was ambiguous and the KP Physician clarifies that order. 7. Any change in admission status must be supported by medical records (KP Physician notes and orders) and be supported by medical necessity. 8. The KP Physician may change or clarify the admission status through a direct written order, a verbal order given to a CMLN and subsequently signed by the KP Physician. 9. Notification of the Care Management department is required in this instance. **The KP Physician/attending physician may not change the patient's status (i.e., inpatient vs. observation) after discharge.* *** Through Provider Reconsideration or other review process, coverage decision can be made and/or changed after the patient discharges.*
CMLN (Care Management Liaison Nurse)	**Rounded and Non-Rounded Facilities:** • CMLN will communicate Observation/Inpatient status decision to hospital UM office within 24 hours after hospital services begin or from time of notification. • Medicare Observation stays over 24 hours are communicated to hospital UM office. **For Rounded Facilities** 1. When working directly with KP Physician during admission, will discuss status based on CMS 2 Midnight Rule and medical necessity. 2. Based upon the review, the KP Physician may provide additional documentation to support the admission status, or convert the admission status to the identified appropriate status 3. If the patient does not meet Inpatient criteria for the admission status, the CMLN will contact the physician and discuss the results of the review. 4. The CMLN may accept a verbal order from the physician to either clarify or change the admission status. The CMLN must notify the Hospital UM Office of the changes. 5. In the event the attending physician does not provide additional documentation to support the admission status or convert the patient to the appropriate status, the CMLN will: a. contact the Clinical Review Unit (CRU) physician for further review, b. arrange for a "Peer to Peer" discussion before the patient discharges. 6. If the peer-to-peer results in a change from IP to Obs, notification of the status change to the hospital UM Office before hour 36 will allow for timely MOON delivery. **Non- Rounded Facilities** 1. When not working directly with KP Physician, CMLN will conduct a review for all patients admitted as inpatient utilizing MCG Care Guidelines. 2. CMLN will communicate Observation/Inpatient status decision to hospital UM office within 24 hours after hospital services begin or from time of notification.

Primary Responsibility	Actions
Clinical Review Unit (CRU) (UM Physician Advisor)	1. CRU may contact the KP Physician and review the recommended level of care determination. If additional clinical information is needed to make a determination. 2. CRU will advise the CMLN of the results of the contact. • The decision from the Peer-to-Peer discussion will be entered into Care Management workflow system and the outcome communicated to the Hospital UM office for the appropriate actions.

Date Created	Date Reviewed	Date Last Revised
04/04/2017	04/04/2017, 04/06/2021[MPC], 04/05/2022[MPC], 04/04/2023[MPC]	06/06/2017

[MPC] Medical Policy Committee

Revision History	Description
06/06/2017	MPC approved revised policy to further clarify language

KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Occipital Nerve Stimulation (ONS) for Primary Headache

NOTICE: Kaiser Foundation Health Plan of Washington and Kaiser Foundation Health Plan of Washington Options, Inc. (Kaiser Permanente) provide these Clinical Review Criteria for internal use by their members and health care providers. The Clinical Review Criteria only apply to Kaiser Foundation Health Plan of Washington and Kaiser Foundation Health Plan of Washington Options, Inc. Use of the Clinical Review Criteria or any Kaiser Permanente entity name, logo, trade name, trademark, or service mark for marketing or publicity purposes, including on any website, or in any press release or promotional material, is strictly prohibited.

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	Peripheral Nerve Stimulation (L37360)
Local Coverage Article	Billing and Coding: Peripheral Nerve Stimulation (A55531) Response to Comments: Peripheral Nerve Stimulation (A56042)

For Non-Medicare Members

Kaiser Permanente has elected to use the MCG* Occipital Nerve Stimulation (A-0716) for medical necessity determinations. This service is not covered per MCG guidelines. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.

***MCG are proprietary and cannot be published and/or distributed**. However, on an individual member basis, Kaiser Permanente can share a copy of the specific criteria document used to make a utilization management decision. If one of your patients is being reviewed using these criteria, you may request a copy of the criteria by calling the Kaiser Permanente Clinical Review staff at 1-800-289-1363 or access the MCG Guideline Index using the link provided above.

See related policy: Deep Brain Stimulation for Primary Headache

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Headache is a major worldwide health problem disabling millions of people and resulting in considerable economic burden. Up to 40% of patients seen in major headache clinics suffer from chronic daily headache. Chronic headache disorders include migraine, cluster headache, cervicogenic headache, occipital neuralgia, and other types of primary headache (Maizels 1998, Jasper 2008).

Cluster headache (CH), an excruciating headache syndrome, is the most common type of trigeminal autonomic cephalalgias, and is thought to be the most severe primary headache disorder. 10-20% of CH patients develop a chronic form in which the attacks persist for more than one year without remissions, or with remissions lasting less than a month. Acute treatment for the attacks includes injectable or intranasal triptans or oxygen inhalation. About one percent will become refractory to medical treatment and fulfill the criteria of intractable headaches. These patients may get some relief with attack treatments, but the disorder could be disabling and may be associated with depression and suicidality (Magis 2007, Leroux 2008).

Migraine headache is a chronic headache that affects about 15% of the population and is one of the most common problems seen in emergency departments and doctors' offices. Migraine is believed to result from changes in the brain and surrounding blood vessels. The attacks typically last from 4-72 hours and vary in

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frequency from daily to less than one per year. Transformed migraines are chronic daily or almost daily headaches (>15/month) that lasts more than 4 hours. There is no cure for migraine, and medications can only help reduce the frequency and severity of disorder (Bigal 2008).
Cervicogenic headache is a chronic hemicranial pain that usually occurs daily. It usually begins at the suboccipital region and spreads anteriorly to the ipsilateral orbital, frontal, and temporal areas. It is typically unilateral bur occasionally affects the two sides. It is believed to be due to convergence of upper cervical and trigeminal sensory pathways allowing pain signals to refer from the neck to the trigeminal sensory fields of the head and face. Treatments with pain medication, physical therapy, manipulative treatment, and surgical interventions may provide only some inconsistent temporary relief of pain (Naja 2006).

Various ablative surgical procedures targeting the trigeminal nerve, or the cranial parasympathetic outflow have been tried to treat these patients with intractable headaches. These include gamma knife surgery or root section of the trigeminal nerve, trigeminal tractotomy, microvascular decompression of the trigeminal nerve, glycerol injection of the Gasserain ganglion, and others. However, none of these procedures has a consistent effect, and many are associated with serious complications (Magis 2007).

Electrical stimulation of the brain was first attempted late in the 19th century, but its application for pain control began in the 1960s with spinal cord stimulation. The neurostimulation technique for ablating pain is based on the theory that peripheral nerve stimulation can produce specific focal analgesia and anesthesia. In addition, the technique may alter perception of pain by blocking cell membrane depolarization and axonal conduction with directly applied current (Shealy 1967, Lim 2007, Trentman 2008).

In the early 2000s, neurostimulation therapy emerged as a potential treatment option for a variety of different intractable primary headache disorders. This is an invasive device- based approach that has two broad types:

1. Peripheral therapy that involves branches of the occipital nerve: occipital nerve stimulation (ONS), and supraorbital nerve stimulation.
2. Central which refers to deep-brain stimulation (DBS) approaches e.g. hypothalamic deep brain stimulation used for chronic cluster headache (Schwedt 2009).

The occipital nerve stimulators (ONS) are implanted surgically in a 3-phase procedure: Phase 1. An incision is made over the occipital region at the level of the first cervical vertebra for the subcutaneous implantation of bilateral electrodes. These are tunneled in a cephalad direction so that they come to lie across the path of the greater occipital nerve on each side of the head. Phase 2. Confirmation of the electrode position by testing each separately by an external stimulator. The operator gradually increases the amplitude delivered to the electrodes from 0 to 4 v, and the patient is asked to locate and describe any sensation he /she feels. Correct placement is confirmed by the patient describing a vibrating sensation that radiates at least 4 cm cephalad from the base of the skull, on the side of the tested electrode, and Phase 3. Implantation of the stimulator battery in the pectoral, abdominal, or gluteal region, and connecting it to the electrodes via subcutaneously tunneled leads. The procedure is performed under sedation or general anesthesia, however during the second phase the patients are required to be awake and to be able to identify the position of the occipital electrodes when the electric stimulus is applied. Potential complications of the procedure include lead migration, infection, localized pain, muscle spasm, and lack or loss of effect (Lim 2007, Trentman 2008).

The deep brain stimulation (DBS) of the posterior hypothalamus has been investigated in patients with chronic cluster headaches or SUNCT (short-lasting, unilateral, neuralgiform headache attacks with conjunctival injection and tearing). DBS involves MRI guided stereotactic placement of an electrode into the brain (e.g. thalamus, globus pallidus, or subthalamic nucleus). It is typically implanted unilaterally on the side corresponding to the most severe symptoms. The use of bilateral stimulation using two electrodes has been investigated in patients with bilateral, severe symptoms. Initially, the electrode(s) is/are attached to a temporary transcutaneous cable to validate treatment effectiveness and, if effective, the patient returns to surgery several days later for permanent subcutaneous implantation of the cable and a radiofrequency-coupled or battery-powered programmable stimulator. After implantation, noninvasive programming of the neurostimulation can be adjusted to control the patient's symptoms. The procedures can be performed only by a highly experienced neurosurgeon and may be associated with a small risk of mortality due to intra-cerebral hemorrhage. Before implantation, all patients must undergo complete preoperative neuro-imaging to exclude disorders associated with increased hemorrhagic risk (Leon 2006, Bartsch 2008).

Neither the occipital nerve stimulation nor the deep brain stimulators are approved to date by the U.S. Food and Drug Administration for the treatment or prevention of primary headaches.

Medical Technology Assessment Committee (MTAC)

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Occipital Nerve Stimulation (ONS)

08/03/2009: MTAC REVIEW

Evidence Conclusion: The literature on brain stimulation for the treatment of chronic primary headache is limited and does not provide sufficient evidence to determine the efficacy or safety of either occipital or deep brain stimulation therapy for the prevention or treatment of chronic headache. There are no published randomized or nonrandomized controlled trials on the intervention to date. The empirical studies consist of a few very small case series with no comparison groups and a number of case reports. The outcome measures varied between studies as some reported change in pain and others reported on headache frequency intensity, disability and/or medication use. Popeney and Alo's (2003), the largest series on ONS studied the response to occipital nerve stimulation in a series 25 consecutive patients with transformed migraine. A comparison between pre- and post-implant measurements, showed significant reductions in headache frequency, severity, and disability after the implant. The study was only an observational case series with potential biases, and with no control or comparison group to rule out the placebo effect of the implant.

Articles: The search yielded almost four hundred articles. The majority was review articles, opinion pieces, or dealt with technical aspects the procedure. ONS: There were around 15 small prospective and retrospective case series with patient sizes ranging from 3-25, and a number of case reports on peripheral nerve stimulation. Popeney CA, Alo KM. Peripheral neurostimulation for the treatment of chronic disabling transformed migraine. Headache 2003,43:369-375. See Evidence Table.

The use of Occipital Nerve Stimulation (ONS) for the treatment of primary headache does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Medicare

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

Non-Medicare - Considered Not Medically Necessary:

CPT® or HCPC Codes	Description
64555	Percutaneous implantation of neurostimulator electrode array; peripheral nerve (excludes sacral nerve)
64575	Incision for implantation of neurostimulator electrode array; peripheral nerve (excludes sacral nerve)
64585	Revision or removal of peripheral neurostimulator electrode array
64590	Insertion or replacement of peripheral or gastric neurostimulator pulse generator or receiver, direct or inductive coupling
64595	Revision or removal of peripheral or gastric neurostimulator pulse generator or receiver
C1767	Generator, neurostimulator (implantable), nonrechargeable
C1778	Lead, neurostimulator (implantable)
C1787	Patient programmer, neurostimulator
C1816	Receiver and/or transmitter, neurostimulator (implantable)
C1820	Generator, neurostimulator (implantable), with rechargeable battery and charging system
C1822	Generator, neurostimulator (implantable), high frequency, with rechargeable battery and charging system
C1823	Generator, neurostimulator (implantable), nonrechargeable, with transvenous sensing and stimulation leads
C1883	Adaptor/extension, pacing lead or neurostimulator lead (implantable)
C1897	Lead, neurostimulator test kit (implantable)
L8679	Implantable neurostimulator, pulse generator, any type
L8680	Implantable neurostimulator electrode, each
L8681	Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only
L8682	Implantable neurostimulator radiofrequency receiver
L8683	Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver
L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension

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L8686	Implantable neurostimulator pulse generator, single array, nonrechargeable, includes extension
L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
L8688	Implantable neurostimulator pulse generator, dual array, nonrechargeable, includes extension
L8689	External recharging system for battery (internal) for use with implantable neurostimulator, replacement only
L8695	External recharging system for battery (external) for use with implantable neurostimulator, replacement only

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
09/16/2009	Added to the annual review because of the Medicare criteria 04/11/2011 MDCRPC, 02/07/2012 MDCRPC, 12/04/2012 MDCRPC, 10/01/2013 MPC, 08/05/2014 MPC, 06/02/2015 MPC, 04/05/2016 MPC, 02/07/2017 MPC, 12/05/2017 MPC, 10/02/2018 MPC, 10/01/2019 MPC, 10/06/2020 MPC, 10/05/2021 MPC, 10/04/2022 MPC, 10/03/2023 MPC	10/05/2021

MDCRPC Medical Director Clinical Review and Policy Committee
MPC Medical Policy Committee

Revision History	Description
09/08/2015	Revised LCD L34886 and L35008 Non-Covered Services.
04/05/2016	Adopted MCG A-0716
10/05/2021	Updated applicable codes

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Clinical Review Criteria
Pacemakers

- Single Chamber
- Dual Chamber
- Leadless Pacemakers
- Cardiac Resynchronization Therapy (CRT)

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	Hospital Outpatient Regulations and Notices Medicare Claims Processing Manual, Change Request - Transmittal 187: The National Coverage Determination (NCD) for Cardiac Pacemakers: Single Chamber and Dual Chamber Permanent Cardiac Pacemakers (NCD 20.8.3)
National Coverage Determinations (NCD)	Leadless Pacemakers (20.8.4) **Leadless pacemakers are non-covered when furnished outside of a CMS approved CED study.* **Effective until April 1, 2024** Singe & Dual Chamber Cardiac Pacemakers require Level of Care review only **Effective April 1, 2024** Singe & Dual Chamber Cardiac Pacemakers require Level of Care review **AND** Medical necessity review using Cardiac Pacemakers: Single Chamber and Dual Chamber Permanent Cardiac Pacemakers (20.8.3)
Local Coverage Determinations (LCD)	None
Local Coverage Article	**Effective until April 1, 2024** Singe & Dual Chamber Cardiac Pacemakers require Level of Care review only **Effective April 1, 2024** Singe & Dual Chamber Cardiac Pacemakers require Level of Care review **AND** Medical necessity review using Billing and Coding: Single Chamber and Dual Chamber Permanent Cardiac Pacemakers Coding and Billing (A54931)
Kaiser Permanente Medical Policy	**Effective until April 1, 2024** Cardiac Resynchronization Therapy (CRT) require Level of

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	Care review only **Effective April 1, 2024** Requires Level of Care review **AND** Due to the absence of an active NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Clinical Review Criteria, ***"Cardiac Resynchronization Therapy (CRT)"*** for medical necessity determinations. Refer to the Non-Medicare criteria below.

For Non-Medicare Members

Service	Criteria
Leadless Pacemakers	There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.
Cardiac Resynchronization Therapy (CRT)	**Effective until April 1, 2024** Requires Level of Care review only **Effective April 1, 2024** Requires Level of Care review AND medical necessity review below: CRT will be considered medically necessary when the following criteria for a given beneficiary are met: • LVEF ≤ 35%, with ischemic or non-ischemic cardiomyopathy, on maximally tolerated guideline-directed medical therapy (GDMT) for at least 3 months and with no reversible causes; *and* a. QRS ≥ 150 ms; and b. Any type bundle branch block with evidence of dyssynchrony; and c. NYHA class III or ambulatory IV HF • LVEF ≤ 35%, on maximally tolerated GDMT for at least 3 months and with no reversible causes; *and* a. QRS ≥ 150 ms; and b. LBBB; and c. NYHA classes II, III or ambulatory IV HF • LVEF ≤ 35%, on maximally tolerated GDMT for at least 3 months and with no reversible causes; *and* a. QRS 130-149 ms; and b. LBBB; and c. NYHA class II, III or ambulatory IV HF • In patients with atrial fibrillation (AF) or in sinus rhythm who have an indication for pacemaker implant for second or third degree atrioventricular (AV) block (including those who have or will have AV nodal ablation), or very prolonged first degree block with PR > 300 ms, *and*: a. with an EF < 50%; and b. with NYHA I, II or III class; and c. anticipated frequent ventricular pacing • Patients who are being paced from the RV frequently (generally considered at least > 40% of the time) and who develop worsening HF symptoms (NYHA class II-IV) with a decline in LVEF to a value < 40% may be considered for upgrade to CRT.*

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	*For an upgrade from standard pacing to CRT, Kaiser Permanente would expect documentation narrative regarding the risk-benefit balance for that individual patient and his/her degree of HF, QRS duration/morphology, etc. A "stand-alone" upgrade in patients with an existing pacemaker or implanted cardiac defibrillator should be considered carefully and based on the individual patient's unique circumstances. Upgrades to CRT from conventional RV pacing at the time of a needed generator change will be covered per the usual criteria as noted in all preceding coverage bullets. In patients with AF and HF for whom CRT is planned, narrative in the medical record is expected regarding plans for AF control so that CRT may be most effective. It is understood that the future for such patients cannot be predicted and thus future therapy cannot be defined precisely; however, a reference to the need for focus on AF control is desirable. HF patients with concomitant moderate-severe chronic obstructive pulmonary disease (COPD) should have documentation related to a reasonable hope for CRT response with a clinically guided rationale that the dyspnea is at least in part significantly related to HF. Patients with end stage or advanced renal disease may benefit less from CRT. Documentation regarding the risk-benefit balance in these patients would also be expected. Patients who meet all CMS coverage requirements for cardiac pacemakers, and who meet the criteria in the NCD for Implantable Automatic Defibrillators (20.4), may receive the combined devices in 1 procedure, at the time the biventricular pacemaker is clinically indicated. Patients with an existing CRT device may receive a generator replacement if it is required due to the end of battery life, elective replacement indicator (ERI), or device/lead malfunction. **Limitations:** Noncovered Services: ((CRT is unlikely to offer benefit and is probably associated with harm) 1. Patients with a QRS < 130 ms (Exception to this non-coverage criterion would be in the case of patients undergoing AV nodal ablation or in need of RV pacing (due to second- or third-degree block or very long first degree block) that is expected to occur a majority of the time.) 2. Patients with an EF ≥ 50% 3. CRT in patients with non-ambulatory NYHA IV HF symptoms or on chronic inotropic HF therapy or with LV assist devices in place
Single & Dual Chamber Cardiac Pacemakers	**Effective until April 1, 2024** Requires Level of Care review only **Effective April 1, 2024** Requires Level of Care review ***AND*** medical necessity review. Kaiser Permanente has elected to use coverage guidance from Medicare's National Coverage Determination (NCD) 20.8.3 Cardiac Pacemakers: Single and Dual Chamber Permanent Cardiac Pacemakers

If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist

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The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Cardiac arrhythmias occur when there is interruption of the normal sinus rhythm. Symptoms include palpitations, dizziness, lightheadedness, syncope, dyspnea, anxiety, weakness, and chest discomfort. One therapeutic option is the implantation of pacemaker which provides electrical impulses to the heart. Conventional pacemakers consist of a pulse generator, which provides electrical impulses, and leads delivering electrical impulses from the generator to the heart. The pulse generator is the battery and is placed in the anterior part of the chest (pre-pectoral) while the leads are placed transvenously.

However, there are several complications associated with traditional pacemakers. Complications due to the pulse generator include hematoma, skin breakdown, and pocket infection (Udo et al., 2012). Complications due to the leads include venous obstruction, lead dislodgement, lead malfunction, lead fractures, and infection (Cheng, Wang, Curtis, & Varosy, 2010; Kirkfeldt et al., 2011; Udo et al., 2012).

Leadless pacemakers have been the center of attention due to its ability to address the limitations of traditional transvenous pacemakers. Two leadless pacemakers have been assessed for single-chamber right ventricular pacing. These include Nanostim LP (Abbott, formerly St. Jude, Lake Bluff, IL) and Micra Transcatheter Pacing System (Medtronic, Minneapolis, MN). Nevertheless, Nanostim is out of the market due to premature battery depletion (Yarlagadda et al., 2018). Leadless pacemakers are composed of a pulse generator, battery, and electrode in the same device (Reddy et al., 2015). It is placed through a catheter and is directly implanted into the right ventricle (Yarlagadda et al., 2018).

The leadless pacemaker's (Nanostim) length is 42 mm and a maximum diameter of 5.99 mm with a battery life ranging from 8.4 to of 12.4 years (Reddy et al., 2015). A sheath is placed in the femoral vein, and with a sleeve-based catheter, the device is delivered to the right ventricle. The sleeve is then withdrawn, and the pacemaker is implanted into the endocardium while the device remains docked. The device is then undocked from the catheter but is still connected to the catheter through tether connections. This allows for device measurements and evaluation of stability without the catheter. Repositioning can be performed if the device is not well positioned. Once positioning is assured and the pacemaker parameters are optimal [(R wave amplitude ≥5.0 mV) and pacing threshold (≤2.0 V at 0.4 ms)] (Yarlagadda et al., 2018), the device is untethered from the catheter resulting in the final implant position (Reddy et al., 2015). The procedure is performed under fluoroscopy. After the procedure, patients are observed over a period of 24 hours and discharged (CADTH 2015). An external programmer is used to program Micra transcatheter pacing system.
Some differences are worth noted. The Nanostim pacemaker is smaller than the traditional pacemaker (<10%), with a battery life ranging between 8.4 years and 12.4 years. The Micra Transcatheter Pacing System pacemaker is 30% smaller than the Nanostim and its estimated battery life ranges from 10 to 15 years. Micra transcatheter pacing is 93% smaller than conventional pacemakers, about the size of a large vitamin capsule (https://www.medtronic.com/us-en/patients/treatments-therapies/pacemakers/our/micra.html). The insertion of these devices takes 20 to 45 minutes compared to 60 minutes for the conventional pacemaker (CADTH 2015).

Medical Technology Assessment Committee (MTAC)

Leadless Pacemakers for the treatment of cardiac arrhythmias

Date: 04/21/2019

Evidence Conclusion:

- In patients with cardiac arrhythmias who require single-chamber ventricular pacing, there is insufficient evidence to compare leadless pacemakers with conventional pacemakers. However, serious complications are non-negligible.
- Randomized controlled trials with longer-term follow-up and direct comparisons are warranted.

Articles: PubMed was searched through March 8, 2019 with the search terms ((Nanostim Leadless Pacemaker OR Micra Transcatheter Pacing System OR leadless pacemaker)) AND (traditional pacemakers OR conventional pacemakers). Other search terms included (Nanostim Leadless Pacemaker OR Micra Transcatheter Pacing System OR leadless pacemaker) filters: observational study. The search was limited to English language publications and human populations. The reference lists of relevant studies were reviewed to identify additional publications. Randomized controlled trials, and observational studies were included in the search. Clinicaltrials.gov was also searched. Three studies were retained and reviewed. See Evidence Table.

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The use of Leadless Pacemakers for the treatment of cardiac arrhythmias does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Hayes Technology Assessment

Micra Transcatheter Pacing System (Medtronic Inc.) for Single Chamber Pacemaker Indications

Date: July 3, 2022

The Micra TPS is a single-chamber right ventricular pacing device. The device senses electrical activity of the heart via electrodes within the device's titanium capsule. Heart rhythm is monitored for bradycardia. Rate-adaptive pacing therapy is provided based on programmed pacing parameters. The Micra TPS is self-contained and does not require a surgical incision in the chest or intravascular leads. It is inserted via a 23-French catheter placed in the femoral vein and held in place within the right ventricle of the heart via nitinol tines that attach to the myocardium.

Conclusion

A low-quality body of evidence suggests that Micra TPS is associated with a high rate of procedural success and that pacing capture thresholds remained low and stable after implantation for up to 36 months. Major complications are comparable with and perhaps lower for Micra TPS versus TVPM, and revision and retrieval rates are lower for Micra TPS than TVPM. However, the clinical significance of any benefits introduced by use of the Micra TPS is uncertain due to the small body of evidence directly evaluating patient-centered outcomes.

Hayes Rating: C

Hayes. Hayes Technology Assessment. Micra Transcatheter Pacing System(Medtronic Inc.) for Single-Chamber Pacemaker Indications. Dallas, TX: Hayes; July 3, 2022. Retrieved May 15, 2023, from https:// https://evidence.hayesinc.com/report/htb.micrapacing4178

References

Centers for Medicare & Medicaid Services (CMS) [website]. Medicare Coverage Database. National Coverage Determinations (NCDs). Updated January 3, 2008. Available at: http://www.cms.hhs.gov/mcd/index_list.asp?list_type=ncd. Accessed November 07, 2023.

Applicable Codes

Leadless Pacemaker

Medicare - Considered Medically Necessary when criteria in the applicable policy statements listed above are met
Non-Medicare - Considered Not Medically Necessary

CPT® Codes	Description
33274	Transcatheter insertion or replacement of permanent leadless pacemaker, right ventricular, including imaging guidance (eg, fluoroscopy, venous ultrasound, ventriculography, femoral venography) and device evaluation (eg, interrogation or programming), when performed
33275	Transcatheter removal of permanent leadless pacemaker, right ventricular, including imaging guidance (eg, fluoroscopy, venous ultrasound, ventriculography, femoral venography), when performed

Single & Dual Chamber Cardiac Pacemaker placement
Effective until April 1, 2024
No medical necessity review required

Effective April 1, 2024

Medicare- Considered medically necessary when criteria in the applicable policy statements listed above are met

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Non-Medicare- Considered medically necessary when criteria in the applicable policy statements listed above are met

CPT® or HCPC Codes	Description
33206	Insertion of new or replacement of permanent pacemaker with transvenous electrode(s); atrial
33207	Insertion of new or replacement of permanent pacemaker with transvenous electrode(s); ventricular
33208	Insertion of new or replacement of permanent pacemaker with transvenous electrode(s); atrial and ventricular
33214	Upgrade of implanted pacemaker system, conversion of single chamber system to dual chamber system (includes removal of previously placed pulse generator, testing of existing lead, insertion of new lead, insertion of new pulse generator)
33216	Insertion of a single transvenous electrode, permanent pacemaker or implantable defibrillator
33217	Insertion of 2 transvenous electrodes, permanent pacemaker or implantable defibrillator
33224	Insertion of pacing electrode, cardiac venous system, for left ventricular pacing, with attachment to previously placed pacemaker or implantable defibrillator pulse generator (including revision of pocket, removal, insertion, and/or replacement of existing generator)
C1779	Lead, pacemaker, transvenous VDD single pass
C1785	Pacemaker, dual chamber, rate-responsive (implantable)
C1786	Pacemaker, single chamber, rate-responsive (implantable)
C1898	Lead, pacemaker, other than transvenous VDD single pass
C2619	Pacemaker, dual chamber, nonrate-responsive (implantable)
C2620	Pacemaker, single chamber, nonrate-responsive (implantable)
C2621	Pacemaker, other than single or dual chamber (implantable)
C7537	Insertion of new or replacement of permanent pacemaker with atrial transvenous electrode(s), with insertion of pacing electrode, cardiac venous system, for left ventricular pacing, at time of insertion of implantable defibrillator or pacemaker pulse generator (e.g., for upgrade to dual chamber system)
C7538	Insertion of new or replacement of permanent pacemaker with ventricular transvenous electrode(s), with insertion of pacing electrode, cardiac venous system, for left ventricular pacing, at time of insertion of implantable defibrillator or pacemaker pulse generator (e.g., for upgrade to dual chamber system)
C7539	Insertion of new or replacement of permanent pacemaker with atrial and ventricular transvenous electrode(s), with insertion of pacing electrode, cardiac venous system, for left ventricular pacing, at time of insertion of implantable defibrillator or pacemaker pulse generator (e.g., for upgrade to dual chamber system)
C7540	Removal of permanent pacemaker pulse generator with replacement of pacemaker pulse generator, dual lead system, with insertion of pacing electrode, cardiac venous system, for left ventricular pacing, at time of insertion of implantable defibrillator or pacemaker pulse generator (e.g., for upgrade to dual chamber system)

Cardiac Resynchronization Therapy (CRT)
Effective until April 1, 2024
No medical necessity review required

Effective April 1, 2024

Medicare- Considered medically necessary when criteria in the applicable policy statements listed above are met
Non-Medicare- Considered medically necessary when criteria in the applicable policy statements listed above are met

CPT® or HCPC Codes	Description
33208	Insertion of new or replacement of permanent pacemaker with transvenous electrode(s); atrial and ventricular
33224	Insertion of pacing electrode, cardiac venous system, for left ventricular pacing, with attachment to previously placed pacemaker or implantable defibrillator pulse generator (including revision of pocket, removal, insertion, and/or replacement of existing generator)

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33225	Insertion of pacing electrode, cardiac venous system, for left ventricular pacing, at time of insertion of implantable defibrillator or pacemaker pulse generator (eg, for upgrade to dual chamber system) (List separately in addition to code for primary procedure)
C2621	Pacemaker, other than single or dual chamber (implantable)

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed	Date Last Revised
05/07/2019	05/07/2019[MPC], 05/05/2020[MPC] , 05/04/2021[MPC], 05/03/2022[MPC], 05/02/2023[MPC]	11/07/2023

[MPC] Medical Policy Committee

Revision History	Description
05/07/2019	MPC approved to adopt a non-coverage policy for leadless pacemakers
05/05/2020	Added applicable CPT codes 33274 and 33275 to policy
05/15/2023	Updated References to include Hayes Technology assessment
11/07/2023	MPC approved adopting Medicare coverage criteria of Defibrillator and Pacemaker placement for Medicare and non-Medicare. 60-day notice required, effective date April 1, 2024.

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Kaiser Foundation Health Plan of Washington

Patient Referral Guidelines
Pancreas Transplant Alone

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Pancreas Transplants (260.3)
Local Coverage Determinations (LCD)	None

For Non-Medicare Members

Transplantation may be considered for patients with end-stage or life-threatening disease who have no prospect for prolonged survival, or whose quality of life is severely impaired. The following are current, accepted guidelines for Pancreas Transplant Alone and Pancreas After Kidney transplantation. These guidelines for referral for transplant evaluation are not intended as an automatic inclusion or exclusion of a candidate for referral. It is important to note that these are guidelines and should be applied together with careful clinical judgment.

1. GENERAL PRINCIPLES
   a. If clinical parameters of end-stage or life-threatening disease indicate the need for transplantation, then early referral should be made.
   b. Patients with a history of malignancy with a moderate to high risk of recurrence (as determined after consultation with oncologist considering tumor type, response to therapy, and presence or absence of metastatic disease) may be unsuitable candidates for transplantation. Patients with low risk of recurrence may be considered.
   c. Uncontrollable active infection is a contraindication to transplant.
   d. Candidates with a history of substance abuse must be free from alcohol and other substance abuse for six (6) months and have been evaluated by a substance abuse program. The risk of recidivism, which has been documented to negatively impact transplant outcomes, must be addressed and considered to be low.[1,2,3] Exceptions may be made on a case-by-case basis.
   e. Candidates for thoracic organ (heart, lung and heart/lung) transplants must be free from tobacco use for the previous six (6) months. Routine monitoring may be required. Specific programs for abdominal organs (liver, intestines, and kidney) may require abstinence from tobacco products in order to be actively listed.
   f. Candidates must have adequate social support systems and display a proven record of adherence to medical treatment.
   g. Patients must be able to travel within short notice to the KP approved transplant Center of Excellence and, if necessary, return for treatment of complications.
   h. Patient must have a care giver or care givers who are physically and cognitively able to assist the patient with self-care activities and are available to travel within short notice to the KP approved transplant Center of Excellence.
   i. The presence of significant irreversible neurologic dysfunction, active psychological and/or psychiatric conditions, and/or other social behaviors that prevent adherence with a complex medical regimen, are considered contraindications for referral for transplant.

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j. Evidence of such non adherence may be: failure to keep appointments, failure to make steady progress in completing pre-transplant evaluation requirements, failure to accurately follow medication regimens or failure to accomplish the activities required for maintenance on the waiting list
k. Whenever transplant is considered as an option and discussed with the patient and/or family, consultation with Advanced Life Care Planning/Palliative Care resources is strongly recommended.

2. PANCREAS TRANSPLANT ALONE (PTA/PAK)
   a. Indications for PTA/PAK Transplant
      i. Type 1 DM with disabling and potentially life threatening complications as seen in brittle diabetes with severe and recurrent episodes of either hypoglycemia (involving seizures, loss of consciousness and/or calls to 911) and or hyperglycemia (episodes of DKA) or hypoglycemic unawareness in which the individual requires constant supervision.
      ii. Optimally and intensively managed by an endocrinologist for at least 12 months[4].
      iii. Age 18 - 55 except under special clinical circumstances.
      iv. Native or transplanted kidney must be functioning well as evidenced by an accepted formula for GFR or a 24-hour urine for creatinine clearance of >50 ml per minute[5,6,7]
3. Contraindications for PTA/PAK Transplant
   a. Significant irreversible coronary artery disease and/or left ventricular dysfunction, and irreversible pulmonary disease.
   b. Irreversible peripheral vascular disease, including carotid vascular disease (Amputation alone is not a contraindication).
   c. Uncontrolled hypertension.

   Relative Contraindications
   a. BMI ≥ 35. Patients may be referred to the COE for individual consideration.
      i. May be concurrently referred for weight loss intervention.
   b. Cachexia and/or malnourishment

1. *Liver Transplantation* 2006, .12:813-820. Alcohol consumption patterns and predictors of use following liver transplantation for alcoholic liver disease.
2. *Liver Transplant Surg,*. 1997, Vol 3, 304 – 310. The natural history of alcoholism and its relationship to liver transplantation.
3. Alcohol abstinence prior to liver transplantation for Alcoholic Liver Disease (G110807), *TPMG New Medical Technology*
4. National Coverage Determination (NCD) for Pancreas Transplants (260.3) version 3. http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?
5. An assessment of the effect on renal function of a calcineurin inhibitor may be required for a creatinine clearance or GFR between 50 and 70 ml/minute.
6. As determined by direct measurement or calculated by an accepted formula, such asthe CKD-EPI creatinine equation (2021) that are refitted without race.
7. National Kidney Foundation, eGFR Calculator: https://www.kidney.org/professionals/kdoqi/gfr_calculator

If requesting these services, please send the following documentation to support medical necessity:

- Copy of final summary report from multidisciplinary transplant team

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Pancreas transplantation is used in patients with type 1 diabetes. After a successful transplantation, many diabetic patients no longer require insulin. Due to the danger of organ rejection in the short- or long-term, pancreas transplant recipients need to take immunosuppressive drugs.

Most pancreas transplants are done in conjunction with (at the same time or following) a kidney transplant. A reason for this combination transplant is that the pancreas induces a strong immune response and therefore requires larger doses of immunosuppressive drugs that can jeopardize kidney function and the transplanted pancreas.

The first clinical pancreas transplant (of any type) was done in 1966. Initially there was a low success rate but clinical outcomes improved in the 1980s due to advances in surgical techniques and the introduction of

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cyclosporine for immunosuppression. Newer immunosuppressants, Tacrolimus and mycophenolate mofetil, were introduced in 1994 and 1995, respectively. Since 1994, there have been improved graft survival rates in patients receiving pancreas transplants alone (PTA).

Medical Technology Assessment Committee (MTAC)

Pancreas Transplant

12/12/2001: MTAC REVIEW

Evidence Conclusion: Only one article reported data on patients receiving pancreas transplants alone. The methodology was not well described, and the intervention procedures varied dramatically over time. The article reported on the experience of the institution; it was primarily a review article rather than a research study. The case series portion of this article had inadequately described methodology and is subject to selection and observation biases. Due to lack of quality scientific data, the evidence is insufficient to draw conclusions about the effect of this technology on health outcomes.

Articles: The search yielded 36 articles, many of which were review articles, opinion pieces or dealt with pancreas transplantation in conjunction with kidney transplantation. There were no empirical studies that presented separate data on the outcomes of PTA. There were several case series that included both pancreas transplantation in conjunction with kidney transplantation and PTA, but the data were not divided by type of procedure. Only one article presented some data separately for patients receiving PTA. This was primarily a review article and included case series data. This study was critically appraised:

Sutherland DER, Gruessner RWG, Dunn DL, Matas AJ, Humar A, Kandaweamy R, Mauer M, Kennedy WR, Goetz FC, Robertson RP, Gruessner AC, Najarian JS. Lessons learned from more than 1,000 pancreas transplants at a single institution. Ann Surg 2001; 233: 463-501.

The use of Pancreas Transplant alone in the treatment of Juvenile Diabetes does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® Codes	Description
48550	Donor pancreatectomy (including cold preservation), with or without duodenal segment for transplantation
48551	Backbench standard preparation of cadaver donor pancreas allograft prior to transplantation, including dissection of allograft from surrounding soft tissues, splenectomy, duodenotomy, ligation of bile duct, ligation of mesenteric vessels, and Y-graft arterial anastomoses from iliac artery to superior mesenteric artery and to splenic artery
48552	Backbench reconstruction of cadaver donor pancreas allograft prior to transplantation, venous anastomosis, each
48554	Transplantation of pancreatic allograft
48556	Removal of transplanted pancreatic allograft

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
12/12/2001	10/05/2010 MDCRPC, 08/02/2011 MDCRPC, 06/05/2012 MDCRPC, 04/02/2013 MDCRPC, 02/04/2014 MPC, 12/02/2014 MPC, 10/06/2015MPC, 11/03/2015 MPC, 08/02/2016MPC, 06/06/2017MPC, 04/03/2018MPC, 04/02/2019MPC, 04/07/2020MPC, 04/06/2021MPC, 04/05/2022MPC, 04/04/2023MPC	01/10/2022

MDCRPC Medical Director Clinical Review and Policy Committee

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Revision History	Description
05/07/2019	MPC approved KP National criteria for Pancreas Transplant.
03/03/2020	MPC approved proposed changes from KP National Transplant Services
04/06/2021	Per National Transplant Guidelines: 1.3 added “active”
01/10/2022	MPC approved proposed changes from KP National Transplant Services. 60-day notice is not required.

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KAISER PERMANENTE®

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Clinical Review Criteria
Integrated Molecular Pathology

- Loss-of-Heterozygosity Topographic Genotyping with PathfinderTG®
- PancraGEN

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	MolDX: Molecular Diagnostic Tests (MDT) (L36256)
Local Coverage Article	None

For Non-Medicare Members

Kaiser Permanente has elected to use the Integrated Molecular Pathology (Topographic Genotyping) - PathFinderTG (A-0632) MCG* guideline for medical necessity determinations. This test is not covered per MCG guidelines. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.

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If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider
- Genetics consult if applicable & requesting provider is not a geneticist

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Background

Pathologic analysis of tissue samples is central to the diagnosis of cancer; however, there are some instances when these results may by inconclusive. Pathfinder TG® is a molecular DNA-based cancer diagnostic test that can aid diagnosis when pathology results are inconclusive. The Pathfinder TG® test uses a method known as topographic genotyping that combines pathology and molecular analysis using specific genetic marker panels to identify acquired mutations in a variety of difference types of cancer.

PancraGEN description

PancraGEN is a DNA-based, integrated molecular pathology test that evaluates the risk of pancreatic cancer in pancreatic cysts. This test can help choose adequate surveillance strategies or surgical options for patients with pancreatic cysts (https://pancragen.com/).

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PancraGEN is a personalized test, that interrogates cumulative oncogene and tumor suppressor gene damage, reporting results in the context of each patient's clinical history, imaging, fluid chemistry and cytology test results. Offering added clarity about the biologic behavior of a pancreatic cyst, PancraGEN provides an overall prognostic assessment that helps inform the best step forward when determining which patients are suited for surveillance vs. surgical intervention (https://pancragen.com/power-of-pancragen/). The test provides high positive predictive value (PPV) for malignancy and can inform surveillance and surgical decisions when first-line results have clinical uncertainty. It determines high and low malignancy potential within pancreatic cysts, masses, and ductal strictures.

PancraGEN identifies the quality and quantity of DNA in cyst fluid (giving those high levels of intact DNA are associated with actively dividing cells), oncogenes (KRAS and GNAS point mutations), tumor suppressor gene mutations (loss of heterozygosity).
PancraGEN is offered by Interpace Biosciences.

PancraGEN can help answer the following questions: 1) Is this cyst benign or aggressive today? 2) What is the likelihood that the cyst will progress to cancer? 3) How do I monitor this patient and what do I do next?

Medical Technology Assessment Committee (MTAC)

Pathfinder TG®

06/18/2012: MTAC REVIEW

Evidence Conclusion: Analytic validity - No studies were identified that evaluated the analytic validity of loss-of-heterozygosity based topographic genotyping with Pathfinder TG® (AHRQ 2010). Clinical validity- Fifteen retrospective studies with methodological limitations were identified that evaluated the clinical validity of loss-of-heterozygosity based topographic genotyping with Pathfinder TG®. Details on patient characteristics, treatments, clinical definitions, and statistical methods were limited. Additionally, only 3 studies had more than 50 patients and it is possible that these publications analyzed the same patient population. There is insufficient high-quality evidence to determine the clinical validity of loss-of-heterozygosity based topographic genotyping with Pathfinder TG® (AHRQ 2010). Clinical utility - No studies were identified that evaluated the clinical utility of loss-of-heterozygosity based topographic genotyping with Pathfinder TG® (AHRQ 2010). Conclusion:
There is insufficient evidence to determine the analytic validity, clinical validity, and clinical utility of loss-of-heterozygosity based topographic genotyping with Pathfinder TG®.
Articles: The literature search revealed a 2010 AHRQ technology assessment that evaluated the analytic validity, clinical validity, and clinical utility of loss-of-heterozygosity based topographic genotyping with Pathfinder TG®. Studies were excluded if they had less than 25 subjects. No relevant articles were identified after the 2010 ARHQ review. The following technology assessment was selected for review: Trikalinos TA, Terasawa T, Raman G et al. A systematic review of loss-of-heterozygosity based topographic genotyping with PathfinderTG®. AHRQ Technology Assessment Program (Project ID GEND0308). March 2010. See Evidence Table.

The use of Pathfinder TG® does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

PancraGEN

01/09/2023: MTAC REVIEW

Evidence Conclusion: There is insufficient evidence to determine the clinical value and utility of pancragen.
Articles: PubMed was searched through 12/7/2022 with the search terms pancragen, pathfinder tg, redpath, and topographic genotyping with variations. The search was limited to English language publications and human populations. The reference lists of relevant studies were reviewed to identify additional publications. See Evidence Table.

Applicable Codes

Medicare - Considered Medically Necessary when criteria in the applicable policy statements listed above are met
Non-Medicare - Considered Not Medically Necessary

CPT® or HCPC Codes	Description
81479	Unlisted molecular pathology procedure
With diagnosis codes	
K86.2	Cyst of pancreas

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K86.3	Pseudocyst of pancreas

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
07/03/2012	07/03/2012[MDCRPC], 05/07/2013[MDCRPC], 03/04/2014[MDCRPC], 01/06/2015[MPC], 11/03/2015 [MPC], 09/06/2016[MPC], 07/11/2017[MPC], 05/01/2018[MPC], 05/07/2019[MPC], 05/05/2020[MPC], 05/04/2021[MPC], 05/03/2022[MPC], 05/02/2023[MPC]	03/04/2014

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
04/20/2023	Added MTAC review for PancraGen.

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Clinical Review Criteria
Positron Emission Mammography (PEM)

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	*Medicare has not specifically addressed this technology in its coverage decision documents. See PET Scan criteria.
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article	None

For Non-Medicare Members

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Breast cancer is the most common non-skin cancer among women in the United States, and one of the leading causes of cancer death among women of all races. Although the incidence rate has increased, there has been a steady decline in the breast cancer death rate since the early 1990s, mostly due to screening, better awareness, and improved treatment. Early detection and accurate staging and restaging of recurrent breast cancer are important to define appropriate therapeutic strategies and increase the chance of a cure (Bartella 2006, CDC 2010, Pan 2010).

Mammography remains the gold standard screening method for women at average risk for breast cancer. It is relatively inexpensive, requires a low dose of radiation, and reliably identifies malignant tumors especially those that are too small to feel. It can also be used to investigate breast lumps and other symptoms. Although the benefit of mammographic screening is widely accepted, its limitations and failure to detect all breast cancers are also recognized. It is reported that the false negative rate of screening mammography ranges between 20-30%. It also has a low specificity resulting in a large number of unnecessary procedures. It is reported that only 25-45% of the biopsies done based on mammographic abnormalities result in a diagnosis of carcinoma. Diagnostic mammography is commonly used to identify possible breast cancers in women with signs and symptoms and has a higher sensitivity (85-93%) compared with screening mammography (Bartella 2007).

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Ultrasound (US) imaging may be used to evaluate abnormalities detected during a breast exam or mammogram and is useful in differentiating solid tumors from fluid filled cysts. It is considered the imaging technique of choice for evaluating palpable masses in women younger than 30 years as well as in pregnant and lactating women. It can also be used for the guidance of interventional procedures and treatment planning for radiation therapy. US is easily accessible, relatively low in cost, and does not involve the use of ionizing radiation. However, it cannot detect microcalcifications, can be time consuming, and its performance is operator dependent (Ferrara 2010).

Breast MRI using a special receiver and injected contrast material is more sensitive and accurate than mammography and ultrasound in detecting invasive lobular cancer. MRI detects blood flow to lesions and does not expose the patient to radiation. The increased blood flow is indicative of vascularization frequently found in cancer. MRI however, has some disadvantages; it can lead to false positive results as both benign and malignant lesions can absorb the contrast, it is less sensitive in detecting in situ cancers, and its interpretation is challenged when the breast is under estrogen modulation during menstrual cycle or HRT use, which affects the glandular tissue of the breast. In addition, MRI is not indicated and/or tolerated by many patients due to renal disease, metallic implants, claustrophobia, large body size, or general medical condition. It is a costly test to use for screening and is not a substitute for mammography. MRI is recommended for screening women at very high risk of breast cancer especially for the BRCA1 and BRCA2 subgroups. Other accepted indications include patients presenting with axillary adenopathy and an unknown primary, patients with equivocal mammograms, the differentiation of scar versus recurrence at lumpectomy site, as well as other indications (Tafreshi 2010, Philpotts 2011, Schilling 2011).

Nuclear breast imaging refers to functional imaging of the breast through the use of radiopharmaceuticals such as 18 F-fluorodeoxyglucose (18FDG) or 99mTc-sestamibi. It takes advantage of the differences in metabolic activity between tumor and normal tissue. Functional imaging can thus show changes in cell metabolism that are due to malignancies as the majority of primary and metastatic cancers take up more glucose than the adjacent normal tissues. Positron emission tomography (PET) with the radiotracer FDG may be able to detect cancer even before vascularization as cancer cell metabolism is usually heightened prior to the stimulation of new vessel growth. It has the potential of improving detection of cancer in dense breasts, illustrating the extent of the disease for surgical planning, and distinguishing between recurrent cancer and scar tissue (Schilling 2011).

The use of whole-body PET (WB- PET) and PET/CT is limited due to the low sensitivity and positive predictive value in detecting early stage breast cancer, invasive lobular and ductal carcinoma in situ, as well regional lymphadenopathy. The reasons reported for this low sensitivity include low spatial resolution, and lower level of FDG tracer uptake in some breast malignancies compared to other cancers (Schilling 2011).

Positron emission mammography (PEM) is a modification of PET that allows for a much more spatial resolution by putting the photon detectors directly on the breast. PEM uses similar principles as PET but is a breast specific imaging tool. Both work through the introduction and detection of a positron-emitting glucose analog 18F-FDG as the imaging radiotracer. The 18F-FDG analog decays by emitting a positron that is annihilated within a few millimeters resulting in emission of two gamma rays that radiate in opposite directions and are detected by the PET instrument. The resolution of PEM is increased by allowing the detectors to be directly placed on the breast. Gentle compression provides the advantage of spreading out the breast tissue for imaging. PEM devices use 2 moving detector heads mounted on compression paddles, with a similar configuration and size as a traditional mammography system. This allows direct correlation of the initial and recurrence images obtained by both devices. PEM images can also be reconstructed into 3D for localization of abnormalities. It is reported that the technique used allows capturing sharp detailed images of breast lesions as small as 2 mm, and the detection of small foci of ductal carcinoma in situ without depending on the presence of calcification for its identification. The whole-body radiation dose the patient receives from PEM is approximately three times higher than that of a mammogram, which may be a barrier to using it as a screening modality in the general population. PEM also cannot take the place of breast cancer staging performed with whole-body PET because PEM is limited to breast views only. It is reported that the same benign conditions that cause high FDG uptake in PET (e.g. infection, inflammation and fat necrosis) may cause false positive results in PEM. Glucose control is another problem with PEM as it is with PET; women with inadequately controlled diabetes cannot undergo either procedure (Tafreshi 2010, Ferrara 2010, Moadel 2011).

PEM 2400 PET scanner and PEM Flex devices have received FDA clearance to perform PET imaging of the breast under gentle compression for patients with confirmed breast cancer.

Medical Technology Assessment Committee (MTAC)

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Positron Emission Mammography (PEM)

08/15/2011: MTAC REVIEW

Evidence Conclusion: Berg et al (2006) study (Evidence table 1) evaluated PEM diagnostic performance in 77 women with 77 index and 15 incidentally discovered lesions, all histologically proven breast cancer. PEM identified 91% of DCIS, and had an overall sensitivity of 93% for the index cancers, and 90% when incidental cancers were included. Combined with conventional imaging (mammography and ultrasonography) the sensitivity of PEM improved to 98%, but with a reduced specificity. The study had its limitations and used nonstandard method for calculating the standardized uptake value (SUV). Berg et al, 2011 (Evidence table 2) examined the diagnostic performance of PEM and its impact on surgical management compared with MRI in 388 women with newly diagnosed, histologically proven breast cancer. The results of the study showed that PEM and MRI had an overall similar accuracy. MRI was more sensitive and less specific than PEM at the lesion level and in detecting incidental additional cancers. MRI was also more accurate than PEM in assessing disease extent and need for mastectomy. Still, as the authors indicate, "the combination of both MRI and PEM did not fully depict the disease extent, particularly in cases with extensive intraductal component, multifocal disease, or multicentric disease, the patient population that would benefit from accurate assessment of the disease extent". Schilling et al, 2011 (Evidence table 3) also compared the performance of FDG-PEM vs. MRI, including their effect on presurgical planning in 208 patients with newly diagnosed, biopsy proven breast cancer. Only 76% or the participants were included in the analysis. Overall, the results show that PEM and MRI had similar sensitivities of 92.8% in depiction of index cancerous lesions. Similar to the Berg's study, MRI was more sensitive and less specific than PEM in detecting additional unsuspected ipsilateral lesions but, the difference was statistically insignificant. However, the authors did not discuss if they performed any power analysis to determine the appropriate sample size. The study did not examine whether PEM results alone influenced surgical treatment as all imaging results were available to the surgeons prior to surgery treatment.

Articles: The literature search revealed around two hundred articles on PET exams for the breast. Many were review articles, technical reports, or studies on the diagnostic accuracy of FDG-PET rather than PEM which is the focus of the review. There were a limited number of studies that compared the accuracy of PEM with mammography or MRI, and most were conducted by one PEM working group. The following studies were selected for critical appraisal: Berg WA, Weinberg IN, Narayanan D, et al. High resolution fluorodeoxyglucose positron emission tomography with compression ("positron emission mammography") is highly accurate in depicting primary breast cancer. *Breast J*. 2006;12:309-323. See Evidence Table. Berg WA, Madsen KS, Schilling K, et al. Breast cancer: comparative effectiveness of positron emission mammography and MR imaging in presurgical planning for the ipsilateral breast. *Radiology.* 2011;25:59-72. See Evidence Table. Schilling K, Narayanan D, Kalinyak JE, et al. Positron emission mammography in breast cancer: presurgical planning f comparison with magnetic resonance imaging. *Eur J Nucl Med Mol Imaging* 2011;25:23-36. See Evidence Table.

The use of Positron Emission Mammography (PEM) does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Considered Not Medically Necessary:

CPT® or HCPC Codes	Description
No specific codes	

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check.**

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Date Created	Date Reviewed	Date Last Revised
09/05/2011	09/06/2011[MDCRPC], 07/03/2012 [MDCRPC], 05/07/2013[MDCRPC], 03/04/2014[MPC], 01/06/2015[MPC], 11/03/2015 [MPC], 09/06/2016[MPC], 07/11/2017[MPC], 06/05/2018[MPC],	09/06/2011

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	06/04/2019[MPC], 06/02/2020[MPC], 06/01/2021[MPC], 06/07/2022[MPC], 06/06/2023[MPC]	

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description

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KAISER PERMANENTE®

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Clinical Review Criteria
Perfusion Computed Tomography (PCT) in Patients with Acute Stroke

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	Computed Tomography Cerebral Perfusion Analysis (CTP) (L38700)
Local Coverage Article	Billing and Coding: Computed Tomography Cerebral Perfusion Analysis (CTP) (A58225)

For Non-Medicare Members

Medical necessity review no longer required.

If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Acute stroke is the third leading cause of death and the third most costly adult disease in the United States. Ischemic stroke is the more common type, and hemorrhagic stroke the more serious. Patients with acute ischemic stroke, who have intracranial arterial obstruction, have poorer prognosis and higher probability of deteriorating at 24 hours. When a cerebral artery is occluded, a core of the brain tissues dies rapidly. Surrounding this infarct core is an area of brain tissue that is hypoperfused but does not die quickly due of collateral blood flow. This area is called the ischemic penumbra, and its fate depends on the rapid reperfusion of the ischemic brain. The presence and extent of the ischemic penumbra is time dependent and may vary among patients. 90-100% of those with supratentorial arterial occlusion show an ischemic penumbra in the first 3 hours of a stroke, but only 75-80% may still have penumbral tissue at 6 hours after a stroke onset. Thus, the rapidity of diagnosis, distinction between types of stroke, and determining the extent and duration of ischemia are all critical in selecting the treatment strategy (Wintermark 2005, Muir 2005, Brunser 2009).

The ischemic penumbra is potentially salvageable with the administration of thrombolytic agents, but irreversibly damaged tissue will not benefit from reperfusion and may be at a higher risk of hemorrhage after thrombolytic therapy. Currently intravenous tissue plasminogen activator (tPA) administered within 3 hours of symptom onset is the only FDA approved drug for acute stroke in North America. Clinical trials showed that it can significantly reduce the effects of stroke and reduce permanent disability when administered within a limited time period. Thrombolytic drugs however, can also cause serious bleeding in the brain which could be fatal, and thus it is crucial to determine which patient would likely benefit from or likely to be harmed by the treatment. This narrow time window for using thrombolytic therapy in patients with acute nonhemorrhagic stroke intensified the need for

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an accurate, rapid, and accessible neuro-imaging technique that is able to identify and quantify ischemic penumbra. MR perfusion, xenon CT, PET and SPECT have been used but are limited by their availability, cost and/or patient tolerance. Clinical assessment scales that predict arterial occlusion have also been developed but are not highly accurate and their use is restricted to the middle cerebral artery (Lev 2001, Hoeffner 2004, Brunser 2009).

Conventional noncontrast CT (NCCT) is the standard initial imaging modality used to evaluate patients with acute stroke symptoms. It is widely available, convenient, and has a high sensitivity for the detection of intracranial hemorrhage which represents an absolute contra-indication to thrombolytic therapy. The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) was developed and validated in 1990 to quantify early ischemic changes on CT scans in the middle cerebral artery territory, before thrombolytic therapy. However, NCCT provides only anatomic and not physiologic information about the vessels. Researchers found that dynamic imaging after rapid injection of contrast material using CT or MRI allows assessing tissue hemodynamics from respective contrast curves, i.e. bolus tracking. MRI is currently the preferred imaging method for determining the core and penumbra tissue. It is the modality used in major clinical trials evaluating the use of tPA for stroke patients. However, MRI scanners may not be available or accessible in some hospitals and rapid imaging of acute stroke patients is of vital importance. CT scanners on the other hand are widely available in emergency rooms, and recent advances in CT and computer technology permit the calculation of contrast curves on a pixel-by-pixel basis providing high resolution perfusion CT (PCT) maps. Perfusion CT imaging has the potential of providing rapid assessment of the structural and functional status of cerebral vessels in patients who would have already undergone unenhanced head CT to exclude acute hemorrhage (Hoeffner 2004, Nabavi 2007).

PCT imaging, using standard nonionic iodinated contrasts can be performed as an adjunct to conventional CT imaging. It adds only a few minutes to the examination and does not require transferring the patient to another imaging device. PCT can be done with any spiral CT scanner and has the advantage of assessing both reversible and irreversible ischemia by generating parametric maps of cerebral blood volume (CBV), cerebral blood flow (CBF), and contrast mean transit time (MTT). The ultimate goal is to discriminate three types of tissues components: 1. The ischemic core that has the most severe ischemia and is the tissue at maximum risk of infarction, 2. Potentially salvageable tissue with mild to moderate ischemia, and 3. Tissue with normal hemodynamics. Unlike conventional CT which is normally assessed visually, perfusion imaging requires quantification of the enhancement in tissues and blood at certain time points following intravenous injection. By demonstrating a regional reduction in perfusion and prolongation of transit time, functional PCT can potentially make a positive diagnosis of acute cerebral ischemia and assess prognosis within the first few hours of stroke onset, when conventional CT images are typically normal. The perfusion maps can be generated in a short time at any workstation equipped by the appropriate software (Hoeffner 2004, Parsons 2005, Miles 2006, Nabavi 2007, Popiela 2008).

PCT however, has limited spatial coverage (20-48 mm thickness) and may not provide information on an ischemia located outside the scanning level. It also cannot detect small lacunae due to its limited spatial resolution. There is considerable variability in the protocols used for PCT scanning, perfusion post procession techniques, and in the threshold between scanners for CBV, CBF, and time to peak enhancement (TTP). Moreover, the reproducibility of PCT postprocessing has not been fully validated, the quantitative accuracy of the results is debated, and the quantitative analysis of the perfusion maps is still evolving, may be time consuming, and is less convenient in an emergency setting. It also has the disadvantage of exposure to ionizing radiation and use of iodinated contrast which may be associated with contrast-induced nephropathy in high risk patients (Wintermark 2005, 2008, Miles 2006, Kohrmann 2007).

The FDA has cleared several software packages (CT perfusion 4, syngo Neuro PBV, syngo perfusion CT and others) for post processing images acquired with CT imaging systems for patients with suspected stroke.

Medical Technology Assessment Committee (MTAC)

Perfusion computed tomography (PCT) for the Treatment of Acute Stroke

08/03/2009: MTAC REVIEW

Evidence Conclusion: Several small studies assessed the accuracy of PCT in identifying the site of occlusion and characterizing the infarct. All had their advantages and limitations; the majority was multicenter, used MRI or follow-up MRI, CTA or clinical condition as gold standards, and had blind assessment of results. However, they were mainly retrospective, did not assess the time of recanalization and /or combined the results of those who received and did not receive thrombolytic therapy, all of which are potential sources of bias and confounding.

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In a small prospective study, Murphy and colleagues (2006) investigated whether PCT can be used to differentiate between penumbra and infarcted tissue. They used noncontrast CT at 5-7 days as a gold standard and showed that the pair of CBV and CBF derived from PCT had a sensitivity and specificity of 97.0% and 97.2% respectively, in differentiating an infarct from a penumbral tissue. Tan and colleagues 2007, retrospectively compared different CT modalities and found that decreased cerebral blood volume (CBV) derived from PCT was more accurate than CT angiography (CTA) in predicting of the anatomic distribution of final infarct core (sensitivity 80.4%, specificity 96.8%), while CTA was more accurate in determining the site of occlusion (sensitivity 94.6%, specificity 100.00%).

Several other small studies including Schramm et al (2004, N=22, Schaeffer 2008, N=45, and Wintermark 2007, N=42) found that the PCT with or without and CTA correlate highly with MRI results in measuring the lesion volume in patients with acute stroke. In conclusion, the overall published evidence suggests that cerebral blood volume and cerebral blood flow values derived from a baseline PCT may have a potential use in differentiating an infarct from penumbral tissue. However, there are no large randomized trials that examined the use of perfusion CT for selection of patients for thrombolysis. All published randomized controlled trials to date used MRI for the selection of the therapeutic strategy based on the presence or absence of tissues at risk. The use of PCT in acute stroke patients needs to be to be investigated further in large RCTs to determine whether it could be used to guide treatment decisions and improve outcomes.

Articles: The search yielded almost three hundred articles on brain CT in acute stroke patients. Many were review articles, opinion pieces, or dealt with technical aspects of the scan.

The search results were screened for the studies on: 1. Accuracy of PCT in determining the site of vessel occlusion, infarct core, salvageable brain tissue, or collateral flow, and in predicting final infarct volume in patients with suspected acute stroke: The literature search identified around thirty prospective and retrospective studies that evaluated the accuracy of PCT in identifying the site of occlusion and characterizing the infarct. PCT with or without noncontrast CT (NCCT) was compared with MRI, CT angiography, or follow-up NCCT. All studies were small with population sizes ranging from 22 to 44, except for one retrospective study that included 132 patients and evaluated both the accuracy and prognostic value of PCT compared to other CT imaging modalities. The studies presented the results in sensitivity and specificity, or just correlated the findings with those of MRI. Few small studies with sample sizes ranging from 19 to 44 patients, evaluated the accuracy of PCT in predicting prognosis of ischemic stroke. Predicting prognosis was based on comparison with delayed perfusion MRI, follow-up CT, or monitoring the evolution of each patient's clinical condition. The majority of the studies were retrospective, used earlier generations of multiline CT scanners with limited spatial coverage, and no adjustments were made for the potential confounding factors. 2. Impact of PCT in management decisions and patient outcomes: The literature search did not reveal any randomized controlled trials that examined the impact of perfusion CT on the management of ischemic stroke patients and /or clinical outcomes. There was one small case-control study that investigated whether the lesion volume on PCT maps within 3 hours of onset of symptoms would predict final infarct volume, and the effect of intravenous tPA on affected brain tissue. The study however, had several limitations and used the 8-section multidetector scanner. The following three studies on the accuracy of PCT in characterizing the cerebral infarct were selected for critical appraisal: Murphy BD, Fox AJ, Lee DH, et al. Identification of penumbra and infarct in acute ischemic stroke using computed tomography perfusion-derived blood flow and blood volume measurements. Stroke 2006; 37:1771-1777. See Evidence Table. Tan JC, Dillon WP, Liu S, et al. Systematic comparison of perfusion-CT and CT-angiography in acute stroke patients. Ann Neuro. 2007; 61:533-543. See Evidence Table. Shramm P, Schellinger PD, Klotz E, et al. Comparison of perfusion computed tomography and computed tomography angiography source images with perfusion-weighted imaging and diffusion-weighted imaging in patients with acute stroke of less than 6 hours duration. Stroke 2004; 35:1652-1658. See Evidence Table.

The use of Perfusion computed tomography (PCT) for the treatment of acute stroke does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Medicare & Non-Medicare-Medical necessity review no longer required

CPT® or HCPC Codes	Description
0042T	Cerebral perfusion analysis using computed tomography with contrast administration, including post-processing of parametric maps with determination of cerebral blood flow, cerebral blood volume, and mean transit time

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***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed	Date Last Revised
09/16/2009	Established annual review because of Medicare criteria 04/05/2011 MDCRPC, 02/07/2012 MDCRPC , 12/04/2012 MDCRPC , 10/01/2013 MPC, 08/05/2014 MPC, 06/02/2015MPC, 04/05/2016MPC, 02/07/2017MPC, 12/05/2017MPC, 10/02/2018MPC, 10/01/2019MPC, 10/06/2020MPC, 10/05/2021MPC , 10/04/2022MPC , 10/03/2023MPC	10/17/2022

MDCRPC Medical Director Clinical Review and Policy Committee
MPC Medical Policy Committee

Revision History	Description
05/26/2015	Added CPT code
09/08/2015	Revised LCD L34886 Non-Covered Services.
04/26/2019	Per discussion with Kaiser Permanente neurology and Kaiser Permanente neuro-radiology, this imaging is considered medically necessary in the setting of an acute stroke to determine brain at risk for possible immediate intervention.
09/07/2021	Removed LCD L35008 and LCA A57642 and added LCD L38700 and LCA A58225 under Medicare section.
10/17/2022	Updated Medicare no longer requires review in applicable codes section as this procedure only done in and emergent setting.

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KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Positron Emission Tomography (PET) Scan

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Positron Emission Tomography (PET) Scans (220.6) (General) *Effective January 1, 2022, the Centers for Medicare & Medicaid Services removed the umbrella national coverage determination (NCD) for Positron Emission Tomography (PET) Scans. In the absence of an NCD, coverage determinations for all oncologic and non-oncologic uses of PET that are not included in another NCD under section 220.6 will be made by the Medicare Administrative Contractors under section 1862(a)(1)(A) of the Social Security Act. All PET indications currently covered or non-covered under NCDs under section 220.6 remain unchanged and MACs shall not alter coverage for indications covered under NCDs.* ***Refer to the Noridian Local Coverage Article (A54668) listed below for coverage indications for specific radiopharmaceuticals**.* • PET for Perfusion of the Heart (220.6.1) *(includes PET stress)* • FDG PET for Myocardial Viability (220.6.8) • FDG PET for Refractory Seizures (220.6.9) • FDG PET for Dementia and Neurodegenerative Diseases (220.6.13) • Positron Emission Tomography (FDG) for Oncologic Conditions (220.6.17) • Positron Emission Tomography (NaF-18) to Identify Bone Metastasis of Cancer (220.6.19) *(not covered per Medicare NCD)* • Beta Amyloid Positron Tomography in Dementia and Neurodegenerative Disease (RETIRED)
Local Coverage Determinations (LCD)	None
Local Coverage Article*	Positron Emission Tomography Scans Coverage (A54668) ***Documents coverage indications for PET scans and radiopharmaceuticals including but not limited to:** *A9587* Gallium GA-68 Dotatate (neuroendocrine tumors) *A9515* Choline C-11, diagnostic (prostate cancer) *A9588* Fluciclovine F-18 (Axumin PET - prostate) *A9593, A9594, A9496, A9800* Gallium GA-68 PSMA-11 (PSMA PET – a) *A9595* Piflufolastat F-18 (PSMA PET – prostate) A9602 Fluorodopa F-18 (Brain PET—Parkinsons)

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For Non-Medicare Members

No Oncologic Diagnosis Confirmed
In the absence of a confirmed oncological diagnosis, PET results may be needed to determine the optimal location to perform an invasive diagnostic procedure due to difficulty accessing potential biopsy sites because of anatomical complexity as described in the medical records.

Solitary Pulmonary Nodule (SPN) Solid or Part Solid	Indications
	1) Newly discovered, without known prior malignancy; and the following are met: a) A concurrent thoracic CT has been performed AND b) A single indeterminate or possibly malignant lesion more than 0.8 cm in diameter has been detected AND c) Not recommended for ground glass opacaities/nodules 2) The purpose of the scan is to determine likelihood of malignancy in order to plan management of care

Oncological Diagnosis Confirmed
For patients with a biopsy proven or confirmed oncologic diagnosis (typically biopsy proven), PET scans may be medically necessary for any of the listed diagnoses below when standard staging/restaging diagnostic and imaging studies are inconclusive AND further characterization is needed to make management decisions. The expected change in clinical management must be documented in the clinical records. The grid below contains the letters TNM. T is for tumor and the number associated describes the tumor. N is for lymph node involvement. M is for extent of metastasis.

Oncological Diagnosis	Indications
Anal	1) New diagnosis – consider PET scan for staging of T3 – T4, N0; or with any T, node positive
Breast Cancer	1) Stage I, II: PET scan is not recommended 2) Stage III A or B: PET scan is not recommended for operable stage III. May be helpful in non opearable stage III if equivocal findings on CT and bone scans 3) Stage IV: PET not routinely covered but may be indicated if conventional imaging is equivocal and results will change management 4) The following indications are not covered for PET scans a) Routine surveillance b) Initial diagnosis of breast cancer and the staging of axillary lymph nodes
Cervical	Staging for Invasive Cervical Cancer as an Adjunct to Conventional Imaging: An FDG PET scan is reasonable and necessary for the detection of metastases during the pre-treatment management phase (i.e., staging) in patients with newly diagnosed locally advanced cervical cancer with no extra-pelvic metastasis on conventional imaging tests, such as computed tomography (CT) or magnetic resonance imaging (MRI). Use of FDG PET as an adjunct may more accurately assist in the non-invasive detection of para-aortic, pelvic nodal involvement and other metastases in the pre-treatment phase of disease. The following conditions must be met: 1) If stage is less than or equal to IB1: PET not routinely recommended 2) If stage is IB2 or greater: CT, PET scan or MRI as clinically indicated
Colorectal Cancer	1) Initial staging Colon cancer appropriate for resection: Not routinely indicated and should not supplant contrast-enhanced CT. a) PET may be indicated for metastatic adeno carcinoma of the large bowel when there is potentially surgically curable metatstatic disease 2) Restaging a) When the post-operative carcinoembryonic antigen (CEA) or liver function tests (LFTs) remain elevated and other attempts at imaging are negative OR

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Oncological Diagnosis	Indications
	b) Evaluation of a potentially resectable metastatic lesion in order to confirm that it is resectable and to confirm absence of other sites of disease OR c) Differentiating local tumor recurrence from post-operative and/or post-radiation scarring 3) Surveillance: not recommended 4) Monitoring therapy progress is not indicated
Esophageal	For staging and restaging 1) If no evidence of metastatic disease on chest/abdominal CT and 2) Individual is a candidate for aggressive therapy
Gastric/GE Junction	For staging and restaging (not necessary for T1 patients) 1) If no evidence of metastatic disease on chest/abdominal CT and 2) Individual is a candidate for aggressive therapy
Gastroenteropancreatic Neuroendocrine Tumors (GEP-NET)	Kaiser Permanente endorses the recommendations for PET imaging using somatostatin receptor (SSR)-PET* for neuroendocrine tumors from the National Comprehensive Cancer Network® (NCCN) Guideline for Neuroendocrine and Adrenal Tumors. *(log-in required to access)* *This service is available at multiple Kaiser Permanente facilities. Please click to view Lutathera criteria
Head and Neck Cancers	1) Staging indicated for: a) Stage III-IV disease of oral cavity, oropharynx, glottic larynx and supraglottic larynx, hypopharynx, ethmoid sinus b) Nasopharynx, Paranasal sinus, and Maxillary sinus: Imaging optional for evaluation of distant metastases (i.e. chest, liver, bone) for stage III-IV disease. Naso-pharyngeal cancer may be appropriate for PET for stage II disease if lymph node positive. 2) Restaging (only for stage III – IV cancers) a) Post-treatment evaluation of cancers of head and neck (minimum 12 weeks after radiation completed). If the study is negative, repeat PET not indicated for surveillance. 3) Lip: No PET is indicated in the absence of advanced stage disease (stage III) 4) Salivary: No PET is indicated; CT & MRI as needed 5) Unknown primary in the head and neck (squamous cell carcinoma, adenocarcinoma, or anaplastic/undifferentiated epithelial tumor on FNA) when no tumor is evident on initial eval: Initial evaluation should consist of a flexible fiberoptic laryngoscopy as well of CT of the neck **For thyroid see below.**
Lung Cancer – Non-small cell	1) A positive PET scan finding can be caused by infection or inflammation, including absence of lung cancer with localized infection, presence of lung cancer with associated infection, and presence of lung cancer with related inflammation. A false negative PET scan can be caused by a small nodule, low cellular density, or low tumor activity for FDG. Serial PET scans are not recommended to follow response to therapy; conventional imaging is preferred. No need for bone scan if PET scan already done. 2) Initial staging: Indicated for stages I-III A or B when active treatment is planned. Not typically recommended for known stage IV. Documentation must show how results will alter treatment for stage IV treatment 3) Radiation planning in patients with significant atelectasis, IV contrast is contraindicated and when improved targeting is sought. (if meets criteria 1 above) See Solitary Pulmonary Nodule Above

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Oncological Diagnosis	Indications
Lung Cancer – Small Cell **Recommended clinical trials only**	1) Initial staging small cell lung cancer (SCLC) when it has been determined to be of limited-stage (i.e. limited to the ipsilateral hemithorax and regional lymph nodes) after standard staging evaluation AND patient is a potential surgical candidate or for a combined modality approach with radiation and chemotherapy 2) Restaging – not recommended for routine follow-up after initial therapy See Solitary Pulmonary Nodule Above
Hodgkin Disease Lymphoma	1) Initial staging a) Essential during initial work-up 2) Early/interim re-staging a) Prognostic value is seen with a PET after 2-4 cycles of standard dose chemotherapy, if change in treatment is anticipated 3) Restaging a) After completion of chemotherapy to assess treatment response and characterize residual mass at the end of treatment OR b) after radiation completion, typically at 3 months 4) Surveillance is not recommended due to risk of false positives 5) Pet Scan – field determination for radiation therapy planning
Melanoma	1) Stage I & II not for routine staging, only to evaluate specific signs or symptoms (CT, MRI also options) 2) Stage III or IV; recommended for baseline staging and/or to address specific signs and symptoms (CT, MRI also options)
Multiple Myeloma	1) Whole-body imaging low-dose CT (*often submitted as CPT 76497*) scan is preferred modality for patient initial workup for patients suspected of having MM, or Solitary Plasmacytoma. 2) FDG/PET CT is reserved for situations when initial whole-body low-dose CT or MRI is non diagnostic. 3) Whole-body imaging low dose CT is preferred for all Myeloma follow up.
Non-Hodgkin's Lymphoma	Low grade lymphoma: PET scan may be indicated for Stage I & II but not routinely for Stage III and IV unless management would be changed See Lymphoma Grade Table below Intermediate & High Grade Lymphoma: PET scan is indicated for restaging after completion of therapy (chemotherapy or radiation); not for surveillance See Lymphoma Grade Table below 1) Diffuse large B-cell lymphoma (intermediate) a) Initial staging is essential b) Restaging i) at completion of treatment (wait 8 weeks minimum) c) Early/interim restaging following 2-4 cycles of chemotherapy is controversial and should be done only if a planned change in management is documented. Biopsy of PET positive sites should be considered 2) AIDS-related B-cell lymphoma a) Initial staging is essential 3) Peripheral T-cell Lymphoma a) Initial staging is essential b) Interim restaging for all ALCL and ALK+ i) Repeat studies for all positive studies c) Restaging i) at completion of treatment ii) Repeat studies for all positive studies 4) Extranodal NK/T-cell lymphoma nasal type a) Initial staging is essential b) Post-radiation therapy the role remains uncertain

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Oncological Diagnosis	Indications
	5) Pet Scan – field determination for radiation therapy planning
Occult Primary	1) Not routinely recommended. Documentation must clearly identify the clinical reason for such testing.
Ovarian	1) PET scan not routinely indicated for initial staging 2) Restaging: may be covered if conventional imaging (CT, MRI) give indeterminate results and PET will alter management 3) May be approved if there is a solitary lymph node that is a possible candidate for surgical resection
Prostate	1) Use is unproven and should be provided within a clinical trial setting
Prostate – Axumin PET	Axumin no longer recommended; please see PSMA PET criteria here
Prostate- PSMA PET	Please see PSMA PET criteria here
Soft Tissue Sarcoma	1) Not routinely recommended 2) Baseline staging, for cases when grade is uncertain or when conventional imaging has not conclusively evaluated the possibility of distant metastasis 3) Differentiation of suspected tumor from radiation or surgical fibrosis
Thyroid	1) Localization to plan treatment for papillary or follicular thyroid carcinoma with the following: a) Previously treated with thyroidectomy and radioiodine ablation AND b) Thyroid Globulin (TG-antibody) positive (stimulated or on suppression) greater than10 AND c) Negative structural imaging i.e. ultrasound and CT negative 2) Initial staging OR follow-up for localization to monitor response to prior treatment (surgery, I131, radiation therapy, or tyrosine kinase inhibitor), for treatment planning or to predict prognosis for the following: a) Aggressive tumors confirmed by histology (Hurthle cell, poorly differentiated, anaplastic) OR b) Aggressive behavior i.e. any tumor with confirmed metastasis showing progression on structural imaging or by rising TG level despite prior treatment
All other cancers not listed above	1) Evaluated on a case by case basis, in conjunction with consultants and national guidelines

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WHO Classification	"Working Formulation" from the N-HLPC Project
The Indolent Lymphomas **B Cell Neoplasms** • **Small lymphocytic lymphoma/B-cell chronic lymphocytic leukemia** • **Lymphoplasmacytic lymphoma** • **Plasma cell myeloma/plasmacytoma** • **Hairy Cell leukemia** • **Follicular lymphoma (grade I and II)** • **Marginal zone B-cell lymphoma** • **Mantle cell lymphoma** **T Cell Neoplasms** • **T-cell large granular lymphocyte leukemia (LGL disease)** • **Mycosis fungoides** • **T-cell prolymphocytic leukemia** • **T-cell large granular lymphocyte leukemia** **Natural Killer cell neoplasm** • **Natural killer cell large granular lymphocyte leukemia**	**Low Grade** A. Malignant lymphoma Small lymphocytic consistent with CLL plasmacytoid B. Malignant Lymphoma, follicular Predominantly small cleaved cell C. Malignant lymphoma, follicular Mixed, small cleaved and large cell
The Aggressive Lymphomas **B Cell neoplasms** • **Follicular lymphoma (grade III)** • **Diffuse large B-cell lymphoma** • **Mantle cell lymphoma** **T cell neoplasm** • **Peripheral T-cell lymphoma** • **Anaplastic large cell lymphoma, T/null cell**	**Intermediate Grade** D. Malignant Lymphoma, follicular Predominantly large cell E. Malignant lymphoma, diffuse Small cleaved cell F. Malignant lymphoma, diffuse Mixed, small and large cell G. Malignant lymphoma, diffuse Large cell cleaved cell non-cleaved cell
The Highly Aggressive Lymphomas **B cell neoplasms** • **Burkitt's lymphoma** • **Precursor B lymphoblastic leukemia/lymphoma**	**High Grade** H. Malignant Lymphoma Large cell, immunoblastic I. Malignant lymphoma Lymphoblastic J. Malignant lymphoma Small non-cleaved cell Burkitt's Non-Burkitt's

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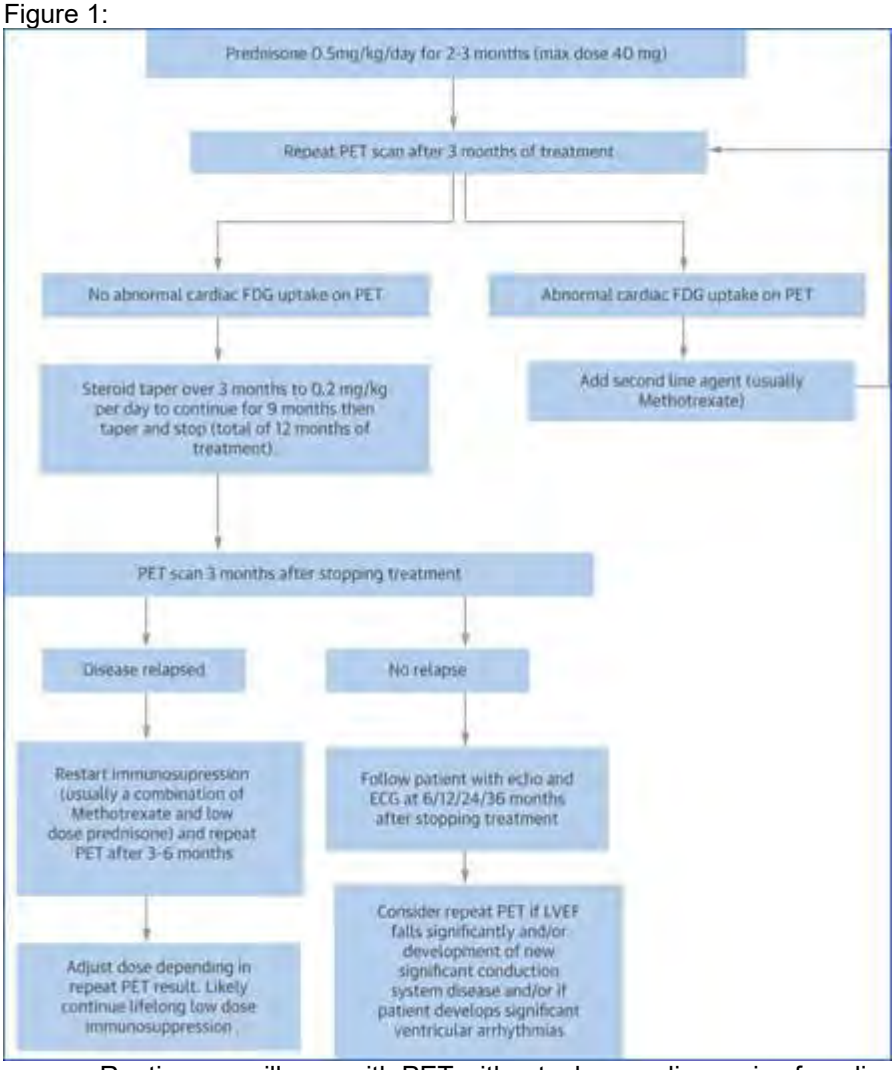
Date Sent: 3/29/24
These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage.
Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

Non-oncological conditions	Indications
Heart For myocardial Viability Using Fluorodeoxy-D-glucose (FDG)	1. Determine myocardial viability prior to revascularization for patients who are potential candidates for CABG or stent if alternate diagnostic testing are not suitable or non-diagnostic a. SPECT is inconclusive or contraindicated due to BMI greater than 40 **AND** b. dobutamine stress echocardiogram is inconclusive or contraindicated **AND** c. cardiac MRI is contraindicated or non-diagnostic 2. Sarcoidosis with suspected/known cardiac involvement a. For initial diagnosis to evaluate active cardiac sarcoidosis a. if MRI cannot be performed b. if MRI is non-diagnostic or inconclusive, and high clinical suspicion for cardiac sarcoidosis remains c. if MRI is positive for cardiac sarcoidosis, a subsequent PET can be done for assessment of active myocardial inflammation b. Repeat PET study as per the algorithm below (Figure 1: Birnie, D. H., Nery, P. B., Ha, A. C., & Beanlands, R. S. B. (2016, July 26). Cardiac Sarcoidosis. Retrieved March 20, 2020, from http://www.onlinejacc.org/content/68/4/411 Figure 1:  c. Routine surveillance with PET without a known diagnosis of cardiac sarcoidosis is not medically indicated. Serial evaluation while on

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Non-oncological conditions	Indications
	treatment for cardiac sarcoidosis should not be more frequent than 3 months. If there is a request in a shorter time frame, Kaiser Permanente Medical Director review is required.
Perfusion of the Heart Using Ammonia N-13 or Using Rubidium 82	1) Following inconclusive SPECT prior to revascularization (other diagnostic tests or alternative test are contraindicated or not suitable).
Epilepsy refractory Seizures	1) pre-surgical evaluation of refractory seizures

Other forms of PET Scans	Indications
^{18} F-florbetapir (Amyvid) PET for Alzheimer's Disease **Flortaucipir F 18 injection PET for Alzheimer's Disease** **FDG Alzheimer's Disease and Dementia** **C-11 Acetate PET for Diagnosing Primary and Metastatic Prostate Cancer** **^{18}F Fluoro-Estradiol PET (FES-PET) to Measure Estrogen Receptor Expression - Breast Cancer** **^{18} F-NaF PET for the Detection of Bone Metastases** **Fluorodopa F-18 injection PET for Parkinsonian syndrome**	There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or will provide better long term outcomes than current standard services/therapies.

If requesting these services, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist
- Last 6 months of radiology notes if applicable

Positron Emission Mammography (PEM) (Click here for link)

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

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Positron Emission Tomography has been studied over the past few years at the University of Washington as well as other academic centers. The efficacy of this scan is still being evaluated. Because medical staff members have asked to have this study covered for cancer detection, a criteria set for medical necessity has been developed which involves review by the Medical Director of the radiology department and maintenance of a request log with determination outcomes.

Positron emission tomography (PET) also known as positron emission transverse tomography (PETT), or positron emission coincident imaging (PECI), is a noninvasive imaging procedure that assesses perfusion and the level of metabolic activity in various organ systems of the human body. A positron camera (tomograph) is used to produce cross-sectional tomographic images by detecting radioactivity from a radioactive tracer substance (radiopharmaceutical) that is injected into the patient.

Positron Emission Tomograghy (PET) is a non-invasive nuclear medicine scanning technique that provides unique diagnostic information that cannot be obtained by other imaging modalities. While CT and MRI provide detailed images of the patient's anatomy; PET scanning reveals vital information concerning cellular function. This functional information can be critical in the evaluation of a variety of common and serious diseases. PET has shown utility in the management of a wide range of malignancies including lung cancer, colon cancer, lymphoma and melanoma. PET scanning also plays an important role in the evaluation of certain neurologic and cardiac diseases and the applications of this unique imaging modality continue to expand.

Recent developments in the field of PET scanning are certain to lead to a rapid expansion in the utilization of this powerful technique. There have been improvements in the resolution of the cameras allowing for higher diagnostic yield. Reimbursement issues are being worked out and HCFA has approved payment for several indications in the area of oncology. Additional indications may be approved in the near future. The problems surrounding the delivery of the radioisotopes are also being solved. This is particularly true for the Puget Sound area where a production facility (cyclotron) has recently been built in Kent.

Several careful studies have shown that there is a cost benefit associated with PET. In many cases PET will reveal findings not identified by CT or MRI, resulting in a more appropriate and timely diagnostic evaluation. Costs for unnecessary procedures are avoided. This results in an overall cost saving, despite the initial cost of performing the PET study.

Interest in PET scanning continues to grow rapidly in both the national and local medical community. Several local hospitals already have PET capability and the number of facilities offering this important diagnostic capability is certain to expand quickly. Many facilities are beginning their PET program by utilizing a mobile service. There are a number of mobile PET companies that are already providing or will soon be providing service to our area. This approach would allow for a minimal initial investment with low risk and could provide the opportunity to provide PET scanning at a number of different GH facilities on a rotating basis. In the future, depending on patient volume, consideration may be given to installing a permanent facility.

Evidence and Source Doucments

Alzheimer's Disease and Dementia
Breast Cancer, Staging and Re-Staging
Cervical Cancer, Staging and Re-Staging
Colorectal Cancer, Staging and Re-Staging
Esophageal Cancer, Diagnosis, Staging and Re-Staging
^{18}F Fluoro-Estradiol to Measure Estrogen Receptor Expression in Advanced Breast Cancer
Head and Neck Cancer, Diagnosis, Staging and Re-Staging
Melanoma, Staging and Re-Staging
Prostate Cancer, C-11 Acetate for Diagnosing Primary and Metastatic
Refractory Seizures, Pre-Surgical Evaluation
^{18} F-NaF PET for the Detection of Bone Metastases
18 F-florbetapir (Amyvid) PET for Alzheimer's disease
Axumin Injection

Medical Technology Assessment Committee (MTAC)

Alzheimer's Disease and Dementia

BACKGROUND

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Dementia is a general decline in multiple cognitive abilities including language, memory, and logical thinking. It is a common disorder in the elderly, and has many potential causes. Alzheimer's disease (AD), a degenerative neurological condition, is the most common form of dementia in the elderly and accounts for approximately two thirds the cases in the USA. Other causes of dementia include vascular dementia, dementia with Lewy bodies, dementia due to Parkinson's disease, frontotemporal dementia and others. These have to be considered in the differential diagnosis and ruled out before a diagnosis of AD is made. Alzheimer's disease is mainly characterized by progressive memory impairment and other cognitive dysfunctions that can interfere with the patient's normal daily activities and social life. Its onset is gradual and involves continuing cognitive decline. The milder forms are classified as "possible" and the more advanced forms as "probable" AD. The standard evaluation of dementia and potential AD is extensive and include medical and psychiatric history, physical examination, neuropsychologic mental status testing, lab tests and structural imaging. MRI and CT scans are used to detect structural changes late in the disease, and in ruling out tumors or other abnormalities in the brain that may cause dementia symptoms. Early and accurate diagnosis of dementia has become of greater concern lately because of the availability of more effective drug therapies to treat the symptoms of the disease. These medications would have a greater impact when used in the earlier stages of the disease (Silverman 1999). The most widely used diagnostic criteria for dementia in North America are based on definitions in the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and related Disorders Association (NINCDS-ADRDA) Work Group. Diagnostic criteria for AD have also been grouped by the American Psychiatric Association in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). The clinical evaluation based on these criteria is relatively accurate in ruling out dementia due to causes other than AD, and in identifying probable AD when the level of dementia is moderate to severe. The clinical criteria that define AD are not the ideal gold standard because the clinical diagnosis does not always conform with the pathological diagnosis. The perfect gold standard for the definitive diagnosis of AD or other specific forms of dementia is the histopathological examination of brain tissue, which is very rarely done during the patient's lifetime. Specific histopathologic findings of AD include gliosis, plaques, tangle formation, and neuronal loss (Hoffman 2000). Numerous studies have found that Alzheimer's disease and other neurodegenerative diseases could produce significant alterations in brain metabolism. AD was found to be associated with focal reduction of the cerebral metabolic rate of glucose (CMR-G1c) mainly in the temperoparietal, and frontolateral regions of the brain. Bilateral temperoparietal hypometabolism were found to be the characteristic patterns seen in AD but are not specific to it. Gamma camera imaging and single photon emission computed tomography (SPECT) have been used to measure the cerebral blood flow in the brain. However, they may not be very effective in identifying localized metabolic defects. Positron emission tomography (PET) is another technique proposed as a means for the diagnosis of dementia. PET is a functional nuclear imaging modality that uses biochemical rather than structural information to produce images. It involves using positron-emitting radioisotopes to generate radioactivity. The levels of radioactivity originating from a given point are recorded using certain camera-like devices. Different radiopharmaceuticals can be use in PET imaging. The most commonly used in brain imaging is ^{18}F-fluorodeoxyglucose (FDG) which has the ability to compete with glucose for absorption and metabolism in a variety of cell types, including neurons. In AD and some other forms of dementias the ability of the cells to take up glucose and FDG is impaired. Theoretically, FDG PET may help in the early diagnosis of AD and other forms of dementia by highlighting these regions of decreased FDG uptake before any structural damage can be detected by MRI or CT scans. FDG PET is usually done under resting conditions, but can be also performed under activation conditions to study the extent of neuronal stimulation. Brain PET scans can be interpreted by visual, quantitative and semi quantitative methods. The visual method, the most commonly used, greatly depends on the observer's experience, and lacks a clear cutoff between normal and pathological findings. PET scanners are approved by the Food and Drug Administration (FDA) for general use. The FDA does not approve imaging devices as PET scanners for specific indications. FDG PET is FDA approved for evaluating seizures, and was determined to be safe and effective in detecting malignancy. However, to date no PET radiotracers have been approved by the FDA for evaluating AD or other forms of dementia.

04/09/2003: MTAC REVIEW

Alzheimer's Disease and Dementia

Evidence Conclusion: There is insufficient evidence to allow us to draw conclusions about the value of PET in the diagnosis of AD and non-AD dementias, or in the assessment of treatment response. There was also no evidence on the impact of PET on the disease management and clinical outcome for patients with AD. The review focused on the use of FDG Pet in the diagnosis of Alzheimer's disease. It also focused on studies with histopathological confirmation, which provides a definitive diagnosis of AD because many forms of dementia have overlapping clinical presentations. The two studies reviewed had this advantage of histopathologic confirmation, but each had some validity threats that limit generalization of their results. Both studies were conducted among selected groups of patients who do not generally represent those who undergo dementia evaluation. In addition, neither study evaluated the impact of PET scanning on the disease management or the health outcome of the

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patients. Among the other limitations of the studies, is the small sample size in Hoffman's study, and the inclusion of two different cohorts with different protocols in Silverman's study. In these studies, Hoffman et al reported that FDG PET scans had a sensitivity of 92.9% and 87.5% in diagnosing AD alone, or with concurrent non AD dementias, and a specificity of only 62.2% and 66.7% respectively. Silverman reported a similar sensitivity of 93.8%, but a higher specificity of 73.2% for patient with neuropathologic confirmation of their AD diagnosis. In conclusion, the available studies do not provide sufficient evidence to support the addition of PET to the standard clinical evaluation of patients with Alzheimer's disease/dementia, and further prospective studies are needed to establish its diagnostic and prognostic values. An ideal study would include a large representative sample of patients, who would be followed up from the development of symptoms until death when histopathologic confirmation can be made. Ideally also the patients would be randomly assigned to different management groups to assess the value of PET scanning on the outcome of the disease.
Articles: *Diagnosis of Alzheimer's disease dementias:* The search revealed 24 studies. All were prospective with the exception of 2 studies. The inclusion/exclusion criteria were not specific in all of the studies, and the blinding of PET interpreters was not always discussed. In 22 of these studies clinical evaluation was the gold standard, and in only 2 studies FDG PET performance was compared to histopathological findings. The use of clinical criteria for the diagnosis of AD does not give an accurate assessment of sensitivity and specificity of PET, and the true accuracy of the test needs histopathologic confirmation. The following two studies with pathological confirmation were selected for critical appraisal: Hoffman JM, Welsh-Bohmer KA, Hanson M, et al. FDG PET in patients with pathologically verified dementia. *J Nucl Med* 2000;41:1920-1928. See Evidence Table. Silverman DH, Small GW, Chang CY, et al. Positron Emission Tomography in Evaluation of Dementia. *JAMA* 2001;286:2120-2127. See Evidence Table. *Diagnosis of non- Alzheimer's disease dementias:* The search revealed 7 studies on the diagnosis of vascular dementia, dementia with Lewy bodies, or frontotemporal dementia using FDG PET. All studies had very small sample sizes (7 to 21 patients), and various methodological issues including nonblinding of PET interpreters, nonspecific inclusion/exclusion criteria, and lack of histological confirmation of the diagnosis. None was selected for critical appraisal. *Assessment of AD treatment response:* The search revealed 5 studies evaluating the role of FDG PET in assessing the treatment response. All had very small sample sizes (10 to 30 patients), and various methodological issues including nonblinding of PET interpreters, nonspecific inclusion/exclusion criteria, and lack of histological confirmation of the diagnosis. Two of these studies were conducted to evaluate the effect of passive audiovisual stimulation on the cerebral metabolic response, and another to study the effect of a therapeutic agent (propentofylline) in enhancing the metabolic response to auditory memory stimulation. None of theses studies was selected for critical appraisal.

The use of FDG PET in the evaluation of Alzheimer's Disease or Dementia does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

12/20/2010: MTAC REVIEW
Alzheimer's Disease and Dementia
Evidence Conclusion: The first retrospective cohort study included 45 patients with dementia and assessed whether the addition of FDG-PET to clinical history and examination improves accuracy in distinguishing frontotemporal dementia (FTD) and Alzheimer's disease (AD). Findings from this study suggest that the addition of FDG-PET to clinical diagnosis improves diagnostic accuracy, sensitivity, and specificity in distinguishing FTD from AD. However, because of the characteristics of this analysis (results were reviewed by six experts who were aware that the entire population had dementia) the result of this study may not be applicable to clinical practice. Additionally, the effect on disease management and health outcomes cannot be determined from this study (Foster 2007).

Diagnostic accuracy, sensitivity, and specificity

	Clinical scenario	Clinical scenario + FDG-PET
	Mean (95% CI)	
Accuracy	78.8% (73-87)	89.2% (87-91)
Alzheimer's disease		
Sensitivity	86% (74-100)	97.6% (94-100)
Specificity	63% (36-79)	73.2% (57-82)

The second retrospective cohort study included 44 patients with and without dementia and evaluated the potential ability of both clinical and imaging diagnoses to detect AD. The results of this study suggest that the addition of FDG-PET to the initial clinical diagnosis of AD increased the sensitivity and specificity of the diagnosis; however, it is unknown whether these results will translate into clinical practice as two reviews rated each PET scan and the diagnosis of AD was determined at a multidisciplinary conference after review of all clinical data. Additionally,

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confidence intervals were not reported and there was a delay between initial examination and PET examination. PET imaging was performed an average of 1.3 years after initial examination (Jagust 2007).

Sensitivity and specificity		
	Initial	Initial + PET
Sensitivity	76%	84%
Specificity	58%	74%

Conclusion:
There is insufficient information to determine whether the addition of FDG-PET to clinical diagnosis will lead to a more accurate diagnosis of AD.

Articles: Several articles were identified that evaluated whether the addition of a FDG-PET scan to clinical diagnosis would lead to a more accurate diagnosis of AD. The majority of these studies compared the addition of FDG-PET to a clinical diagnosis, which may be inaccurate and therefore not an ideal gold standard. Two small retrospective cohort studies that compared the addition of FDG-PET to a clinical diagnosis to a postmortem pathologic diagnosis of AD were selected for review. The following studies were critically appraised:
Foster NL, Heidebrink JL, Clark CM, et al. FDG-PET improves accuracy in distinguishing frontaltemporal dementia and Alzheimer's disease. *Brain 2007;* 130:2616-2635. See Evidence Table. Jagust W, Reed B, Mungas D, et al. What does fluorodeoxyglucose PET imaging add to a clinical diagnosis of dementia? *Neurology 2007;* 69:871-877. See Evidence Table

The use of FDG PET in the evaluation of Alzheimer's Disease or Dementia does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Breast Cancer: Diagnosis, Staging and Restaging

BACKGROUND
Positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) has the potential for demonstrating tumor metabolic activity before structural changes can be shown by other methods such as computed tomographic (CT) imaging. FDG is a biological tracer that allows the evaluation of glucose metabolism. Tumor cells have increased glucose metabolism compared to benign cells and PET imaging with FDG takes advantage of this metabolic difference. Elevated uptake of FDG has been shown in several types of malignant primary tumors. FDG PET is potentially useful for diagnosis, staging and restaging of breast cancer. Diagnosis: While mammography remains the main imaging technique for screening breast lesions, it may be nondiagnostic in women with dense breasts and fibrocystic disease. Staging: Detection of tumor-involved lymph nodes is important. If PET can accurately detect axillary node involvement, patients may be able to avoid surgical morbidity from axillary dissection. Restaging: Another potential use of PET is to detect metastatic breast cancer outside of the breast and axillary nodal basins. This can help identify patients who are most likely to benefit from chemotherapy or radiation therapy. Monitoring response to chemotherapy: The response to chemotherapy could be monitored by PET because FDG uptake may decrease more in tumors that respond to chemotherapy than those that do not respond (Hoh & Schiepers, 1999).

06/07/2001: MTAC REVIEW
Breast Cancer: Diagnosis, Staging and Restaging
Evidence Conclusion: Diagnosis - The one study reviewed, Avril, found that FDG PET was insufficiently sensitive and specific at diagnosing breast tumors. Using the more conservative image interpretation, the negative predictive value was only 61%. This was a reasonably well-done study with a sample size of 144. Staging (staging of axilla) - The three studies had sensitivities varying from 79-90% and specificities varying from 91-97%. FDG PET seemed to perform better than clinical examination. False-negative results do occur with FDG PET. Restaging - The one study reviewed (Moon) suggests that FDG PET may not have sufficiently high sensitivity and specificity to forgo biopsy. This was a reasonably well-done study with n=57 patients. Replication of this study and comparisons with other diagnostic tests would provide stronger evidence about whether or not FDG PET and other non-invasive procedures can be used to restage breast cancer. Monitoring response to chemotherapy - The Smith study, which had a small sample size, found that primary breast cancers that improved clinically had a greater reduction in the rate of FDG uptake after one pulse of chemotherapy than cancers that did not respond to chemotherapy. As the authors conclude, these findings need to be replicated in larger studies with strong methodologies. In addition, more work needs to be done on determining the appropriate amount in decrease of FDG update to indicate a clinical response to chemotherapy.

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Articles: The search yielded 120 articles. Articles that were opinion pieces, basic science, dealt with technical aspects of the FDG PET procedure or had very small numbers of patients (i.e. <30) were excluded. Articles on diagnosis, staging and restaging were considered separately. There was one empirical study on the use of FDG PET for initial diagnosis of breast cancer. Four articles were identified on the use of PET for staging of the axilla. One of these did not have well described methodology and results; a summary evidence table was created for the other three articles which were similar methodologically. One article focused on the use of FDG PET for restaging breast cancer (detecting recurrent or metastatic disease). There were two articles that addressed the use of FDG PET for monitoring patients' response to chemotherapy. The study with the stronger methodology was reviewed. Evidence tables were created for: Diagnosis: Avril N, Rose M, Schelling J, Dose W, Kuhn S, Weber W. et al. Breast imaging with Positron Emission Tomography and fluorine-18 fluorodeoxyglucose: Use and limitations. J Clin Oncol 2000; 18: 3495-3502. See Evidence Table. Staging: Smith IC, Ogston KN, Whitford P, Smith FW, Sharp P, Norton M et al. Staging of the axilla in breast cancer: accurate in vivo assessment using positron emission tomography with 2-(fluorine-18)-fluoro-2-deoxy-d-glucose. Ann Surg 1998; 228: 220-227. See Evidence Table. Avril N, Dose J, Janicke F, Ziegler S, Romer W, Weber W et al. Assessment of axillary lymph node involvement in breast cancer patients with positron emission tomography using radiolabeled 2-(fluorine-18)-fluoro-2-deoxy-D-glucose. J Natl Cancer Inst 1996; 88: 1204-9. See Evidence Table. Crippa F, Agresti R, Seregni E, Greco M, Pascali C, Bogni A et al. Prospective staging of fluorine-18-FDG PET in presurgical staging of the axilla in breast cancer. J Nucl Med 1998; 39: 4-8. See Evidence Table. Restaging: Moon DS, Maddahi J, Silverman DHS, Glapsy JA, Phelps ME, Hoh CK. Accuracy of whole-body fluorine-18-FDG PET for the detection of recurrent or metastatic breast carcinoma. J Nucl Med 1998; 39: 431-435. See Evidence Table. Monitoring response to chemotherapy: Smith IC, Welch AE, Hutcheon AW, Miller ID, Payne S, Chilcott F et al. Positron emission tomography using 18-F-Fluorodeoxy-D-glucose to predict the pathologic response of breast cancer to primary chemotherapy. J Clin Oncol 2000; 18: 1676-1688. See Evidence Table

FDG PET for diagnosis, staging and restaging breast cancer did not pass the *Kaiser Permanente Medical Technology Assessment Diagnostic Test Evaluation Criteria*.

Cervical Cancer, Staging and Re-Staging

BACKGROUND

Cervical cancer is the second most frequently diagnosed gynecological malignancy in women worldwide (Chung et al., 2006). An analysis by the Centers for Disease Control and Prevention (Saraiya et al., 2007) identified about 60,000 cases of incident cervical cancer in the United States between 1998 and 2002. Rates were substantially higher among African-American and Hispanic women than other groups. If detected early, there is a high rate of treatment success with initial cervical cancer. However, the prognosis for women with recurrent cervical cancer is poor. There are limited treatment options, and treatment is often of a palliative nature (Dreyer et al., 2005). There is no generally accepted surveillance approach to detect recurrence in women with a history of cervical cancer. 80-90% of patients with recurrence will have signs or symptoms of disease, leading to investigations to confirm the diagnosis. Biopsy is routinely performed in symptomatic patients to confirm diagnosis. CT and MRI scanning, anatomic imaging techniques, are commonly used for cervical cancer imaging. In particular, CT-scan-directed biopsy is believed to be useful for obtaining histological confirmation of recurrence. There are concerns, however, that these techniques may result in false-positives due to the inability to distinguish between tumor masses and masses of necrotic or scar tissue, and false-negatives due to the inability to identify small tumors (Dreyer et al., 2005; Havilesky et al., 2005).Positron emission tomography (PET) with 18F-fluorodeoxyglucose (FDG) is proposed as an alternative to CT and MRI to confirm cervical cancer recurrence in symptomatic patients. In addition, it is proposed as a method for early detection of cervical cancer recurrence in asymptomatic women. Unlike CT and MRI, PET is a functional imaging method and examines cellular function. PET is commonly used with the biological tracer FDG, a glucose analog, which allows the evaluation of glucose metabolism. This is useful for detecting cancer since FDG is preferentially taken up by and retained within malignant cells. PET has shown utility in the management of a wide range of malignancies including lung cancer, colon cancer, lymphoma and melanoma.

08/04/2007: MTAC REVIEW

Cervical Cancer, Staging and Re-Staging

Evidence Conclusion: Diagnostic accuracy - The best available evidence on diagnostic accuracy of PET for cervical cancer recurrence is from a meta-analysis of observational studies (Havrilesky et al., 2005). To be included in the meta-analysis, diagnostic accuracy studies needed to include a reference standard (histology or clinical follow-up) for all participants. The Havrilesky analysis is limited, however, because all of the available studies were observational, retrospective and with small sample sizes (most had fewer than 40 patients). A pooled analysis of 3 studies in patients with a clinical suspicion of recurrence found a pooled sensitivity for PET of 0.96 (0.87-0.99) and specificity of 0.81 (0.58-0.94). A pooled analysis of 2 studies in patients without a clinical

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suspicion of recurrence found a sensitivity of 0.92 (0.77-0.98) and specificity of 0.74 (0.69-0.90). There is insufficient evidence on the diagnostic accuracy of PET compared to CT or MRI. No studies were identified that compared the accuracy of these tests in women with a clinical suspicion of cervical cancer recurrence. Diagnostic impact - Three small studies addressed the diagnostic impact of PET (The Lai and Belhocine studies were discussed in the Havrilesky meta-analysis). The Lai and Yen studies were both conducted among women with biopsy-documented recurrent cervical cancer. The Belhocine study included women with a clinical suspicion of recurrence as well as a small number of women who were undergoing routine post-treatment surveillance. Lai et al. (2004) reported that 22 out of 40 patients with known cervical cancer recurrence had their treatment changed after PET imaging, 15 changed from curative to palliative care. In the Yen et al. (2005) study, 36 out of 55 patients had their treatment plans modified after PET, 9 had a change in curative therapy and 27 switched to palliative therapy. Belhocine et al. (2002) reported that PET findings “induced a treatment” in 24 of the 25 patients with confirmed recurrence, and that PET was “particularly contributive” to the treatment plans of the 13 patients with an equivocal or false-negative result in the routine protocol. The studies on diagnostic impact were all limited by small sample sizes, particularly for sub-group analysis. Moreover, none of the studies provided detailed descriptions of treatment decisions based on CT or MRI versus treatment decisions based on PET. In addition, in the Yen and Lai studies, PET images were fused with CT/MRI results for patients with positive findings, so decisions were based on the combination imaging, not PET alone. Therapeutic impact - There is insufficient evidence on therapeutic impact. None of the studies reported health outcomes in patients managed by PET to those managed without PET. The Lai study included a historical control group; none of the other studies identified had comparison groups. Compared to historical controls, the 15 patients who had undergone surgery for their initial cervical cancer had a better 2-year survival rate. There was no significant difference in survival in the 25 patients who received radiation for their initial cervical cancer compared to historical controls.
Articles: There was a meta-analysis of observational studies on the use of FDG-PET for managing cervical cancer (Havrilesky et al., 2005). The authors systematically searched the literature through April, 2003. The Havrilesky analysis was critically appraised, as well as two studies included in the meta-analysis that reported on changes in treatment plan after PET scans (Belhocine et al., 2002 and Lai et al., 2004). Two studies published after the Havrilesky meta-analysis were considered for review. One study (Chung et al., 2006) was ultimately excluded because did not systematically select patients for scanning or evaluate the impact of PET findings on therapy. The other study (Yen et al., 2005) examined change in treatment following PET and was critically appraised. The studies that were critically appraised include:
Havrilesky LJ et al. FDG-PET for management of cervical and ovarian cancer. Gynecol Oncol 2005; 97: 183-191. See Evidence Table. Lai G-H, Huang K-G, See L-C et al. Restaging of recurrent cervical carcinoma with dual-phase 18F fluoro-2-deoxy-d-glucose positron emission tomography. Cancer 2004; 100: 544-552. See Evidence Table. Belhocine T, Thille A, Fridman V et al. Contribution of whole-body FDG PET imaging in the management of cervical cancer. Gynecol Oncol 2002; 87: 90-97. See Evidence Table. Yen T-C, See L-C, Change T-C et al. Defining the priority of using FDG-PET for recurrent cervical cancer. J of Nuclear Med 2005; 45: 1632-1639. See Evidence Table.

The use of FDG-PET in the diagnosis of cervical cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Colorectal Cancer, Staging and Re-Staging
BACKGROUND
Positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) has the potential for demonstrating tumor metabolic activity before structural changes can be shown by other methods such as computed tomographic (CT) imaging. FDG is a biological tracer that allows the evaluation of glucose metabolism. Tumor cells have increased glucose metabolism compared to benign cells and PET imaging with FDG takes advantage of this metabolic difference. Elevated uptake of FDG has been shown in several types of malignant primary tumors. On March 12, 2000, the FDA published a notice in the Federal Register that expanded approval of FDG for new indications. The use of FDG PET for the diagnosis, staging and restaging of colorectal cancer is one of the newly approved indications. In particular, FDG PET may be potentially useful for distinguishing local recurrences from postoperative scarring, for detecting hepatic and extrahepatic metastases prior to any surgery/therapy and for assessing recurrent colorectal cancer when there are indicators other than rising carcionoembryonic (CEA) levels. For these uses, a high negative predictive value (NPV) (the proportion of people who test negative who actually do not have the disease) is desired.

05/30/2001: MTAC REVIEW
Colorectal Cancer, Staging and Re-Staging
Evidence Conclusion: Diagnosing/ Primary staging: The evidence supporting the effectiveness FDG PET for primary staging of colorectal cancer in the absence of CT testing is weak. The strongest article (Abdel-Nabi et al.)
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was limited by the small sample size and the fact that assessors had access to CT information when they reviewed PET scans. Recurrence/Restaging: There is evidence to support the accuracy of FDG PET in identifying colorectal cancer recurrence and metastases. There were two reasonably well done comparison of diagnostic test studies (Staib, Imdahl), more recent than the meta-analysis. Study quality was defined as having a sample size >50 (ideally >100), prospective, blinded evaluation of FDG PET scans and use of an appropriate gold standard. Both studies found that PET performed well and was more accurate than CT. There is evidence from Staib that PET findings influence surgical decision-making (61% of patients in the study). The meta-analysis, which had weak methodology, found that there was a a change in management for 29% of patients based on PET findings. However, there is no published evidence on the impact of FDG PET for colorectal cancer on health outcomes (e.g. survival).
Articles: The search yielded 63 articles. Articles on primary staging and diagnosis of colorectal cancer and colorectal cancer recurrence were examined separately. There were two articles. There were 7 empirical studies examining primary staging/diagnosis of colorectal cancer and 17 empirical studies examining staging of colorectal cancer recurrences. Most of the studies were case series on FDG PET findings or a comparison of diagnostic tests and had small sample sizes. There was 1 meta-analysis of colorectal cancer recurrence. The rest of the articles were reviews or opinion pieces, assessed non-clinical outcomes or concerned technical aspects of FDG PET usage. The meta-analysis and the case series studies with the strongest methodology and the largest sample sizes were evaluated in detail. Evidence tables were created for the following articles: Diagnosis/ Primary staging:
Abdel-Nabi H, Doerr RJ, Lamonica DM, Cronin VR, Galantowicz PJ, Carbone GM, Spaulding MB. Staging of primary colorectal carcinomas with fluorine-18 fluorodeoxyglucose whole-body PET: Correlation with histopathologic and CT findings. Radiology 1998; 206: 755-760. See Evidence Table . Recurrence/ Restaging: Huebner RH, Park KC, Shephard JE, Schwimmer J, Czernin J, Phelps ME, Gambhir SS. A meta-analysis of the literature for whole-body FDG PET detection of recurrent colorectal cancer. J Nucl Med 2000; 41: 1177-1189. See Evidence Table . Recurrence/ Restaging: Huebner RH, Park KC, Shephard JE, Schwimmer J, Czernin J, Phelps ME, Gambhir SS. A meta-analysis of the literature for whole-body FDG PET detection of recurrent colorectal cancer. J Nucl Med 2000; 41: 1177-1189. See Evidence Table . Imdahl A, Reinhardt MJ, Nitzsche EU, Mix M, Dingeldey A, Einert A. et al. Impact of 18F-FDG-positron emission tomography for decision making in colorectal cancer recurrences. Langenbeck's Arch Surg 2000; 385: 129-134. See Evidence Table . Staib L, Schirrmeister H, Reske SN, Beger, HG. Is 18F-fluorodeoxyglucose positron emission tomography in recurrent colon cancer a contribution to surgical decision making? Am J Surg 2000; 180: 1-5. See Evidence Table .

The use of FDG PET as a diagnostic tool for Colon cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Esophageal Cancer, Diagnosis, Staging and Re-Staging
BACKGROUND
2 fluoro-2-deoxy-D-glucose (FDG) freely enters glycogen pathways; however, it gets trapped in these cycles, and significant intracellular accumulation occurs in cells with active glucose metabolism. Degeneration of this radioactive material can be detected by PET. Malignant tumor cells have increased glucose metabolism compared to benign cells. This increased glycolytic activity can be used to detect early-stage disease before any structural abnormality is evident. It can also help exclude the presence of malignant disease in an anatomically altered structure. Esophageal cancer is associated with unfavorable prognosis, and thus accurate determination of the tumor size, extent of local invasion, lymph node involvement, and distant metastases, provides valuable information for prognosis, assessment, and treatment selection. The standard noninvasive staging modalities are CT of the chest and abdomen for evaluating the local tumor extent, and detecting distant metastases, and endoscopic esophageal ultrasound (EUS) for the evaluation of tumor depth and locoregional LN staging in non-obstructing esophageal cancer. However, these techniques entirely depend on structural characteristics for diagnosis. This may cause limitations in diagnostic specificity (false positive findings in enlarged inflammatory LN) and sensitivity (false negative findings in non enlarged invaded LN). FDG PET has been reported to accumulate in 92% to 100% of esophageal cancers and is potentially useful for diagnosis, staging, and restaging.

05/30/2001: MTAC REVIEW
Esophageal Cancer, Diagnosis, Staging and Re-Staging
Evidence Conclusion: Apparently, three of these studies, two on staging (Flamen and Lerut) and one on restaging (Flamen) of esophageal cancer were made by the same group, and published in different medical journals. These were reasonably well done studies, yet not without biases. The Luketich study had several threats to its validity. Diagnosing and staging: These studies showed that FDG PET is not an appropriate first line diagnostic procedure in the detection of esophageal cancer. It also did not solve the problem of accurate clinical
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staging. There was no relationship between the primary tumor standardized uptake value (SUV) and the depth of the tumor invasion (T classification). FDG PET, could not define the esophageal wall, or paraesophageal tissue, and was not helpful in detecting local invasion by the primary tumor. It over staged when it did not distinguish inflammatory from neoplastic nodes, and under-staged when it could not identify minimally involved nodes, or tumors. It also did not discriminate the primary tumor from peritumoral lymph nodes. However, FDG PET was more sensitive than CT scan in detecting distant nodes and occult organ metastases. It also had a higher specificity than CT and EUS combined, in detecting distant nodal metastases. It was recommended by Flamen et al, in their two studies, that the positive findings on a FDG PET scan must be interpreted cautiously and verified histologically or radiologically, before a patient is considered as having unresectable disease and denied a curative treatment. Restaging: There was only one study found that focussed on the utility of FDG PET for the diagnosis and staging of recurrent esophageal cancer. The Flamen study showed that FDG PET was highly sensitive in staging symptomatic recurrent esophageal cancer. However, its higher sensitivity was statistically insignificant compared to the other conventional diagnostic procedures. Moreover, the false positive uptake at inflammatory lesions offered a major problem. More studies are recommended to study the potential benefit of PET on earlier diagnosis of recurrent disease. Change in patient management: In two of these studies, Luketich (staging) and Flamen (re-staging), patient management was changed in 15% and 11% of cases respectively. The effect of changing the treatment course on the patient survival and quality of life was not studied.
Articles: The search yielded 22 articles. Articles on diagnosis and primary staging of esophageal cancer and cancer recurrence were examined separately. There were six empirical studies on diagnosis and primary staging of esophageal cancer, and only one study on esophageal cancer recurrence. Most of the articles were case series on FDG PET findings or a comparison of diagnostic tests and had small sample sizes. Some were reviews or opinion pieces. There was no meta-analysis done. The studies with the strongest methodology and larger sample sizes were evaluated in detail. Three of the stronger studies, Flamen (J Clin Oncol), Flamen (J Thorac Cardiovasc Surg), and Lerut, were made by the same group. The Luketich study, that had several threats to its validity, was included to add a different view. Evidence tables were created for the following studies:
Staging: Flamen P, Lerut A, Van Cutsem E, De Wever W, Peeters M, et al. Utility of Positron Emission Tomography for the Staging of Patients with Potentially Operable Esophageal Carcinoma. J Clin Oncol 2000; 18:3202-3210. See Evidence Table . Luketich JD, Friedman DM, Wiegel TL, Meehan MA, Et al. Evaluation of Distant Metastases in Esophageal Cancer: 100 Consecutive Positron Emission Tomography Scans. Ann Thorac Surg 1999; 68: 1133-7. See Evidence Table . Lerut T, Flamen P, Ectors N, Van Cutsem E, Peeters M, et al. Histopathologic Validation of Lymph Node Staging with FDG-PET Scan in Cancer of the Esophagus and Gastroesophageal Junction. A Prospective Study Based on Primary Surgery with Extensive Lymphadenectomy. Annals of Surgery 2000; 232(6): 743-752. See Evidence Table . Restaging: Flamen P, Lerut A, Van Cutsem E, Cambier JP, Et al. The Utility of Positron Emission Tomography for the Diagnosis and Staging of Recurrent Esophageal Cancer. J Thorac Cardiovasc Surg 2000; 120: 1085-92. See Evidence Table.

The use of FDG PET As a diagnostic tool for Esophogeal Cancer failed criterion 1 of the diagnostic modality evidence criteria for evaluating efficacy of the evidence for re-staging and passed all criteria for diagnosis.

18F Fluoro-Estradiol to Measure Estrogen Receptor Expression in Advanced Breast Cancer

BACKGROUND

Estrogens are involved in the growth and development of both normal and cancerous breast tissues. The activity of estrogens in breast tissue is mediated by ligand-dependent transcription factors called estrogen receptors (ER). ER expression is generally categorized as ER-positive (ER+) and ER-negative (ER-). ER+ means that a significant number of cancer cells have receptors, generally 5-10% of cells. About 70% of invasive breast cancers are ER-positive. Higher ER expression has been found to be associated with an increased likelihood of response to endocrine therapy. (Murphy & Watson, 2006; Linden et al., 2006). Measurement of ER expression by biopsy at the time of primary diagnosis of breast cancer is standard care. However, it may be difficult to accurately measure ER expression in metastatic breast cancer because ER expression can be heterogeneous. That is, cells at one site may be ER+, while other sites may be ER-. In addition, ER expression may change over time. Recurrent breast cancer may have low ER expression even when the original primary tumor is ER+ (Murphy & Watson, 2006; Linden et al., 2006). 18F Fluoro-Estradiol PET (FES-PET) is proposed as an alternative to biopsy to assess ER expression in metastatic breast cancer. FES-PET for advanced breast cancer has not been previously reviewed by MTAC.

12/04/2006: MTAC REVIEW

18F Fluoro-Estradiol to Measure Estrogen Receptor Expression in Advanced Breast Cancer

Evidence Conclusion: The evidence on accuracy of FES-PET for assessing ER expression in breast cancer tumors is insufficient due to the availability of only one small study on this topic. Mortimer et al., (1996) compared biopsy and FES-PET findings in 41 breast cancer patients. Out of 21 patients identified on biopsy to be ER+,

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FES-PET identified 16 (sensitivity=76%). All 20 patients identified on biopsy as ER- were also negative according to FES-PET (specificity=100%). In addition to the limited quantity of evidence, biopsy is an imperfect gold standard so when there is discordance between biopsy and FES-PET findings, it is not possible to conclusively determine which method identified the "true" ER status. There are preliminary data from another small study with 47 patients (Linden et al., 2006). This study found that quantitative but not qualitative analysis of FES-PET significantly predicted response to hormonal therapy among patients with ER+ breast tumors confirmed by immunochemical analysis. The Linden study was not designed to evaluate the diagnostic accuracy of FES-PET.
Articles: The ideal study would evaluate the ability of FES-PET to identify ER-positive tumors using biopsy as the best available gold standard. One study (Mortimer et al., 1996) was identified that included both FES-PET imaging and biopsy of breast cancer tumors, although the primary purpose of the study was to correlate ER status with response to systemic therapy, not diagnostic accuracy. One other study was identified (Linden et al., 2006) that evaluated the ability of FES-PET to predict response to hormonal therapy in patients with breast cancer; the second study was restricted to patients with tumors already known to be ER-positive. These two studies were critically appraised: Mortimer JE, Dehdashti F, Siegel BA et al. Positron emission tomography with (FDG and FES) in breast cancer: correlation with estrogen receptor status and response to systemic therapy. Clin Cancer Res 1996; 2: 933-939. See Evidence Table. Linden HM, Stekhova SA, Link JM et al. Quantitative fluoroestradiol positron emission tomography imaging predicts response to endocrine treatment in breast cancer. J Clin Oncol 2006; 24: 2793-2799. See Evidence Table.

The use of ^{18}F Fluoro-Estradiol PET (FES-PET) in the treatment of advanced breast cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Head and Neck Cancer, Diagnosis, Staging and Re-Staging

BACKGROUND
Positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) has the potential for demonstrating tumor metabolic activity before structural changes can be shown by other methods such as computed tomographic (CT) imaging. FDG is a biological tracer that allows the evaluation of glucose metabolism. Tumor cells have increased glucose metabolism compared to benign cells and PET imaging with FDG takes advantage of this metabolic differences. Elevated uptake of FDG has been shown in several types of malignant primary tumors.

With head and neck cancer, FDG PET can be used to identify lymph node involvement to stage newly diagnosed patients. Lymph node status is the principal prognostic factor affecting the survival of head and neck cancer patients. Another possible application of FDG PET in initial stating is identification of unknown sites of primary cancer in patients who present with cervical nodal disease. An unknown primary cancer site occurs for only 1-5% of patients (Chisin & Macapinlac), but this group is presents special challenges in diagnosis and treatment. FDG PET could also be used to identify disease post-treatment residual disease or disease recurrence. Recurrent head and neck cancer is difficult to diagnose with conventional imaging techniques or clinical examination because of the anatomic changes, inflammation and scarring caused by surgery and radiotherapy.

05/30/2001: MTAC REVIEW
Head and Neck Cancer, Diagnosis, Staging and Re-Staging
Evidence Conclusion: Diagnosing and staging (including identifying lymph node metastases): There were two reasonably well-done prospective studies with sample sizes > 50 comparing FDG PET with other diagnostic modalities. Both showed FDG PET to have superior performance (higher sensitivity and specificity). Positive predictive value of FDG PET and CT varied considerably in the two studies. This provides some evidence about the effectiveness of FDG PET, although the variation in estimates across studies is concerning. Neither of the studies specifically discussed the ways in which FDG PET findings affect patient management. Restaging: Studies were not as strong methodologically as those for staging (e.g. had inconsistent use of a "gold standard"). In the Lapela study, FDG PET did not clearly perform better than CT (in one classification system, FDG PET had higher sensitivity and somewhat lower specificity; in the other classification system, FDG PET performed slightly better, statistical difference in performance is unknown). In the Lonneux study, FDG PET clearly performed better than CT plus MRI, but specificity was low. The available evidence does not permit clear conclusions about the effectiveness of FDG PET at detecting recurrence of head and neck cancer.
Articles: The search for the period 1997 through February 2001 yielded 83 articles. Articles that were opinion or discussion pieces or addressed technical aspects of FDG PET were excluded. There were 4 prospective comparisons of diagnostic test studies with sample sizes for diagnosis/staging and 1 for restaging. Evidence tables were created for the two staging articles with n>50 and with the strongest methodologies. An evidence table was created for the prospective restaging article and for a study of restaging where n=44 but that presented data on the impact of FDG PET on patient management. There are evidence tables for the following studies:

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Adams S, Baum RP, Stuckensen T, Bitter K, Hor G. Prospective comparison of 18F-FDG PET with conventional imaging modalities (CT, MRI, US) in lymph node staging of head and neck cancer. Eur J Nucl Med 1998; 25: 1255-1260. See Evidence Table . Stokkel MPM, ten Broek F-W, Hordjik G-J, Kooke R, van Rijk PP. Preoperative evaluation of patients with primary head and neck cancer using dual-head 18-fluorodeoxyglucose positron emission tomography. Ann Surg 2000; 231: 229-234. See Evidence Table . Lapela M, Eigtved A, Jyrkkio S, Grenman R, Kurki T, Lindholm P. et al. Experience in qualitative and quantitative FDG PET in follow-up of patients with suspected recurrence from head and neck cancer. Eur J Cancer 2000; 36: 858-67. See Evidence Table . Lonneux M, Lawson G, Ide C, Bausart R, Remacle M, Pauwels S. Positron emission tomography with fluorodeoxyglucose for suspected head and neck tumor recurrence in the symptomatic patient. Laryngoscope 2000; 110: 1493-97. See Evidence Table .

The use of FDG PET As a diagnostic tool for head and neck cancers failed criterion 4 of the diagnostic modality evidence criteria for evaluating efficacy of the evidence.

Melanoma, Staging and Re-Staging

BACKGROUND

Positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) has the potential for demonstrating tumor metabolic activity before structural changes can be shown by other methods such as computed tomographic (CT) imaging. FDG is a biological tracer that allows the evaluation of glucose metabolism. Tumor cells have increased glucose metabolism compared to benign cells and PET imaging with FDG takes advantage of this metabolic differences. Elevated uptake of FDG has been shown in several types of malignant primary tumors. A potential benefit of FDG PET for patient outcome is the ability to improve the selection of patients for surgery and other treatments. On March 12, 2000, the FDA published a notice in the Federal Register that expanded approval of FDG for new indications. One new indication was the use of FDG PET for the diagnosis, staging and restaging of melanoma. FDG PET is not covered for regional lymph node evaluation.

05/30/2001: MTAC REVIEW

Melanoma, Staging and Re-Staging

Evidence Conclusion: The evidence concerning the effectiveness of FDG PET for diagnosing, staging and restaging melanoma is inconclusive. The three best studies identified that examined the efficacy of FDG PET (excluding Wagner which looked only at regional lymph node basins) varied in their findings on sensitivity and specificity:

PET (By lesion) Sensitivity Specificity
Schwimmer* 92 87
Tyler (restaging) 87 43
Rinne (staging) 100 94
Rinne (restaging) 92 94
*Unclear whether staging and/or restaging

In particular, Tyler found substantially lower specificity than the other studies. The Tyler study included patients with advanced melanoma (Stage III) whereas the Rinne study had at least some patients with less advanced disease. Possibly, effectiveness varies by stage of disease but this is not clear from the available evidence. Only the Rinne study compared FDG PET results with conventional imaging and found that PET had superior sensitivity and specificity. However, conventional diagnostics may not have been consistently performed. No study directly compared PET and CT. In addition, the Wagner study found that sentinel node biopsy was more effective than PET for regional lymph node metastases. FDG PET may be useful for some aspects of melanoma staging and not others. There is a deficiency of evidence on long-term patient outcome following FDG PET for melanoma and on any possible adverse effects.

Articles: The search yielded 37 articles. Many of the studies included mixed groups of patients (primary and recurrent melanoma). There was one meta-analysis and several case series or cross-sectional analyses of FDG PET. The rest of the articles were reviews or opinion pieces, assessed non-clinical outcomes or concerned technical aspects of FDG PET usage. Evidence tables were created for the meta-analysis (staging vs. restaging unclear) and the three evaluations of FDG PET with the strongest methodologies. These articles are: Restaging: Tyler DS, Onaitis M, Kherani A, Hata A, Nicholson E, Keogan M et al. Positron emission tomography scanning in malignant melanoma. Cancer 2000; 89: 1019-25. See Evidence Table . Staging and restaging: Rinne D, Baum RP, Hor G, Kaufmann R. Primary staging and follow-up of high risk melanoma patients with whole-body 18f-fluorodeoxyglucose positron emission tomography. Cancer 1998; 82: 1664-71 See Evidence Table . Wagner JD, Schuwecker D, Davidson D, Coleman JJ, Saxman S, Hutchins G, Love C, Hayes JT. Prospective study of fluorodeoxyglucose positron emission tomography imaging of lymph node basins in melanoma patients undergoing sentinel node biopsy. J Clin Oncol 1999; 17: 1508-15 See Evidence Table . Staging/restaging not specified: Schwimmer J, Essner R, Patel A, Jahan A, Shephard JE, Park K et al. A review of the literature for

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whole-body FDG PET in the management of patients with melanoma. Q J Nucl Med 2000; 44: 153-67 See Evidence Table .

The use of FDG PET As a diagnostic tool for Melanoma permits conclusions about the accuracy for diagnosing distant metastases. This excluded accuracy for diagnosing local disease and regional lymph node metastases.

Prostate Cancer, C-11 Acetate for Diagnosing Primary and Metastatic

BACKGROUND

Positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) is used to identify tumors by their increased rates of glucose metabolism compared to benign cells. Prostate tumors grow slowly and have lower rates of glucose metabolism than other types of tumors. Thus, FDG PET is less useful for the diagnosis and monitoring of prostate cancers than for other cancers such as such as colorectal and head and neck cancer. Carbon-11 (C-11) acetate has been proposed as a more promising tracer for prostate tumor cells. C-11 has a short half-life, only about 20 minutes and the application of C-11 acetate PET is limited to sites that have an on-site medical cyclotron for radiotracer production.

02/13/2003: MTAC REVIEW

Prostate Cancer, C-11 Acetate for Diagnosing Primary and Metastatic

Evidence Conclusion: There is insufficient evidence to determine the ability of C-11 acetate PET to accurately diagnose or monitor prostate cancer. Only one study was identified that compared C-11 acetate PET to a gold standard (Kotzerke et al., 2002) and this study had too small a sample size for meaningful statistical analysis.

Articles: The search yielded 11 articles. All of the empirical studies had small sample sizes (fewer than 50 patients). One study (Kotzerke) compared C-11 acetate PET to a gold standard (transrectal ultrasound and biopsy). However, this study had only 31 patients and the authors did not calculate sensitivity and specificity or do any other statistical analysis due to the small number of patients evaluated. This study was not critically appraised because of its small sample size and lack of statistical analysis.

The use of C-11 Acetate PET in the evaluation of Primary and Metastatic Prostate Cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Refractory Seizures, Pre-Surgical Evaluation

BACKGROUND

Positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) has the potential for identifying areas of seizure focus (epileptogenic region). FDG is a biological tracer that allows the evaluation of glucose metabolism and areas of seizure focus have decreased glucose metabolism (hypometabolism). For patients whose seizures are uncontrolled by medication, surgery may eliminate seizures or make them easier to control. Most patients who are surgical candidates have complex partial seizures of temporal lobe origin. The most common surgical procedure performed is an anterior temporal lobectomy which consists of resection of the lateral temporal neocortex and the mesiobasal temporal cortex. Invasive recording techniques are the most accurate way to localize the epileptogenic region but noninvasive tests are preferred. Possible noninvasive tests are surface EEG, MRI, ictal single photon emission computed tomography (SPECT) and FDG PET.

05/30/2001: MTAC REVIEW

Refractory Seizures, Pre-Surgical Evaluation

Evidence Conclusion: The studies evaluating FDG-PET for the presurgical evaluation of seizures tended to be small and have methodological flaws. Studies suggest that FDG-PET may be useful for presurgical evaluation, but larger, better-done studies need to be done.

Articles: The search yielded 101 studies. Articles that were opinion or discussion pieces, addressed technical aspects of FDG PET, only included children or did not address presurgical evaluation of seizures were excluded. Nine case series/evaluation of diagnostic test studies remained. Two were by the same research group. None of the studies had sample sizes > 50. The two studies with the strongest methodology were reviewed. Strong methodology was defined as including as many of the following elements as possible: prospective, relatively large sample size, comparative studies, quantified PET results, blinded interpretation of FDG PET, consecutive patients. Only one study (Theodore) was prospective, quantified PET results and included > 30 patients. Evidence tables were created for: Theodore WH, Sato S, Kufta CV, Gaillard WD, Kelly K. FDG-positron emission tomography and invasive EEG: Seizure focus detection and surgical outcome. Epilepsia 1997; 38: 81-86. (The more recent Theodore study). See Evidence Table . Knowlton RC, Lazer KD, Ende G, Hawkins RA, Wong STC, Matson GB et al. Presurgical multimodality neuroimaging in electroencephalographic lateralized temporal lobe epilepsy. Ann Neurol 1997; 42: 829-37. See Evidence Table .

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The use of FDG PET As a diagnostic tool for Refractory Seizures failed criterion 2 of the diagnostic modality evidence criteria for evaluating efficacy of the evidence for pre-surgical evaluation.

18 F-NaF PET for the Detection of Bone Metastases

BACKGROUND

Bone metastases occur in 50% of oncologic patients, and in up to 70% of patients with breast and prostate cancer. These may result in significant morbidity including pain, pathological fractures, spinal cord compression, bone marrow suppression, and hypercalcemia. In the initial phase, metastatic lesions in the bone infiltrate the bone marrow disturbing the balance and enhancing osteolytic or osteoblastic processes. Fast-developing and aggressive metastases are usually lytic while the slow developing lesions are typically accompanied by osteoblastic processes. Prostate cancer predominantly demonstrates osteoblastic metastases, lung cancer predominantly demonstrates osteolytic metastases, and breast cancer often demonstrates osteolytic or mixed osteolytic and osteoblastic metastases (Cook 2010, Qu 2011, Tarnawska-Pierscinska 2011). Evaluation of metastatic bone lesions is crucial for determining the therapeutic plan and improving patient prognosis. Radionuclide whole-body bone scintigraphy (BS) using technetium-99m-labelled radiopharmaceuticals, such as methylene disphosphonate (99mTc MDP) tracers has been the standard modality used for the evaluation of skeletal malignancy for decades. It is widely available and has the ability of evaluating the entire skeleton within a reasonable amount of time, and at a relatively low cost. BS provides information on the presence, location, extent, and response to therapy of bone metastases. However, it identifies an increased turnover state associated with osteoblastic activity rather than proliferation of tumor cells, and therefore may be less sensitive in detecting early metastases, metastatic tumors that are small in size or confined to the bone marrow, osteolytic lesions, or lesions with minimal or no osteoblastic activity. Lytic lesions are visible by scintigraphy studies as “cold” areas that are difficult to interpret. BS may also lead to false positive findings in cases of osteoarthritis, healing fractures, and inflammation (Yen 2010, Cheng 2011, Chang 2012, Tarnawska-Pierscinska 2011). More recent improvements and developments of other non-invasive methods are increasingly being used for detecting bone metastases. These include multidetector computed tomography (CT), magnetic resonance imaging (MRI), SPECT/CT, and positron emission tomography (PET) with or without computed tomography (PET/CT). Each modality has its advantages and limitations, as well as imaging capability which could be morphologic, functional, or a combination of both. MRI and CT are anatomic imaging modalities that analyze tumor tissue based on their morphologic appearance; while 99mTc MDP bone scintigraphy and PET are functioning imaging modalities. Bone scintigraphy identifies bone metastasis by detecting the osteoblastic response to bone destruction by tumor cells and the accompanying increase in blood flow. 18F-FDG PET identifies viable tumors based on the higher glycoloytic rates in the neoplasm than in normal tissue, and 18F- labeled sodium fluoride (18 F-NaF), a radiotracer used with PET bone scans, has a skeletal uptake mechanism similar to that of 99mTc, but clears from circulation faster as it does not bind to plasma proteins. 18 F-NaF relies on the exchange of hydroxyl ions in the in the hydroxyapatite crystal and is an indicator of bone metabolic activity. The increased uptake of the tracer in malignant bone lesions reflects the increase in regional blood flow and bone turnover characterizing these lesions. 18 F-NaF PET scans may identify lytic bone metastases that may not be detected by 99mTc scintigraphy. The accumulation of fluoride however, is not tumor specific and it may be difficult to differentiate metastases from benign bone lesions such as degenerative diseases (Hetzel 2003, Evan-Sapir 2006, Cook 2010, Liu 2011, Tarnawska-Pierscinska 2012).18 F-NaF, introduced in the early 1960s, was the first radiopharmaceutical agent used for imaging bone lesions. It was initially used as a planar scintigraphy tracer and has the advantage of high and rapid bone uptake and very rapid blood clearance. It was abandoned however, with the introduction of 99mTc in the 1970s, because the relatively high energy of the annihilation photons produced by the decay of 18F required the use of special scanners. More recently, 18 F-NaF for bone imaging re-emerged with the introduction of PET and the availability of electronic generators that may allow its use. The interest in 18 F-NaF was also increased due to the worldwide shortages of 99mTc-MDP (Grant 2008, Chua 2009, Cook 2009, Yen 2010).

18 F-NaF was cleared by the Food and Drug Administration (FDA) for clinical use in 1972. The approval was then withdrawn, and it is unclear whether it was-re-approved.

10/15/2012: MTAC REVIEW

18 F-NaF PET for the Detection of Bone Metastases

Evidence Conclusion: There is limited published evidence on the use of ^{18}F-NaF PET for the detection of bone metastases. The majority of published studies were on the use of ^{18}F-FDG PET and ^{18}F-FDG PET/CT. The studies that evaluated ^{18} F-NaF PET were small in size, more than half were retrospective in design, and the specific diagnosis was not reported in some and was a variety of carcinomas in others. ^{18}F-NaF PET with or without CT was mainly compared with bone scintigraphy or FDG PET. No direct comparisons were made vs. MRI. In addition histopathological confirmation as a gold standard was performed in a small number of these studies and not for all participants in the studies. Tateishi and colleagues’ meta-analysis as well as Lagaru et al’s study

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show that ^{18}F-NaF PET or ^{18}F-NaF PET/CT, may be more sensitive, but with similar specificity to bone scintigraphy and ^{18}F-FDG PET in the detection of bone metastases. Patients included in the studies had a variety of carcinomas which may affect the accuracy of the imaging modalities used. Safety and effect of the using ^{18}F-NaF PET on patient management were not evaluated. The results of the published studies to date should be interpreted with caution. Larger prospective studies among cohorts of patients with specific malignancies are needed to determine whether 18F-NaF PET is safe, improves the detection rate of bone metastases, and has a positive impact on patient management. A randomized prospective multicenter study of almost 500 patients is conducted by the Academy of Molecular Imaging (AMI) is underway in the US to compare ^{18} F-NaF PET with ^{99m}Tc.

Articles: There literature search revealed one meta-analysis and a limited number of small studies that evaluated ^{18} F-NaF PET and compared its performance to one or more other diagnostic modalities used for the detection of bone metastases in patients with lung cancer, breast cancer, prostate cancer, and/or hepatocellular carcinoma. The meta-analysis and a more recent study with generally valid methodology were selected for critical appraisal. Tateishi U, Morita S, Taquri M, et al. A meta-analysis of ^{18}F-Fluoride positron emission tomography for assessment of metastatic bone tumor. Ann Nucl Med 2010.24:523-531. See Evidence Table . Lagaru A, Mittra E, Dick DW, et al. Prospective evaluation of ^{99m}Tc MDP scintigraphy, ^{18}F NaF PET/CT, and ^{18}F FDG PET/CT for detection of skeletal metastases. Mol Imaging Biol. 2012;14:252-259. See Evidence Table.

The use of ^{18}F-FDG PET and ^{18}F-FDG PET/CT for bone metastases does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Axumin Injection for PET Scans

BACKGROUND

Prostate cancer is the second most frequently diagnosed cancer across the globe (Wolff et al., 2015). A 2008-2010 data estimated that 15% of men in the United States will be diagnosed with prostate cancer at some point in their lives (Wolff et al., 2015). However, the mortality rate is low because it is a slow growing cancer.

Treatment is based on a number of factors including tumor stage, prostate specific antigen (PSA) value, Gleason score (GS), patient's age, concomitant diseases, life expectancy and patient's preference (Warmuth, Johansson, & Mad, 2010). A wide range of options are available for prostate cancer and these include active surveillance, watchful waiting, radical prostatectomy, hormone therapy, radiotherapy, external beam radiotherapy (EBRT), brachytherapy and chemotherapy (Wolff et al., 2015).

Iimportant proportion (20 to 50%) of men treated for prostate cancer will experience recurrence (Bruce, Lang, McNeel, & Liu, 2012; Roehl, Han, Ramos, Antenor, & Catalona, 2004; Simmons, Stephenson, & Klein, 2007). Of those with recurrent prostate cancer, a high proportion (25%) will develop metastatic disease with morbidity and mortality (Boorjian et al., 2011; James et al., 2015). Given the impact of recurrence, and for better treatment, it is crucial to determine the sites of the recurrence. Diagnostic tests include MRI, bone scintigraphy, CT. However, the accuracy of these standard imaging tests is low (diagnostic yield of 11%) (Choueiri, Dreicer, Paciorek, Carroll, & Konety, 2008). Therefore, tests with better diagnostic yield are necessary. Positron emission tomography (PET) with fluciclovine radiotracer has been the center of attention.

PET is a molecular imaging technique using tumor biology to improve detection of prostate cancer (Parent & Schuster, 2018). PET with tracers visualize receptor profile of tumor cells. Axumin or fluciclovine or Anti-1-amino-3-18F-flurocyclobutane-1-carboxylic acid (18F-fluciclovine) is an amino acid PET radiotracer. The characteristics of the tumor-imaging of this radiotracer is similar to the increased amino acid transport found in prostate cancer (Parent & Schuster, 2018). It visualizes the increased amino acid transport associated with tumor cells compared to normal tissues.

One of the benefits of Axumin PET/CT is helping to select optimal treatment strategy (i.e., salvage surgery vs. XRT vs. systemic therapy, depending on site(s)/extent of disease involvement). This can help with resource utilization and patient morbidity: e.g., bypassing futile surgery or local XRT if PET (which is generally more sensitive) identifies more extensive and/or distant disease than CT/MR identify; alternatively, using focal XRT or SABR and avoiding systemic therapy if only isolated or oligometastatic disease.

01/14/2019: MTAC REVIEW

Evidence Conclusion:

Low evidence demonstrates that:

- The clinical performance of PET with fluciclovine tracer is high in men with suspicion of prostate cancer recurrence after having treatment

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- Compared to standard imaging and other radiotracers (111In-capromab, 11 C-choline, and contrast-enhanced CT alone), the diagnostic performance of PET with fluciclovine is high
- PET with fluciclovine tracer is clinically useful in defining target volume, and changing management plan
- No acute toxicity was reported. Longer term studies are warranted

Articles:

PubMed was searched through September 4, 2018 with the search terms (Axumin OR fluciclovine) AND PET AND prostate cancer. The search was limited to English language publications and human populations. The reference lists of relevant studies were reviewed to identify additional publications.The search yielded several articles but six met the inclusion criteria and framework. The articles can be found in evidence tables 1 & 2. See Evidence Table.

The use of Axumin Injection for PET Scan does not meet the Kaiser Permanente *Medical Technology Assessment Criteria.*

18 F-florbetapir (Amyvid) PET for Alzheimer's disease

BACKGROUND

Alzheimer's disease (AD) is the most common cause of dementia in the elderly people. It is an age- dependent neurodegenerative disease characterized by progressive cognitive impairment, behavior disturbance, and irreversible memory loss. It is estimated that approximately 5 million people aged 65 years or older in the US are diagnosed with AD. The number continues to increase and is estimated to reach 6.7 million by 2025. The etiology of AD has not been established and there is no proven treatment to prevent or slow the progression the disease. It is however, necessary to examine the accuracy of the currently used diagnostic methods as these are critically important for AD research and prevention and treatment studies. Traditionally diagnosis of dementia in North America is based on clinical criteria defined by the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's disease and related Disorders Association (NINCDS-ADRDA) Work Group in 1984. In 2011, the National Institute of aging (NIA) and the Alzheimer's Association recommended broadening and refining the 1984 criteria by proposing some changes in the classification criteria of AD, and incorporating biomarkers into the AD criteria. By most diagnostic criteria currently in use, AD is a diagnosis of exclusion based on evidence of chronic progressive cognitive and functional decline of insidious onset in middle aged and elderly patients with no other identifiable alternative explanation such as major, stroke, brain tumor, or systemic disease. Definitive diagnosis of AD depends on the histological examination of brain tissue, which is contraindicated for AD during the patient's lifetime due to the high risk/benefit ratio. While the clinical criteria for diagnosing AD have not changed substantially since they were introduced in 1984, the neuropathological diagnostic criteria have been changed several times in the past three decades. A recent analysis of clinical and neurologic data collected by the National Alzheimer's Coordinating Center from 2005-2010, showed that the sensitivity for AD diagnosis ranged from 70.9-87.3% and the specificity ranged from 44.3-70.8% depending on clinical criteria used. It was also found that as many as 20% of patients diagnosed with AD do not have AD pathology at autopsy (Jack 2011, Beach 2012, Kingwell 2012, Grundman 2013, Newberg 2012). The pathological process of AD is still unclear, but the most widely accepted theory is the amyloid cascade hypothesis, which explains that the accumulation and aggregation of amyloid -ß protein in the brain triggers a pathologic cascade ultimately leading to neuronal degeneration and dementia. Autopsy studies showing extracellular accumulation of amyloid plaques and intracellular neurofibrillary tangles support this hypothesis. On the other hand, some investigators postulate that the amyloid-ß aggregates are protective, and that the soluble oligomers and not the aggregates are toxic. Another argument against the amyloid-ß theory is the failure of a drug that reduces the amyloid -ß from the brain to improve cognition in patients with AD. Despite the disagreement about the role that the amyloid-ß protein plays in AD, the currently accepted pathologic definitions of AD require the presence of abnormal levels of amyloid-ß deposits throughout the cerebral cortex of the patient. Some argue that fibrillary plaques containing amyloid-ß may be necessary but insufficient for the diagnosis of AD. Amyloid plaques are also seen in other diseases such dementia with Lewy bodies, vascular dementia, and spongiform encephalopathy. They can also be detected in cognitively normal older adults, and according to researchers, individuals' brains may differ in their ability to tolerate amyloid aggregates based on genetic factors, lifestyle choices, environmental factors, and neuropathological comorbidities, all of which may alter the threshold for the onset of cognitive impairment associated with ß-amyloid aggregation (Okamura 2010, Clark 2011, Lister-James 2011, Herholz 2012, Newberg 2012). Lately, *in vivo* amyloid imaging techniques have received a lot of attention for their potential pre-symptomatic detection of amyloid -ß pathology. It is believed that *In vivo* imaging agents that are specific and sensitive for detecting amyloid plaques would be very useful for the molecular diagnosis of AD. Investigators suggest that a test which can rule out the presence of pathologically significant levels of amyloid-ß plaque in the brain, can rule out a diagnosis of AD even in patients with signs and symptoms consistent with the common forms of dementia. In contrast, the test that indicates abnormal levels of amyloid-ß in the brain, may add confidence to the clinical diagnosis of AD, but does not provide a definite diagnosis of AD. On this basis, a number of ß-sheet-

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biding radiotracers have been developed for PET. The most widely used agent is the ^{11}C-labeled Pittsburgh compound B (^{11}C-PIB). However, the short half- life (20 minutes) of the radioisotope ^{11}C limits the utility of the compound in the clinical setting as a tool for diagnosis and therapeutic evaluation of AD (Okamura 2010, Wong 2010, Lister-James 2011, Newberg 2012). More recently Avid Radiopharmaceuticals have developed an ^{18}F-labeled amyloid- ß PET tracer for the potential detection of AD. The ^{18} F-florbetapir is an amyloid- ß avid imaging agent selected from four styryl- pyridine derivatives due to its high affinity and specific binding for amyloid, fast uptake, and fast washout kinetics in the brain. ^{18}F-florbetapir is a radioactive agent with a half-life of 110 minutes that is given before positron emission tomography (PET) imaging of the brain. According to the manufacturer, ^{18} F-florbetapir crosses the blood brain barrier and binds to amyloid aggregates in the brain. A PET scanner can detect the signal emitted by the drug's radioactive fluorine and the resultant image will show the density of amyloid-ß neuritic plaques in the brain. The PET-tracer ^{18} F- florbetapir does not measure tau proteins (proteins that stabilize microtubules), which some experts believe plays a crucial role in AD (Okamura 2010, Wong 2010, Lister-James 2011, Newberg 2012, Rosenberg 2013). The PET-tracer ^{18} F-florbetapir (Amyvid,[Avid Radiopharmaceuticals, a subsidiary of Eli Lilly &Co), received FDA approval in 2012 for imaging of the brain in subjects under evaluation for AD and other cases of cognitive impairment. The FDA approval announcement indicated that Amyvid is not a test for predicting the development of AD-associated dementia and is not for monitoring patient response to AD therapy, nor does it replace other diagnostic tests used for the evaluation of cognitive impairment. The labeling explicitly states that a positive scan does not establish a diagnosis of AD or other cognitive disorder.

10/21/2013: MTAC REVIEW
18 F-florbetapir (Amyvid) PET for Alzheimer's disease
Evidence Conclusion: Analytic validity: Clark and colleagues (2011, 2012), evaluated the accuracy of the ^{18}F-florbetapir -PET scans among terminally ill patients who consented to undergo a postmortem biopsy. The mean age of the participants was 79.3 years, 48.6% had AD as their diagnosis, 8.6% had mild cognitive impairment, 17% had another dementing disorder, and 25.7% were cognitively normal. In the initial study (Clark et al, 2011) participants were followed-up until 35 individuals had died and underwent postmortem brain biopsy. Surviving individuals were followed for an additional 1 year after initial study or for up to 2 years after the florbetapir PET scan (Clark et al, 2012). The premortem scan was then compared to the postmortem brain autopsy findings. Each scan was interpreted with at least three nuclear medicine physicians who had undergone training on reading the florbetapir-PET scans. The results of the study showed a mean (among readers) sensitivity of florbetapir-PET scan of 87% and mean specificity of 95% with an overall mean accuracy of 90%. The authors performed a florbetapir -PET scan on a group of 74 healthy young individuals (mean age 26.7 years) to evaluate the specificity of the test. They assumed, and interpreted a negative scan in these patients as amyloid negative without comparing it to the gold standard. The study had the advantage of comparing ^{18}F-florbetapir-PET findings with the gold standard of histopathological findings. However, it also had a number of limitations, many of which were acknowledged by the investigators. These include but are not limited to:The accuracy of Florbetapir-PET was assessed in a nonrandom sample of terminally ill patients who were generally older and/or with poorer health conditions than those in the population that would typically be evaluated for AD in clinical practice. Mean time interval from of onset of symptoms of AD (among patients with the disorder) to enrollment was 9 years. This makes it hard to determine how early in the disease course, the amyloid plaques can be detected. Relatively small number of patients underwent postmortem brain biopsies. 22% of the autopsies were performed more than 12 months after the scan: according to the authors, "The relation between post-mortem pathological changes and actual changes in the brain at the time of PET scan might decrease with increasing scan-to autopsy interval (majority reading sensitivity of scan was 96% when autopsy was performed within 1 year from scan and 92% for that performed within 2 years). Both the imaging and histopathological results were distributed bimodally i.e. amyloid positive (moderate to frequent plaques) or negative (no or sparse plaques). There was no intermediate category (sparse to moderate). It is hard to determine whether measurable, but low levels of amyloid at pathology that are not associated with amyloid positive scan represent an early stage of the disease, variant of amyloid deposition, or normal aging. Each scan was interpreted with 3-5 nuclear medicine physicians who had underwent extensive training on reading the scan, which would not be the case outside of an investigational setting.
There were variations between the readers interpreting the scan especially with borderline amyloid levels leading to more false negative results. It is worth noting that the study was sponsored by Avid Radiopharmaceuticals, the developer of Amyvid, which was also involved in the collection, analysis, and interpretation of the data, as well as writing the report. Clinical validity - There is weak, insufficient published evidence to determine the usefulness of florbetapir-PET imaging in identifying individuals with mild cognitive impairment or cognitive symptoms who would progress to AD. Doraiswamy and colleagues (2012) investigated whether ^{18}F-florbetapir- PET scan can predict subsequent cognitive decline in older at-risk subjects. The study included 69 cognitively normal individuals at baseline, 51 with mild cognitive impairment (MCI), and 31 patients with AD. All underwent ^{18}F-florbetapir- PET scanning at baseline, and the images were interpreted by three readers as amyloid -ß (Aß) positive or Aß
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negative. The participants were followed-up for 18 months after which they were re-assessed for their cognitive status and function. The results showed that MCI patients who were amyloid positive had significantly greater decline in the majority of psychomotor tests vs. those who were amyloid negative. There was a small yet significantly higher conversion rate from MCI to AD among those who were amyloid positive versus amyloid negative patients. These results have to be interpreted with caution due to limitations of the study. It was relatively small, conducted in an investigational setting, had only 18 months of follow-up, the authors did not adjust for multiple comparisons, and the images were interpreted with three readers with some disagreement.
Clinical utility - Grundman and colleagues (2013) conducted a study to determine the impact of amyloid imaging with ^{18}F-florbetapir PET on the physicians' diagnostic thinking and intended management of 229 patients with progressive cognitive decline undergoing evaluation for suspected AD and diagnostic uncertainty. The treating physicians provided a provisional diagnosis, an estimate of their diagnostic confidence, and their plan for diagnostic evaluation and management both before and after receiving the results from amyloid imaging with ^{18}F-florbetapir. The scan was amyloid positive in 133 patients and amyloid negative for 116 patients. No histopathological confirmations were done.The results of the analysis shows that after receiving the results of the florbetapir scan, diagnosis changed in 125/229 (54.6%) patients. Intended medication management of AD increased by 17.7% for patients with positive scans and decreased by 23.3% among those with negative scans. Among subjects who had not yet undergone a completed work up, planned brain structural imaging decreased by 24.4% and planned neuropsychological testing decreased by 32.8%. The analysis also showed that 55% of the subjects were classified with an indeterminate diagnosis after a negative scan rather than a non-AD diagnosis which may reflect lack of confidence in the scan results.The study had the advantage of investigating the clinical utility of ^{18}F-florbetapir PET scan. However, the physicians were asked whether they would change their management plan, rather than observing the actual patient management over time. The study included patients with progressive cognitive decline and diagnostic uncertainty, and was conducted in a clinical trial setting by memory disorder experts experienced in the diagnosis and treatment of AD, and the scans were over-read by expert nuclear medicine specialists, thus the results may not be generalizable to the overall population evaluated for cognitive complaints. The effect of ^{18}F-florbetapir PET scan on patient outcome has not been examined and to date, there is no proven therapy for Alzheimer's disease or for lowering and/or reversing amyloid aggregates.
Safety - The most common adverse reactions reported in these published clinical trials include headache (1.8%), musculoskeletal pain (0.8%), fatigue (0.6%), nausea (0.6%), anxiety (0.4%), back pain (0.4%), increased blood pressure (0.4%), claustrophobia (0.4%), feeling cold (0.4%), insomnia (0.4%), and neck pain (0.4%). In conclusion, there is insufficient evidence to determine whether the use of ^{18}F-florbetapir-PET can accurately predict the risk of AD, would have impact on patient management, or improve net health outcomes of patients at risk of AD. More prospective studies are needed to verify its accuracy and role in the diagnosis and management of the AD. Alzheimer's Disease Neuroimaging initiative 2 (ADNI2) is an ongoing large longitudinal multicenter study that may determine the relationships among clinical, imaging, genetic, and biochemical biomarker characteristics of the entire spectrum of Alzheimer's Disease (AD), as the pathology evolves from normal aging through very mild symptoms, to mild cognitive impairment (MCI).
Articles: The literature search revealed a large number of articles on amyloid-ß imaging with PET, but only a limited number of studies was related to the current review. There was one phase III trial and a small number of phases I and II studies on the use of 18F-florbetapir-PET in patients with mild cognitive impairment (MCI) or dementia due Alzheimer's disease. The search also identified one study on the prognostic utility of the scan, and another on the potential impact of the imaging on patient management. The phase III study (submitted to the FDA), the study on the prognostic utility the imaging, as well as the larger study on its impact on patient management were selected for critical review. Doraiswamy PM, Sperling RA, Coleman RE, et al. Amyloid-β assessed by florbetapir F 18 PET and 18-month cognitive decline: a multicenter study. Neurology.2012;79:1636-1644. See Evidence Table. Clark CM, Schneider JA, Bedell BJ, et al for the AV45-A07 Study Group. Use of florbetapir-PET for imaging beta-amyloid pathology. JAMA. 2011;305:275-283. See Evidence Table. Clark CM, Pontecorvo MJ, Beach TG, et al for the AV-45-A16 Study Group. Cerebral PET with florbetapir compared with neuropathology at autopsy for detection of neuritic amyloid-β plaques: a prospective cohort study. Lancet Neurol. 2012;11:669-678. Grundman M, Pontecorvo MJ, Salloway SP, et al for the 45-A17 Study Group. Potential impact of amyloid imaging on diagnosis and intended management in patients with progressive cognitive decline. Alzheimer Dis Assoc Disord. 2013;27:4-15. See Evidence Table.

The use of ^{18} F-florbetapir (Amyvid) PET for Alzheimer's disease does not meet the Kaiser Permanente *Medical Technology Assessment Criteria.*

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

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CPT® Codes	Description
78811	Positron emission tomography (PET) imaging; limited area (eg, chest, head/neck)
78812	Positron emission tomography (PET) imaging; skull base to mid-thigh
78813	Positron emission tomography (PET) imaging; whole body
78814	Positron emission tomography (PET) with concurrently acquired computed tomography (CT) for attenuation correction and anatomical localization imaging; limited area (eg, chest, head/neck)
78815	Positron emission tomography (PET) with concurrently acquired computed tomography (CT) for attenuation correction and anatomical localization imaging; skull base to mid-thigh
78816	Positron emission tomography (PET) with concurrently acquired computed tomography (CT) for attenuation correction and anatomical localization imaging; whole body
78608	Brain imaging, positron emission tomography (PET); metabolic evaluation
78609	Brain imaging, positron emission tomography (PET); perfusion evaluation
78429	Myocardial imaging, positron emission tomography (PET), metabolic evaluation study (including ventricular wall motion[s] and/or ejection fraction[s], when performed), single study; with concurrently acquired computed tomography transmission scan
78459	Myocardial imaging, positron emission tomography (PET), metabolic evaluation study (including ventricular wall motion[s] and/or ejection fraction[s], when performed), single study;
78430	Myocardial imaging, positron emission tomography (PET), perfusion study (including ventricular wall motion[s] and/or ejection fraction[s], when performed); single study, at rest or stress (exercise or pharmacologic), with concurrently acquired computed tomography transmission scan
78491	Myocardial imaging, positron emission tomography (PET), perfusion study (including ventricular wall motion[s] and/or ejection fraction[s], when performed); single study, at rest or stress (exercise or pharmacologic)
78492	Myocardial imaging, positron emission tomography (PET), perfusion study (including ventricular wall motion[s] and/or ejection fraction[s], when performed); multiple studies at rest and stress (exercise or pharmacologic)
78431	Myocardial imaging, positron emission tomography (PET), perfusion study (including ventricular wall motion[s] and/or ejection fraction[s], when performed); multiple studies at rest and stress (exercise or pharmacologic), with concurrently acquired computed tomography transmission scan
78432	Myocardial imaging, positron emission tomography (PET), combined perfusion with metabolic evaluation study (including ventricular wall motion[s] and/or ejection fraction[s], when performed), dual radiotracer (eg, myocardial viability);
78433	Myocardial imaging, positron emission tomography (PET), combined perfusion with metabolic evaluation study (including ventricular wall motion[s] and/or ejection fraction[s], when performed), dual radiotracer (eg, myocardial viability); with concurrently acquired computed tomography transmission scan
78434	Absolute quantitation of myocardial blood flow (AQMBF), positron emission tomography (PET), rest and pharmacologic stress (List separately in addition to code for primary procedure)
HCPC Codes	**Description**
A9587	Gallium Ga-68, dotatate, diagnostic, 0.1 mCi
A9515	Choline C-11, diagnostic, per study dose up to 20 mCi
A9592	Copper Cu-64, dotatate, diagnostic, 1 mCi
A9593	Gallium Ga-68 PSMA-11, diagnostic, (UCSF), 1 mCi
A9594	Gallium Ga-68 PSMA-11, diagnostic, (UCLA), 1 mCi
A9595	Piflufolastat f-18, diagnostic, 1 mCi
A9596	Gallium Ga-68 gozetotide, diagnostic, (Illuccix), 1 mCi
A9597	Positron emission tomography radiopharmaceutical, diagnostic, for tumor identification, not otherwise classified
A9598	Positron emission tomography radiopharmaceutical, diagnostic, for nontumor identification, not otherwise classified
A9601	Flortaucipir F 18 injection, diagnostic, 1 mCi
Q9982	Flutemetamol F18, diagnostic, per study dose, up to 5 mCi
Q9983	Florbetaben F18, diagnostic, per study dose, up to 8.1 mCi

Non-Medicare Members:
Axumin – PET is no longer recommended

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HCPCS Codes	Description
A9588	Fluciclovine F-18, diagnostic, 1 mCi

Medicare – Considered not covered
Non-Medicare - Considered Medically Necessary when criteria in the applicable policy statements listed above are met

HCPC Codes	Description
G0235	PET imaging, any site, not otherwise specified
G0252	PET imaging, full and partial-ring PET scanners only, for initial diagnosis of breast cancer and/or surgical planning for breast cancer (e.g., initial staging of axillary lymph nodes)
G0219	PET imaging whole body; melanoma for noncovered indications

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed	Date Last Revised
12/1997	02/02/2010[MDCRPC], 12/07/2010[MDCRPC], 10/04/2011[MDCRPC], 08/07/2012[MDCRPC], 11/06/2012[MDCRPC],09/03/2013[MPC] ,12/03/2013[MPC],12/02/2014[MPC], 10/06/2015[MPC], 08/02/2016[MPC], 06/06/2017[MPC], 04/03/2018[MPC], 04/02/2019[MPC], 04/07/2020[MPC], 04/06/2021[MPC], 04/05/2022[MPC], 04/04/2023[MPC]	04/18/2023

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
08/05/2015	Added Medicare Link to NCD 210.3 for Colorectal Cancer Screening Test
01/03/2017	Added Coverage Article A54668
05/01/2018	MPC approved to adopt Axumin PET non-coverage criteria
10/02/2018	Updated guidelines for head and neck cancers
12/7/2018	Added clarification about Medicare Radiopharmaceuticals
02/05/2019	MPC approved to adopt coverage criteria for Axumin Injection for PET scan. Added to background MTAC review from 01/2019.
03/05/2019	Added indications for Gastroenteropancreatic Neuroendocrine Tumors (GEP-NET)
04/02/2019	MPC approved criteria for Axumin PET for prostate cancer
05/07/2019	MPC approved to adopt criteria for Cardiac PET
01/27/2020	Updated Site of Service for Gastroenteropancreatic Neuroendocrine Tumors (GEP-NET)
05/05/2020	MPC approved to adopt updates for cardiac sarcoidosis
06/01/2021	MPC approved to endorse the recommendations for PET imaging using somatostatin receptor (SSR)-PET for neuroendocrine tumors from the National Comprehensive Cancer Network® (NCCN) Guideline for Neuroendocrine and Adrenal Tumors. Also, removed reference to using Swedish as the site of service and added Kaiser Permanente locations. Requires 60-day notice, effective date 11/01/2021.
01/07/2022	Listed covered radiopharmaceuticals in Medicare section as per LCA A54668. Added Gallium GA-68 PSMA-11 and Piflufolastat F-18 (PSMA PET for prostate) as currently not medically necessary for non-Medicare.
01/31/2022	Updated NCD 220.6.19 link
12/06/2022	Care Delivery Medical Necessity Review for ENT/OTO and Pulmonary audit has been reviewed; prior authorization with no medical review has been awarded for another year
01/10/2023	MPC approved to adopt coverage for Whole Body CT for Multiple Myeloma; 60-day notice required, effective June 1, 2023.
01/10/2023	MPC approved to adopt coverage for PET-PSMA; 60-day notice required, effective June 1, 2023. PSMA PET located in separate criteria.

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1/23/2023	Added new codes A9601, A9596 effective 7/1/2023
03/03/2023	Added New HCPC code A9602 effective 10/01/2022
04/18/2023	Clarified language for imaging modality for Multiple Myeloma

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KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria

Pharmacogenomic Testing

- ALK Gene Rearrangement and Non-Small-Cell Lung Cancer
- BRAF-v600E Mutation
- Breast Cancer Index
- ChemoFx® Assay
- Conductance Regulator (CFTR) Gene
- Cytochrome P450 Genotyping Test Drug Metabolizing Enzyme Genotyping System
- EndoPredict
- Epidermal Growth Factor Receptor (EGFR) Testing for Predicting Response of Patients with NSCLC to Tyrosine Kinase Inhibitors (TKIs)
- G551D Mutation in the Cystic Fibrosis Transmembrane
- IL28B (IFNL3) Polymorphisms in Patients with Hepatitis C
- Invader UGT1A1 Molecular Assay
- KRAS/NRAS
- Oncotype DX
- Platelet Function Testing (VerifyNow P2Y12 Assay)
- Prosigna Breast Cancer Prognostic Gene Signature Assay
- Warfarin Sensitivity DNA Test

NOTICE: Kaiser Foundation Health Plan of Washington and Kaiser Foundation Health Plan of Washington Options, Inc. (Kaiser Permanente) provide these Clinical Review Criteria for internal use by their members and health care providers. The Clinical Review Criteria only apply to Kaiser Foundation Health Plan of Washington and Kaiser Foundation Health Plan of Washington Options, Inc. Use of the Clinical Review Criteria or any Kaiser Permanente entity name, logo, trade name, trademark, or service mark for marketing or publicity purposes, including on any website, or in any press release or promotional material, is strictly prohibited.

Kaiser Permanente Clinical Review Criteria are developed to assist in administering plan benefits. These criteria neither offer medical advice nor guarantee coverage. Kaiser Permanente reserves the exclusive right to modify, revoke, suspend or change any or all of these Clinical Review Criteria, at Kaiser Permanente's sole discretion, at any time, with or without notice. **Member contracts differ in health plan benefits. Always consult the patient's Evidence of Coverage or call Kaiser Permanente Member Services at 1-888-901-4636 (TTY 711), Monday through Friday, 8 a.m. to 5 p.m. to determine coverage for a specific medical service.**

Preferred Lab for Genetic Testing for Kaiser Permanente non-Medicare enrollees (for in-network coverage)

Prevention and Invitae Corporation is the preferred lab for genetic testing when the test(s) is/are available at Prevention or Invitae and medical necessity criteria are met.*

Invitae's test catalog can be found here: Invitae Test Catalog
Prevention test catalog can be found here: Prevention Test Catalog

**Note: This does not affect processing of tumor or other pathology specimens as they are not performed by Invitae/Prevention.*

PPO/POS members may use non-preferred labs at the out of network cost share.

Exceptions
For the genetic test(s) listed below, please use the lab specified:

- ***Next Generation Sequencing for Advanced Cancer*** **–** —Any of these three labs can be used:
  - o CellNetix SymGene Panel
  - o Oncoplex (University of Washington)
  - o Caris Life Sciences

Related Policies:

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Genetic Panel Testing
Genetic Screening and Testing

Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	
National Coverage Determinations (NCD)	Pharmacogenomic Testing for Warfarin Response (90.1)
Local Coverage Determinations (LCD)	MolDX: Pharmacogenomics Testing (L38337) MolDX: Molecular Diagnostic Tests (MDT) (L36256) MolDX: Breast Cancer Index™ (BCI) Gene Expression Test (L37824) (CPT 81518) MolDX: ENDOPREDICT® Breast Cancer Gene Expression Test (L37311) (CPT 81522) MolDX: NRAS Genetic Testing (L36339) (CPT 81311, 81479) MolDX: Breast Cancer Assay: Prosigna (L36386) (CPT 81520)
Local Coverage Article	Billing and Coding: MolDX: Pharmacogenomics Testing (A57385)

Palmetto GBA is the Medicare contractor for Molecular Diagnostic Testing – this site has the most up to date Medicare coverage guidelines for genetic testing.
MolDX® Program (Administered by Palmetto GBA)

For Non-Medicare Members

Members must meet **ALL the following** criteria:

1. The member is at clinical risk for a genetic condition because of current documented symptoms being displayed or a strong family history of the condition.
2. The test is scientifically valid and can be adequately interpreted.
3. The results will directly affect a member's clinical management or reproductive decisions.
4. After appropriate clinical work-up, and informed consent by the appropriate practitioner, the genetic test is indicated.

Genetic testing is not covered for the medical management of a family member who does not have Kaiser Permanente coverage.

*For **specific tests listed** below the member must meet the criteria above **AND** the specific test criteria below:
For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under *Quick Access*.

Genetic Test	Criteria Used
Abacavir HLA-B*5701 CPT 81381	This test is covered when: 1) Prior initiation of therapy with abacavir
Anaplastic Lymphoma Kinase (ALK) Gene Rearrangement Testing for Locally Advanced or Metastatic Non-Small-Cell Lung Cancer CPT 88377	No longer requires review

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Genetic Test	Criteria Used
Breast Cancer Index™ CPT 81518	Considered medically necessary for a woman with early-stage breast cancer when **ALL of the following** criteria are met: • Testing will be used to inform medical decision making regarding extending endocrine therapy • Breast cancer was diagnosed within the last five years • Patient was diagnosed with early-stage disease {Tumor, Node, Metastasis (TNM) stage T1-3, pN0-N1, M0} • Patient has completed at least four years of endocrine therapy • Molecular testing demonstrates that the patient's cancer was estrogen receptor (ER) and/or progesterone receptor (PR) positive • Molecular testing demonstrates that the patient's cancer was human epidermal growth factor receptor 2 (HER2) negative • There is no evidence of active cancer, local recurrence or distant metastasis, at the time of testing request
Carbamazepine Pharmacogenetics - HLA-B*1502 Allele CPT 81381	MCG* A-0649 For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under *Quick Access*.
ChemoFx Assay CPT 89240, 81535, 81536	There is insufficient evidence in the published medical literature to show clinical utility.
Colorectal Cancer - BRAF V600E Testing CPT 81210	Does not require medical review
Colorectal Cancer - KRAS and NRAS Genes	Does not require medical review
ENDOPREDICT® CPT 81522	There is insufficient evidence in the published medical literature to show clinical utility.
GenoSure Archive CPT 87900, 87901, 87906 Trofile DNA phenotype CPT 87999	These tests are covered when: 1) Maraviroc is being considered, AND 2) A positive test is required to initiate use of this drug
CYP2:	
• CYP2B6/CYP3A4/CYP2A6 Efavirenz CPT 80299, 81401, 81479 • CYP2C19 Proton Pump Inhibitors (PPI) for Treating Helicobacter Pylori CPT 81225, 81226, 81227, 81401, 81479 • Immunosuppressants for Organ Transplant CYP3A5 and CYP3A4 CPT 81401	There is insufficient evidence in the published medical literature to show clinical utility.
Clopidogrel (Plavix) Pharmacogenetics - CYP2C19 Gene CPT 81225	MCG* A-0631 For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under *Quick Access*.
Tamoxifen Pharmacogenetics – CYP2D6 Gene CPT 81226, 0070U, 0071U, 0072U, 0073U, 0075U, 0076U	MCG* A-0647 For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under *Quick Access*.

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Genetic Test	Criteria Used
Epidermal Growth Factor Receptor (EGFR) Testing for Predicting Response of Patients with NSCLC to Tyrosine Kinase Inhibitors (TKIs) Such as VeriStrat CPT 81235	No longer requires review
IFNL3 (previously IL28B) Polymorphisms in Patients with Hepatitis C CPT 81283	There is insufficient evidence in the published medical literature to show clinical utility.
5-Fluorouracil Pharmacogenetics - DPYD, MTHFR, and TYMS Genes CPT 81232, 81291, 81346	MCG* A-0665 - Kaiser Permanente will not cover this per MCG guideline. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under *Quick Access*.
Irinotecan Dosing - UGT1A1 Gene (Invader) CPT 81350	MCG* A-0624 Current role remains uncertain For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under *Quick Access*.
KRAS and/or NRAS KRAS: CPT 81275, 81276, 0111U NRAS: CPT 81311, 0111U	No longer requires review
Malignant Melanoma (Cutaneous) - BRAF V600 Testing CPT 81210	Does not require medical review
Oncotype Dx – Breast CPT 81519, S3854	Covered when the following criteria are met: 1. Axillary node biopsy is negative for tumor or is positive only for micrometastasis, defined as no focus of tumor > 2 mm diameter. 2. Newly diagnosed invasive ductal carcinoma of breast, stage I or II 3. Outcome of testing will guide decision making regarding adjuvant chemotherapy. 4. Patient is female. 5. Primary tumor is estrogen receptor positive. 6. Primary tumor is HER-2 receptor-negative.
Oncotype DX – Colon Cancer CPT 81525 Oncotype DX – Prostate CPT 0047U	Colon MCG* A-0651 and Prostate MCG* A-0712- Current Role Remains Uncertain. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under *Quick Access*.
Opioid Pharmacogenetics - CYP450 Polymorphisms, OPRM1 Gene, and Gene Panels CPT 81225, 81226, 81227, 81230, 81231, 0031U, 0070U, 0071U, 0072U, 0073U, 0075U, 0076U, 0078U	MCG* A-0992 Current role remains uncertain For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under *Quick Access*.
Platelet Function Testing (VerifyNow P2Y12 Assay) CPT code 85576	Medical necessity review no longer required

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Genetic Test	Criteria Used
Psychotropic Medication Pharmacogenetics - CYP450 Polymorphisms CPT 81225, 81226, 81479, 0070U, 0071U, 0072U, 0073U, 0075U, 0076U Psychotropic Medication Pharmacogenetics – ABCB1, ADRA2A, BCNF, COMT, DRD, FKBP5, GNB3, HTR, MC4R, OGFRL1, SLC6A4, and TPH1 Genes CPT 81403, 81479, 0032U, 0033U	MCG* A-0692 Current role remains uncertain. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under *Quick Access*. MCG* A-0859 Current role remains uncertain For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under *Quick Access*.
Prosigna Breast Cancer Prognostic Gene Signature Assay CPT 81520	There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.
Rasburicase Pharmacogenetics - G6PD Gene CPT 81247, 82148, 81249	MCG* A-0653 For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under *Quick Access*.
Statin Pharmacogenetics - SLCO1B1 Gene CPT 81328	MCG* A-0981 Current role remains uncertain. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under *Quick Access*.
Azathioprine and 6-Mercaptopurine Pharmacogenetics - NUDT15 and TPMT Genes CPT 0034U, 0169U, 81335, 84433	MCG* A-0628 For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under *Quick Access*.
Warfarin Sensitivity DNA Test CPT 81227, 81355, G9143	This test is covered once in a lifetime to guide the Warfarin dosing strategies when the patient has had no more than 5 doses of Warfarin prior to testing.

***MCG Manuals are proprietary and cannot be published and/or distributed**. However, on an individual member basis, Kaiser Permanente can share a copy of the specific criteria document used to make a utilization management decision. If one of your patients is being reviewed using these criteria, you may request a copy of the criteria by calling the Kaiser Permanente Clinical Review staff at 1-800-289-1363 or access the MCG Guideline Index using the link provided above.

If requesting any of these services, please send the following documentation to support medical necessity:

- Any genetic counseling notes if applicable
- Last 6 months of specialist notes of that is being reviewed (neurological - neurology notes)

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Pharmacogenetics is defined as the study of the genetic basis for differences in a population's response to a drug. It seeks to identify polymorphisms (genetic variations) that result in different systemic concentration levels of drugs, which may help explain differing responses to the same medication. The field of pharmacogenetics began as the

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study of gross ethnic variations (e.g., variation by ethnic groups) and evolved into the study of variations of genes and proteins within individuals. Kaiser Permanente is evaluating the evidence for each test as the evidence is published.

Evidence and Source Documents

ALK Gene Rearrangement and Non-Small-Cell Lung
Breast Cancer Index
Cancer BRAF-v600E Mutation
ChemoFx Assay
Cytochrome P450 Genotyping Test Drug Metabolizing Enzyme Genotyping System
Epidermal Growth Factor Receptor (EGFR) Testing for Predicting Response of Patients with NSCLC to Tyrosine Kinase Inhibitors (TKIs)
IL28B (IFNL3) Polymorphisms in Patients with Hepatitis C
Invader UGT1A1 Molecular Assay
KRAS
Oncotype DX
Platelet Function Testing (VerifyNow P2Y12 Assay)
Prosigna Breast Cancer Prognostic Gene Signature Assay
Warfarin Sensitivity DNA Test

Medical Technology Assessment Committee (MTAC)

ALK Gene Rearrangement and Non-Small-Cell Lung Cancer

BACKGROUND

Lung cancer is one of the most common causes of cancer death, accounting for over 1 million deaths annually. Lung cancer is comprised of two histological types: small-cell lung cancers and non-small-cell lung cancers. Non-small-cell lung cancer (NSCLC) accounts for approximately 85% of lung cancers. Traditionally, treatment decisions have been based on histological type. For patients with NSCLC, platinum-based chemotherapy constitutes standard first-line treatment. However, a therapeutic plateau has been reached with conventional chemotherapy for NSCLC patients. Advances in the knowledge of molecular mechanisms of carcinogenesis have led to a change in the treatment strategy for patients with NSCLC. Research efforts are now focusing on new therapies that target molecular subtypes of NSCLC (Janku 2010, Pao 2011, Sasaki 2010). Anaplastic lymphoma kinase (ALK) is a tyrosine kinase that is not normally expressed in lung cancer. Fusions of ALK with echinoderm microtubule-associated protein-like 4 (EML4), an upstream promoter, were found in NSCLC in 2007. However, EML4 does not appear to be the exclusive fusion partner with ALK. Biologically, these fusions result in constitutive activation of the kinase. It has been reported that approximately 3 to 7% of tumors harbor EML4-ALK fusions. Although associations with clinical and pathological characteristics are not well established, research suggests that EML4-ALK fusions are associated with never smokers or light smokers, younger patient age, patients with adenocarcinomas, and patients with more advanced NSCLC. While the frequency of epidermal growth factor receptor (EGFR) mutations also increases in patients with these characteristics, EML4-ALK rearrangements are generally not found in patients with EGFR or KRAS mutations (Janku 2010, Pao 2011, Sasaki 2010). Currently, clinical trials are underway to determine the safety and efficacy of ALK kinase inhibitors for the treatment of NSCLC in patients with EML4-ALK rearrangements.

08/15/2011: MTAC REVIEW

ALK Gene Rearrangement and Non-Small-Cell Lung Cancer

Evidence Conclusion: Analytic validity: Several methods are available for detecting EML4-ALK rearrangements in patients with NSCLC; however, there is currently no gold standard method. Clinical validity: There is insufficient evidence to determine the clinical validity of testing for EML4-ALK rearrangements in patients with NSCLC. Clinical utility: There is insufficient evidence to determine the clinical utility of testing for EML4-ALK rearrangements in patients with NSCLC.

Articles: Assessment objective: Analytic validity: Are the clinical assays for the detection of ALK gene rearrangements accurate and reliable? Clinical validity: Does the presence of an ALK gene rearrangement predict clinical outcome? Clinical utility: Will the results of the clinical assays for the detection of ALK gene rearrangements alter clinical management and improve clinical outcomes? Several methods including polymerase chain reaction (PCR), immunohistochemistry (IHC), and fluorescence in situ hybridization (FISH) are currently being evaluated for the detection of ELM4-ALK rearrangements. Each of these methods has its advantages and limitations. Currently,

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there is no gold standard method for detecting EML4-ALK rearrangements in patients with NSCLC (Sasaki 2010). A small retrospective cohort study was identified that addressed the clinical validity of testing patients with NSCLC for EML4-ALK gene rearrangements; however, this study was not selected for review as it only included 19 patients with EML4-ALK rearrangements. Results from this study suggest that patients with EML4-ALK rearrangements have similar response rates to platinum-based combination chemotherapy as patients without these mutations. Additionally, patients with EML4-ALK rearrangements do not appear to respond to tyrosine kinase inhibitors (Shaw 2009). Larger studies are needed to confirm these findings. To date there are no FDA approved agents for the treatment of NSCLC in patients with EML4-ALK gene rearrangements. Results from a phase 1 open-label, prospective case-series that included 82 subjects with EML4-ALK rearrangements suggest that crizotinib, an orally available small-molecule inhibitor of the ALK tyrosine kinase, may be effective for the treatment of NSCLC in patients with EML4-ALK rearrangements. The overall response rate, which included confirmed partial and complete responses, was 57% and 33% of patients had stable disease. The most commonly reported adverse effects were nausea (54% of patients) and diarrhea (48% of patients) (Kwak 2010). Phase 3 clinical trials are now underway to determine the safety and efficacy of crizotinib compared to pemetrexed or docetaxel in patients with advanced NSCLC and EML4-ALK gene arrangements (ClinicalTrials.gov number, NCT00932893).

The use of ALK gene rearrangement does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

BRAF^{V600E} Mutation

BACKGROUND

In the past year, several therapies for late-stage melanoma have been approved, including peg-interferon α-2b (Sylatron) and ipilimumab (Yervoy). Until now, ipilimumab was the only agent to demonstrate an improvement in overall survival for patients with advanced melanoma. Vemurafenib is approved for the treatment of advanced melanoma as well but targets a specific patient population. It is an inhibitor of mutated forms of BRAF serine-threonine kinase, including BRAF^{V600E}, and also inhibits other kinases at similar concentrations. Some mutations in the BRAF gene, including V600E, result in constitutively activated BRAF proteins, which can cause cell proliferation in the absence of growth factors that would normally be required for proliferation. Confirmation of BRAF^{V600E} mutation-positive melanoma as detected by the cobas® 4800 V600 Mutation Test, is required for selection of patients prior to administration of vemurafenib. This test is designed to detect BRAF^{V600E} mutations in DNA isolated from formalin-fixed, paraffin-embedded human melanoma tissue. This test is marketed by the same company that manufactures vemurafenib, and its FDA approval is based on the same data that supported approval of vemurafenib.

09/2011: Pharmacy and Therapeutics Committee (P&T) BRAF^{V600E} Mutation

Evidence Conclusion: From P&T Committee: Evidence of benefit[2-4]: Preliminary data from BRIM-2, a phase 2 trial, showed that patients with BRAF^{V600E} mutation + melanoma who had received prior treatment and were subsequently treated with vemurafenib, had an objective response rate >50%. Based on this data, the FDA recommended modification of the statistical plan for BRIM-3, a phase 3 trial, to accommodate an interim analysis and accelerate the approval process. Median follow-up in BRIM-3 was ~3 months. In the BRIM-3 trial, vemurafenib, 960mg BID was superior to dacarbazine in progression-free survival (5.3 months vs 1.6 months; p<0.001) and objective tumor response rate (48% vs 5%, p<0.001).

Complete responses were seen in 2 patients (0.9%) of patients in the vemurafenib group and 0 in the dacarbazine group. Median overall survival was not reached in the vemurafenib group, but was 7.9 months in the dacarbazine group. At 6 months, overall survival was 84% in the vemurafenib group and 64% in the dacarbazine group; p<0.001. In BRIM-2 and BRIM-3, all enrolled patients tested positive for the BRAF^{V600E} mutation using the cobas® 4800 V600 Mutation Test. Evidence of harm[1-3]: The most common adverse reactions of any grade (≥ 30% in either study) reported in patients receiving vemurafenib were arthralgia, rash, alopecia, fatigue, photosensitivity reaction, nausea, pruritus and skin papilloma. The most common (≥5%) Grade 3 adverse reactions were cutaneous squamous cell carcinoma (cuSCC) and rash; 24% of patients treated with vemurafenib were reported to have at least one cuSCC. These lesions were excised, and none required dose-modifications. The incidence of Grade 4 adverse reactions was ≤ 4% in both studies. In BRIM-3, the incidence of adverse events resulting in discontinuation was 7% in the vemurafenib arm and 4% for the dacarbazine arm. There are no contraindications to vemurafenib. Safety issues addressed in the package insert include cuSCC, serious hypersensitivity reaction, Stevens-Johnson syndrome and toxic epidermal necrolysis, QT-prolongation, liver laboratory abnormalities, photosensitivity, uveitis and other ophthalmologic reactions, and new primary malignant melanomas. Pregnancy category D, may cause fetal harm based on its mechanism of action. Women of childbearing potential and men should be advised to use

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appropriate contraceptive measures during therapy and for at least 2 months after discontinuation.

Articles: Table 1. Summary of results from BRIM-2: an open-label, single-arm, Phase II trial

Study population	Outcome	Vemurafenib 960mg BID (95% CI) , n=132
$BRAF^{V600E}$ mutation + melanoma who have completed prior 1st line therapy	Best overall response rate	52.3% (43, 61)
	Median duration of response	6.8 months (5.6, not reached)
	Median PFS	6.2 months (5.6, 6.8)

Table 2. Summary of results from BRIM-3: a randomized double-blind placebo-controlled Phase III trial

Study population	Outcome	Vemurafenib n=337	Dacarbazine n=338	HR (95% CI) *p*-value	ARR (95% CI)	NNT (95% CI)
Unresectable stage IIIC or IV melanoma, + $BRAF^{V600E}$ mutation, treatment naïve	Overall survival	Median not reached 84% at 6 months	7.9 months (7.3, 9.6) 64% at 6 months	0.37 (0.26, 0.55) *p*<0.001	20% (13, 26)	5 (4, 7)
	Progression-free survival	5.3 months (4.9, 6.6)	1.6 months (1.6, 1.7)	0.26 (0.2, 0.33) *p*<0.001	NA	NA
	Objective tumor response rate	48% (n=219)	5% (n=220)	*p*<0.001	43% (35, 50)	2 (2, 3)

HR – Hazard ratio ARR – Absolute Risk Reduction NNT – Number Needed to Treat to benefit one person

This was not considered at MTAC but went to P&T instead.

Breast Cancer Index

BACKGROUND

Breast cancer is the most common cancer diagnosed and the second most common cause of cancer death in women in the United States. Patients with breast cancer can present with a variety of symptomatology that originates from heterogeneous molecular pathology (Dowsett et al., 2010). Breast cancer can be staged using the Tumor, Node, Metastases classification (TNM). The treatment of invasive breast cancer is based on the stage and involves radiation, surgery, and adjuvant therapy. The management based on adjuvant therapy derives from many factors such as the TNM characteristics, the grade, the presence or absence of estrogen and progesterone receptors, and the human epidermal growth factor 2 (HER2) receptor. However, some patients are still mistreated. Molecular tests that can predict the prognosis and the response to adjuvant therapy might accurately evaluate the recurrence risk and impact disease management. The literature has described several molecular tests including the Breast Cancer Index (BCI).

The BCI is a reverse transcriptase polymerase chain reaction (rt-PCR) test that helps to guide treatment decision in women with early stage breast cancer who are ER+, LN- or LN+, and are distant recurrence-free (https://www.breastcancerindex.com/). The test assesses the overall (10 years) and late distance recurrence (5-10 years) (prognostic) and who benefits from extended endocrine therapy (predictive) after an initial 5-years of endocrine therapy (https://www.breastcancerindex.com/). The test can also be performed after treatment has begun to determine late distance recurrence and the likelihood of benefit from extended endocrine therapy.

The assay is a combination of two markers, the HOXB13/IL17BR (H/I) which is based on two genes, and a proliferation marker which is the molecular grade index (MGI) (based on 5 genes) (Sanft et al., 2015; Dennis C Sgroi, Carney, et al., 2013). These markers evaluate the prognostic component by generating a risk score that varies from 0 to 10. For overall risk, BCI score is classified into three categories: BCI score <5.1 is low risk; 5.1 ≤ BCI score ≤6.5 is intermediate risk, and BCI score ≥6.5 is high risk (Sanft et al., 2015). For the risk of late distant recurrence in patients with lymph node negative, BCI score is classified as low risk BCI < 5.0825 and high risk BCI ≥ 5.0825 (Hayes, 2016). In addition to gene expression, BCI score is determined in N1 patients by adding tumor size and grade (https://www.breastcancerindex.com/about-breast-cancer-index).

The predictive part is based on the quantitative molecular assessment of estrogen signaling pathways (based on

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H/I) and is indicative of who benefits from extended endocrine therapy after an initial course (5 years) of endocrine treatment (https://www.breastcancerindex.com/about-breast-cancer-index#).

06/05/2017: MTAC REVIEW

Evidence Conclusion:

- Analytic validity: there is insufficient evidence to recommend for or against the analytical validity of the BCI assay in ER+, LN- or LN+ breast cancer patients.
- Clinical validity:
  - Level IB evidence (based on Simon et al. 2009 revised determination of levels of evidence using elements of tumor marker studies) supports the prognostic effect of early recurrence, distant recurrence, and distant recurrence over 10 years in ER+, LN- breast cancer patients. In addition, there is insufficient evidence to assess clinical validity in LN+ patients.
  - Low evidence supports extended use of endocrine therapy in high risk patients with ER+, LN- breast cancer patients.
- Clinical utility: there is insufficient evidence to make a conclusion on the clinical utility of the BCI assay in ER+, LN- or LN+ breast cancer patients.

Articles: PubMed was searched through April 10, 2017 with the search terms breast cancer index bci with variations. The search was limited to English language publications and human populations. The reference lists of relevant studies were reviewed to identify additional publications. The search yielded 20 articles; however, six met our criteria.

The use of Breast Cancer Index for predicting response of solid tumors to chemotherapeutic agents does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

04/10/2023: MTAC REVIEW

Evidence Conclusion:

- Analytical validity: Evidence is insufficient
- Clinical validity: Low quality evidence suggest that BCI is significantly predictive of response to extensive endocrine therapy and adds a prognostic value beyond clinicopathologic characteristics in ER+, LN- or LN+ breast cancer patients. The test may be clinical useful in terms of optimizing duration of endocrine therapy.
- Clinical utility: One new study indicates that BCI test may influence treatment recommendation. However, the quality of evidence is very low.

Articles: PubMed was searched from 2018 to January 25, 2023, with the search terms breast cancer index bci. The search was limited to English language publications and human populations. The reference lists of relevant studies were reviewed to identify additional publications.

The use of Breast Cancer Index for predicting response of solid tumors to chemotherapeutic agents does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

ChemoFx® Assay

BACKGROUND

It is widely recognized that patients with the same histological stage and grade of cancer may vary considerably in their clinical response and tolerability to chemotherapy. An individual may be resistant to one chemotherapeutic and sensitive to another, suggesting that there is considerable clinical heterogeneity in tumor chemosensitivity. Unfortunately, resistance to chemotherapy cannot be predicted by clinical or histological examination. The administration of an ineffective therapy is associated with unnecessary toxicity, delay of potentially useful drug, added risk of the development of resistant clones, and needless cost. Many attempts have been made over the years to develop an ex-vivo test that would provide clinically relevant tumor-specific information, i.e. measures how a patient cancer cells respond to specific types, doses and combinations of chemotherapy (Gallion 2006, Cree 2007). A number of in-vitro chemosensitivity response tests have been, and are currently used. These include assays that measure cellular metabolic activity, tests that measure radioactive precursor incorporation, and tests that measure cell viability. Chemoresponse assays are not intended to be used as an alternative to the traditional empiric methods for selecting chemotherapy but as an aid to the oncologists when selecting the most appropriate chemotherapy regimens on an individual basis especially when a number of equivalent options are available (Ness 2002, Gallion 2006, Cree 2007). ChemoFx® (Precision Therapeutics) is an ex-vivo, cell death

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assay based on the biological phenomenon that when cells that grow adherent in culture as a monolayer, die they lose their adherent qualities and lift from the culture surface. The test is reported to use as little as 35 mg of tissue, and have the results available in about 3 weeks after receiving the specimen. It involves growing tumor cells (excised from individual cancer patients through biopsy or surgery, or recovered from fluid specimens), in primary cultures as monolayers. Once a sufficient number of cells are grown, they are exposed to a variety of chemotherapeutic agents in a range of concentrations. A full dose-response curve is generated for each drug evaluated, and the data are presented graphically as the cytotoxic index (% kill), defined as 1-[No of cells in treated wells/No. of cells in control wells] x100. Features of each dose-response curve are used to score a tumor's response to each ex vivo treatment as responsive, intermediate response, or nonresponsive. Drug responses are scored from 0-5 and is determined by the number of drug doses where the cytotoxic index was >35%. Collectively these scores may be used by the oncologist in his treatment decisions (Peters 2005, Zhibao 2008).

10/05/2009: MTAC REVIEW
ChemoFx® Assay
Evidence Conclusion: Clinical validity: ChemoFx assay was not prospectively compared head to head to another cellular or molecular chemo responsive test or gold standard. Two retrospective cases series correlated the results of ChemoFx with cancer free survival in ovarian cancer patients, and one small series correlated its results with pathological complete response of small breast lesions to neoadjuvant therapies. Gallion, and colleagues 2006, retrospectively correlated the results of ChemoFx assay to progression free interval (PFI) in a case series of 304 patients with ovarian or peritoneal carcinoma. The study was a case series with potential selection and observational biases. It was not blinded, had no comparison group, and while selection of chemotherapy was at the discretion of the treating physician, some used the results of the assay to help determine the appropriate regimen. Overall, the results of show that 256 cases had an exact or partial match between drugs assayed and received, and 135 cases had an exact match. In the latter group the median PFI was 9 months for patients treated with drugs assayed as resistant, 14 months for those treated with drugs assayed as intermediate and had not been achieved (during study period) for those with drugs assayed as sensitive. The calculated hazard ratio for progression of the resistant group vs. the sensitive group was 2.9 (95% CI: 1.4-6.3), and that of the intermediate vs. sensitive group was 1.7 (95% CI; 1.2-2.5). Clinical utility: The literature search did not identify any published randomized or nonrandomized controlled trials that evaluated the effect of ChemoFx testing on individualizing chemotherapeutic regimen and /or its impact on survival. Other observational non-comparative prospective studies examining the outcomes associated with the use ChemoFx are underway. Conclusion: There is insufficient evidence to date to determine the clinical validly and utility of ChemoFx in selecting the most appropriate chemotherapy regimens and improving survival of cancer patients.
Articles: The published literature on ChemoFx® is very limited. There were only two case series (N=304, and N=18) that retrospectively evaluated the predictive value of ChemoFx assay by correlating its results with progression free interval (PFI) in patients with ovarian cancer, and another small case series among 34 women with breast cancer, that correlated the pathological complete response to a neoadjuvant chemotherapy with the results of ChemoFx® testing. As regards the clinical utility of the test, the literature search did not reveal any randomized or non-randomized controlled trials that compared outcomes among patients managed with and without ChemoFx® testing. The larger case series on the predictive value of ChemoFx was critically appraised Gallion H, Christopherson WA, Coleman RI, et al. Progression –free interval in ovarian cancer and predictive value of an ex vivo chemo responsive assay. Int J Gynecol Cancer 2006;16:194-201. See Evidence Table

The use of ChemoFx Assay for predicting response of solid tumors to chemotherapeutic agents does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Cytochrome P450 Genotyping Test Drug Metabolizing
BACKGROUND
Pharmacogenetics is the study of the genetic causes of individual variation in drug response. There has been growing interest in the use of pharmacogenetics to predict response to medications in terms of safety and efficacy. Cytochrome P450s, in particular CYP3A4, CYP2D6, CYP2C19, CYP1A2, and CYP2B6, have a central role in the metabolism of many clinically used drugs. Genetic polymorphisms in the cytochrome P450 enzymes may help to explain the observed variation in the concentrations of certain drugs and their metabolites. Genetic variability can significantly affect drug metabolism and lead to distinct subgroups of the populations that differ in their ability to metabolize various drug. The resulting phenotypes are poor metabolizers (PM), intermediate metabolizers (IM), extensive metabolizers (EM), and ultra-rapid metabolizers (UM). Clinically, the most important phenotypes are ultra-rapid metabolizers and poor metabolizers. Subjects who possess the ultra-rapid metabolizer phenotype may

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experience a reduced response to standard doses of medications because their ability to rapidly metabolize these medications makes it difficult to sustain therapeutic levels. They are also more likely to suffer from adverse drug reactions due to the formation of toxic metabolites and excess levels of the active drug. Because poor metabolizers have low metabolic capacity, usual doses may lead to higher than expected drug concentrations, placing them at increased risk for adverse drug reactions. Additionally, PM may not respond to drugs that require activation by the enzyme in question (Ingelman-Sunberg 2010). It is thought that knowledge of the genetic metabolizer status may enable physicians to more accurately identify the appropriate drug and/or drug dose that maximizes efficacy and minimizes toxicity in each individual patient. The AmpliChip test uses microarray DNA chip technology developed by Affymetrix. The microarray chip is similar to a computer microchip, but instead of circuits, the microarray chip contains millions of DNA fragments, called probes, that are chemically synthesized at precise locations on the coated quartz surface. The genetic test is performed by extracting DNA from the patient's blood. Prepared DNA samples are applied to the array and matched to the sequence of the probe molecules. The AmpliChip cytochrome P450 genotyping test was cleared for marketing by the FDA in December 2004. It is the first FDA-approved laboratory gene test to evaluate genetic information for medication selection.

PLAVIX In the Unites States, cardiovascular disease is the leading cause of death in both men and women (Heron 2009). Clinical trials have shown that clopidogrel (Plavix), an anti-blood clotting medication, reduces the morbidity and mortality associated with several cardiovascular diseases. However, there is a significant amount of inter-individual variability in clopidogrel responsiveness, which leads some patients to experience decreased platelet inhibition (poor response) with clopidogrel (Momary 2010b). It is thought that the primary source of variability in clopidogrel responsiveness lies in the pharmacokinetics of clopidogrel. Clopidogrel is a pro-drug that is metabolized into its active metabolite through the action of several enzymes (CYP2C19, CYP1A2, CYP3A4, CYP3A5, and CYP2B6). A polymorphism in any of the enzymes could result in decreased responsiveness. One of the enzymes associated with clopidogrel non-responsiveness is CYP2C19. Patients with the wild-type CYP2C19*1 allele have normal metabolic activity. However, four variant CYP2C19 alleles are associated with reduced metabolic activity. Drug interactions, clinical factors, such as diabetes and increased weight, and patient non- compliance are other proposed mechanisms of clopidogrel non-responsiveness. The prevalence of clopidogrel resistance varies from 3-30% (Momary 2010a, Momary 2010b, Ma 2010). On March 12th, 2010, the FDA added a boxed warning to the label for clopidogrel to alert healthcare professionals and patients of the reduced effectiveness of clopidogrel for patients who are poor metabolizers and includes information on the role of CYP2C19 genotype in clopidogrel responsiveness. There has been growing interest in the use of CYP2C19 genotyping to identify patients who are non-responsive to clopidogrel. The AmpliChip CYP450 Test (Roche Diagnostics Inc, Indianapolis, IN) has received FDA approval for CYP2C19 genotyping.

TAMOXIFEN Aside from non-melanoma skin cancer, breast cancer is the most common form of cancer in women. It is the number one cause of cancer death in Hispanic women, and the second leading cause of cancer death in white, black, Asian/Pacific Islander, and American Indian/Alaska Native women (CDC 2010). Tamoxifen is used as an adjuvant endocrine therapy to prevent estrogen receptor-positive breast cancer recurrence, as a treatment for metastatic breast cancer, and to prevent disease in high-risk women with ductal carcinoma in situ (Lash 2009). Tamoxifen is a "pro-drug", several enzymes (CYP2B6, CYP2C8, CYP2C9, CYP2C10, CYP3A4, CYP3A5, and CYP2D6) transform the pro-drug into its active metabolites 4-hydroxytamoxifen (4-OH tamoxifen) and 4-hydroxy-N-desmethyltamoxifen (endoxifen). Research indicates that both endoxifen and 4-OH tamoxifen have nearly 100-fold higher affinity for estrogen receptors than tamoxifen; however, endoxifen is found at a 6 to 12 fold higher concentration than 4-OH tamoxifen. Every secondary tamoxifen metabolite except for endoxifen is formed by two enzymes CYP3A4 and CYP3A5. Endoxifen production is almost totally dependent on the enzymatic activity of CYP2D6. In vivo studies suggest that endoxifen is the major active metabolite of tamoxifen (Higgins 2009). The observed variation in the concentrations of tamoxifen and its metabolites might be explained through genetic polymorphisms in the genes that encode the CYP2D6 enzyme. There are more than 100 allelic variants of CYP2D6 with incidence varying according to race and ethnicity. The most prevalent allele is the wild-type allele CYP2D6*1. Patients with two copies of this allele produce an enzyme with normal activity. Because individuals have two CYP2D6 alleles, various combinations of the alleles result in a spectrum of CYP2D6 function ranging from no activity to increased activity. In the Caucasian population, approximately 5-10% of patients are poor metabolizers and 10-15% of patients are intermediate metabolizers of tamoxifen. It is thought that tamoxifen- treated patients who are poor metabolizers and intermediate metabolizers are at an increased risk for recurrence (Dezentjé 2009, Higgins 2009, Lash 2009). CYP2D6 inhibiting drugs, such as SSRIs, may also decrease tamoxifen metabolism (Lash 2009). Due to the association between tamoxifen metabolism and the CYP2D6 genotype, there is growing interest in the use of CYP2D6 genotyping to direct treatment for patients with breast cancer. *Atomoxetine* Atomoxetine is a norepinephrine reuptake inhibitor that is used to treat attention-deficit hyperactivity disorder (ADHD). Atomoxetine is metabolized via the CYP2D6 enzyme and has a broad therapeutic window. Currently,

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dosing is determined by the patient's weight with dose adjustments according to clinical response and adverse effects. Studies have suggested that in PM the plasma concentration of atomoxetine is higher and the half-life is longer compared to EM (Michelson 2007). *Codeine for nursing mothers*
Opioid analgesics, such as codeine, are commonly used for pain relief in labor and postpartum. Codeine is a pro-drug that is predominantly metabolized by the CYP2D6 enzyme into morphine. While codeine is effective for the majority of individuals, a subset of patients, CYP2D6 poor metabolizers, do not possess any active gene copies and experience poor analgesia due to the deficient formation of the active metabolite (morphine). Additionally, approximately 2-40% of individuals (depending on ethnic background) are ultra-rapid metabolizers and possess functional duplications of the CYP2D6 gene. These duplications lead to enhanced biotransformation of codeine into morphine and have been associated with adverse effects including death in breastfed infants (Madadi 2009a, Alfirevic 2010). *Efavirenz* Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI). Treatment with efavirenz plus two nucleoside reverse transcriptase inhibitor (NRTI) is recommended among the first line regimens in patients initiating highly active antiretroviral therapy (HAART). In addition, efavirenz is used with other antiretroviral agents as a part of post exposure prophylaxis regimen to prevent HIV transmission. Efavirenz is metabolized primarily by CYP2B6 with partial involvement from CYP3A4 and CYP2A6. It is hypothesized that polymorphisms in these genes may contribute to interindividual differences in efavirenz plasma concentration and half-life. Studies have found that poor metabolizers were at greater risk of high plasma levels of efavirenz. It had been suggested that high plasma levels may be associated with central nervous system (CNS) side effects, such as abnormal dreams, dizziness, somnolence, insomnia, and impaired concentration (Rakhmanina 2010, Tozzi 2010). *Proton pump inhibitors (PPI) for treating Helicobacter pylori* H. pylori infection is closely related to many gastrointestinal diseases, including gastritis, peptic ulcer disease, and gastric cancer. Eradication of H. pylori is important for reducing the relapse rate of ulcers and the risk of gastric cancers. Current treatment for the eradication of H. pylori consists of a PPI and two antibiotics (amoxicillin and either clarithromycin or metronidazole). The majority of proton pump inhibitors are metabolized primarily by the CYP2C19 enzyme. PPIs work by raising the intragastric pH, which increases the stability and bioavailability of antibiotics making them more effective. Factors associated with treatment failure include, but are not limited to: antibiotic resistance, non- compliance, smoking habits, bacterial and host-related factors, and CYP2C19 genotype (Yang 2010, Sugimoto 2009). *Immunosuppressants for organ transplant*
Immunosuppressant drugs are used in transplant patients to prevent rejection. Regimens usually include a combination of different drugs. Immunosuppressants have a narrow therapeutic range. Overdosing can lead to infection, malignancy, and organ toxicity, whereas under dosing can lead to rejection. The current approach to prevent over- or under dosing is therapeutic drug monitoring where blood or plasma concentrations are measured and dosage is adjusted to ensure that drug concentrations remain within a narrow therapeutic range. The first 72 hours after transplantation is the most critical time as inadequate drug exposure increases the risk for rejection. Therapeutic drug monitoring is not useful for predicting the initial dose.
Thus, there has been growing interest in using a pharmacogenetic approach to predict initial dose. Tacrolimus is a calcineurin inhibitor that is metabolized by CYP3A5 and CYP3A4. Patients with a functional copy of the CYP3A5 enzyme are referred to as functional expressers; patients without a functional copy of the CYP3A5 enzyme are referred to as functional non-expressers. CYP3A5 expression is thought to be associated with reduced tacrolimus exposure following oral administration, thus patients who are functional expressers may be more likely to experience rejection (Ware 2010, Staatz 2010). *Selective serotonin reuptake inhibitors (SSRIs)*
SSRIs are a popular class of antidepressant medications. CYP2D6 and CYP2C19 are the primary CYP450 enzymes involved in the metabolism of SSRIs. Other CYP450 and non-CYP450 enzymes also play a role in the metabolism of some SSRIs. It is thought that polymorphisms in the CYP450 enzymes can lead to variability in response to some SSRIs. Knowing a patients genotype may be helpful in choosing an initial SSRI that is more likely to be effective (Berg 2007).

10/03/2005: MTAC REVIEW
Cytochrome P450 Genotyping Test Drug Metabolizing
Evidence Conclusion: There is no published evidence on using the AmpliChip cytochrome P450 genotyping test to help select medications or doses of medications. The ideal study would compare the safety and effectiveness of medications selected with and without the results of the AmpliChip cytochrome P450 genotyping test, preferably in a randomized trial. This type of study has not been published.
Articles: No empirical studies were identified that reported on medication selection using the AmpliChip test, or clinical outcomes following medication selection guided by the AmpliChip test. Several articles on the Affymetrix GeneChip were identified, but none of the mentioned using the technology with the AmpliChip test. In addition, the studies on the Affymetrix GeneChip used it for genetic profiling (e.g., to estimate prognosis of colon cancer patients), not to aid physicians in the selection of medications.

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The use of in the evaluation of does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

08/16/2010: MTAC REVIEW
Cytochrome P450 Genotyping Test Drug Metabolizing Evidence
Conclusion: *Plavix:* Analytic validity
No published studies on the accuracy of commercially available tests for detecting CYP2C19 variants were identified. Clinical validity A recent meta-analysis investigated the relationship between CYP2C19*2 polymorphisms and adverse clinical outcomes in patients with coronary artery disease (CAD) being treated with clopidogrel. Results from this analysis showed that the presence of the CYP2C19*2 allele was associated with an increased risk of a subsequent cardiovascular event (RR 1.96, p=0.02) and stent thrombosis (RR 3.82, p<0.01). There was significant heterogeneity between the studies. Studies varied with regard to clopidogrel dose, duration of follow-up, and patient type. Additionally, not all studies adjusted for confounding factors. Because only one CYP2C19 variant was studied misclassification is possible (Sofi 2010). While the majority of data suggest that patients possessing at least one variant CYP2C19 allele are at an increased risk for adverse cardiovascular events, not all studies have found this association. A genetic sub-study of the Impact of the Extent of Clopidogrel- Induced Platelet Inhibition on Clinical Event Rate (EXCELSIOR) study, found that the CYP2C19 genotype was not associated with risk of death or myocardial infarction (MI); however, increased platelet reactivity was associated with the risk of death or MI and patients with at least one CYP2C19*2 allele had increased platelet reactivity. The study was not powered to address this issue (Trenk 2008). Clinical utility No published studies were identified that prospectively compared patient outcomes managed with and without CYP2C19 genotyping. Conclusion: Analytic validity: There is insufficient evidence to determine whether CYP2C19 genotyping assays accurately and reliably detect variant CYP2C19 alleles. Clinical validity: There is insufficient evidence to determine whether the presence of CYP2C19 variant genotypes predict clinical outcomes. Clinical utility: There is insufficient evidence to determine if using CYP2C19 gene testing for predicting clopidogrel responsiveness will improve clinical outcomes.
Tamoxifen: Analytic validity No published studies on the accuracy of commercially available tests for detecting CYP2D6 variants were identified. Clinical validity the results of the published studies on the clinical validity of CYP2D6 gene testing for tamoxifen metabolism were conflicting. Goetz et al conducted a retrospective review of archived sample of patients from the North Central Cancer Treatment Group RCT (89-30-52) tamoxifen only arm. The objective of this study was to determine the effect of CPY2D6 metabolism on breast cancer recurrence and survival. By taking into account genotype and CYP2D6 inhibitor use, patients were classified as either poor metabolizers, intermediate metabolizers, or extensive metabolizer (normal). When extensive metabolizers were compared to decreased metabolizers (intermediate and poor metabolizers), patients with decreased metabolism had significantly shorter time to recurrence (p=0.034), relapse-free survival (p=0.017), and disease-free survival (p=0.027). Overall survival did not differ significantly between extensive and decreased metabolizers. When poor metabolizers were compared to extensive metabolizers, poor metabolizers had significantly shorter time to recurrence (p=0.007), relapse-free survival (p=0.005), and diseases-free survival (p=0.008) than extensive metabolizers. Overall survival did not differ significantly between poor and extensive metabolizers. There was no significant difference in any of the measures of recurrence or survival between intermediate and extensive metabolizers. The major advantage of this study is that is accounted for CYP2D6 inhibitor use. One of the limitations of this study is that there were only sixteen poor metabolizers and forty intermediate metabolizers. Because of the small number of subjects, the study may lack the power to detect significant differences. Also, the study only accounts for one CYP2D6 variant. Because only one variant was studied there is the possibility for misclassification (Goetz 2007). A retrospective analysis of 1,325 subjects from German and U.S. cohorts found that patients with reduced or absent CYP2D6 function had significantly shorter time to recurrence, event-free survival, and disease-free survival compared to extensive metabolizers. There was no difference in overall survival between decreased and extensive metabolizers. Patients from the 89-30-52 trial, the same population studied by Goetz, were included in this analysis. One of the limitations of the study was that the cohorts that were combined had different lengths of follow-up. Additionally, the study did not account for CYP2D6 inhibitor use. Advantages of this trial include its size and that it accounted for 5 different variant alleles (Schroth 2009). Another retrospective cohort study also found that relapse-free survival and event-free survival were significantly poorer for decreased metabolizers compared to extensive metabolizers (Schroth 2007). Not all studies have shown an association between CYP2D6 metabolism and treatment outcomes. Nowell and colleagues conducted a retrospective review of 337 archived samples. The objective of this study was to determine whether genetic variability in the tamoxifen metabolic pathway influenced overall survival in breast cancer patients treated with tamoxifen. In the study, extensive metabolizers were compared to decreased metabolizers (intermediate and poor metabolizers). Relapse- free and overall survival did not differ significantly between extensive and decreased metabolizers. One of the limitations of the study was that the authors did not control for CYP2D6 inhibitor use. Because of the small number of subjects the study may lack

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power to detect significant differences. There is a potential for misclassification as only one CYP2D6 allele was accounted for. Additionally, the effects of CYP2D6 genotype on tamoxifen metabolism were not assessed separately for poor and intermediate metabolizers (Nowell 2005). Clinical utility
No published studies were identified that prospectively compared patient outcomes managed with and without CYP2D6 genotyping. Conclusion: Analytic validity: There is insufficient evidence to determine whether CYP2D6 genotyping assays accurately and reliably detect variant CYP2D6 alleles. Clinical validity: There is insufficient evidence to determine whether the presence of CYP2D6 variant genotypes predict clinical outcomes.
Clinical utility: There is insufficient evidence to determine if using CYP2D6 gene testing for predicting tamoxifen metabolism will improve clinical outcomes.
Articles: *Plavix:* Assessment objective: Analytic validity: Do the CYP2C19 genotyping assays accurately and reliably detect variant CYP2C19 alleles? Clinical validity: Does the presence of CYP2C19 variant genotypes predict clinical outcome? Clinical utility: Will the results of the CYP2C19 genotype assay alter clinical management and improve clinical outcomes? Medline was searched through June 2010 with the search terms *clopidogrel*, *Plavix*, and *CYP2C19* with variations. The search was limited to English language publications and human populations. The reference lists of relevant studies were reviewed to identify additional publications. Sofi F, Giusti B, Marcucci R, et al. Cytochrome P450 2C19*2 polymorphism and cardiovascular recurrences in patients taking clopidogrel: a meta-analysis. *Pharmacogenomics J 2010;* 30 March 2010. [Epub ahead of print] See Evidence Table *Tamoxifen:* Assessment objective: Analytic validity: Do the CYP2D6 genotyping assays accurately and reliably detect variant CYP2D6 alleles? Clinical validity: Does the presence of CYP2D6 variant genotypes predict clinical outcome? Clinical utility: Will the results of the CYP2D6 genotype assay alter clinical management and improve clinical outcomes? No randomized controlled trials were identified. The literature consisted mainly of retrospective case series and cohort studies. The results from the studies evaluating the association between tamoxifen metabolism and breast cancer recurrence and survival were conflicting, with some showing a positive association and some showing a negative association. The study by Goetz et al was selected because it took into account CYP2D6 inhibitor use. Goetz MP, Knox SK, Suman VJ, et al. The impact of cytochrome P450 2D6 metabolism in women receiving adjuvant tamoxifen. Breast Cancer Res Treat 2007; 101:113-121. See Evidence Table U.S. Cancer Statistics Working Group. United States Cancer Statistics: 1999–2006 Incidence and Mortality Web-based Report. Atlanta (GA): Department of Health and Human Services, Centers for Disease Control and Prevention, and National Cancer Institute; 2010. Available at: http://www.cdc.gov/uscs.

The use of in the evaluation of Plavix and Tamoxifen metabolization does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

12/20/2010: MTAC REVIEW
Cytochrome P450 Genotyping Test Drug Metabolizing
Evidence Conclusion: *Atomoxetine* The literature search did not reveal any studies pertaining to the analytic validity or clinical utility of CYP2D6 genotyping to predict response to atomoxetine. Several studies were found that combined data from various clinical trials to address the clinical validity of CYP2D6 genotyping. The results from these studies are presented below. Michelson et al combined data from multiple studies to examine the effect of CYP2D6 on the efficacy and safety of atomoxetine. Efficacy data was available for 589 patients (559 EM and 30 PM). The primary outcome measure was defined as a ≥25% decrease in ADHD total symptoms measured using the Attention-Deficit Hyperactivity Disorder Rating Scale-Parent Version: Investigator Scored and Administered (ADHDRS-IV-Parent:Inv). Significantly more PM than EM responded to treatment (80% vs. 59.4%, P=0.033). However, PM were more likely to experience insomnia (P=0.035), abrasion (P=0.012), tremor (P<0.001), and decreased appetite (P=0.008) compared to EM. Limitations: small sample size, power was not addressed, not controlled for concomitant medications or other confounding factors, subjects were grouped into either PM or EM, included studies differed with regard to dosing and follow-up, and the research was funded by Eli Lilly (Michelson 2007). Another study combined data from two clinical trials to determine the effect of CYP2D6 genotype on the efficacy and tolerability of atomoxetine. Data was available for 1,326 patients (1,239 EM and 87 PM). Unlike the Michelson study, Trazepacz and colleagues did not find a significant difference in response, defined as a ≥25% decrease in the ADHDRS-IV-Parent:Inv, between PM and EM (84.9% vs. 81.6%, P=0.56). There were no significant differences in adverse events or treatment discontinuation. Limitations: power was not addressed, not controlled for concomitant medications or other confounding factors, subjects were grouped into either PM or EM, and the research was funded by Eli Lilly (Trzepacz 2008). Ramoz and colleagues combined data from two cohort studies and also found no significant difference in treatment response, defined as a ≥25% decrease in the ADHDRS-IV-Parent:Inv, between PM and EM (Ramoz 2009). Codeine for nursing mothers No randomized controlled trials or cohort studies were identified pertaining to the analytic validity, clinical validity, or clinical utility of genotyping nursing

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mothers for CYP2D6 status before prescribing codeine. The literature search revealed one case-control study with 17 infants with symptoms of opioid toxicity, central nervous system (CNS) depression, and 55 infants without symptoms of opioid toxicity following exposure to codeine while breastfeeding. Findings from this study indicate that there was good concordance between maternal and infant CNS depression. When the baby exhibited CNS depression, there was a 71% probability (12/17) that the mother also exhibited such signs.
Mothers of symptomatic infants were 8 times more likely to have the combined CYP2D6 UM and UGT2B7*2 genotype. UGT2B7*2 is also associated with higher production of the active morphine metabolite. Results from this analysis are inconclusive as there were only 2 women with the combined genotype (Madadi 2009b).
Efavirenz No studies were identified that addressed the analytic validity or clinical utility of genotyping to predict dosing of efavirenz. The literature pertaining to clinical validity consisted mainly of small cohort studies. Several small studies have demonstrated an association between CYP2B6 poor metabolizers and efavirenz plasma concentration. However, the number of poor metabolizers included in these studies ranged from 6 to 14. Additionally, not all individuals who were poor metabolizers had higher plasma concentrations (Haas 2004, Gatanaga 2007, Leger 2009). CYP2B6 polymorphisms are not the only factors that affect plasma levels, other drugs and enzymes may also predict efavirenz plasma concentration. To date there is insufficient evidence regarding the effects of CYP2B6 polymorphisms on clinical outcomes such as long-term virological and immunological response to efavirenz therapy. Proton pump inhibitors The literature search revealed several studies pertaining to the clinical validity of genotyping to predict response to proton pump inhibitors. The majority of these studies were small and performed in Asian populations, which are known to have a higher percentage of CYP2C19 poor metabolizers, as such the results may not be generalizable to other populations. A small randomized controlled trial was identified that compared *H. pylori* eradication rates in patient receiving rabeprazole with different antibiotic regimens was not selected for review as it did not have adequate power to address differences in eradication rates by CYPC19 metabolizer status (Yang 2009). A meta-analysis of 20 observational studies was selected for review (Zhao 2008). No studies were identified that addressed the analytic validity or clinical utility of genotyping to predict response to proton pump inhibitors. The objective of the meta-analysis was to determine whether CYP2C19 polymorphisms affect *H. pylori* eradications rates obtained with first-line PPI- based triple therapies. Eradication rates using the PPI lansoprazole and omeprazole were significantly higher for PM and IM compared to EM; however, there was no significant difference between PM and IM. There was no significant difference in eradication rates among the three genotypes for therapies using the PPI rabeprazole. The studies included in this analysis were mostly observations and thus are more prone to bias and confounding.
Studies using difference antibiotic combinations were analyzed together. Additionally, other factors such as antibiotic resistance rates may affect *H. pylori* eradication rates (Zhao 2008). Not all studies have found an association between CYP2C19 genotype and *H. pylori* eradication rates. A cohort study conducted in Korea that included 174 subjects and was published after the meta-analysis found no significant difference in eradication rates by CYP2C19 genotype for patient treated with pantoprazole, amoxicillin, and clarithromycin twice daily. As this study was not randomized it may be prone to bias. There were only 39 poor metabolizers included in the study, so it may lack the statistical power to detect a difference between the CYP2C19 genotypes (Oh 2009).
Immunosuppressant for organ transplantation The literature search did not reveal any studies addressing the analytic validity of genotyping to predict response to tacrolimus. With regard to clinical validity, several cohort, case-control, and cross sectional studies were identified that looked at the effect of CYP3A5 polymorphisms on tacrolimus concentrations. A prospective cohort study was selected for review (Hesselink 2008). One randomized controlled trial was identified that addressed the clinical utility of genotyping to predict initial does; however, this study was not selected for review as patients were genotyped after transplantation and tacrolimus was not initiated until 7 days after transplantation (Thervet 2010). RCT are currently underway to determine the efficacy of genotype guided initial dosing. A recent prospective cohort study compared the effect of CYP3A5 genotype on (weight-adjusted) tacrolimus exposure and dose, as well as the incidence of acute rejection after kidney transplantation. Results from this study suggest that CYP3A5 expressers require higher drug doses than non-expressers to reach target pre-dose concentrations. The overall daily tacrolimus dose was 60% higher for CYP3A5 expressers compared to non-expressers (95% CI, 35-89%, P<0.001). Additionally, significantly more CYP3A5 expressers had a pre-dose concentration below 10 ng/ml, which is the recommended minimum pre-dose concentration in the early phase after transplantation, compared to non-expressers on day 3 after transplantation (28 vs. 10%, P=0.02). On study day 10 and thereafter pre-dose concentration was comparable between the two groups. There was no statistically significant difference in the incidence of biopsy-proven acute rejection (P=0.36) (Hesselink 2008). A prospective study of 44 renal transplant patients also failed to find an association between genotype and risk of rejection; however, this study did find that CYP3A5 expressers required a higher dose of tacrolimus to reach target concentrations (Roy 2006). It should be noted that the pharmacogenetics of tacrolimus are complex. Other factors such as genetic polymorphisms in drug transporters, differences between the donor organ and recipient's intestinal

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genotype, and drug interactions may all contribute to differences in the pharmacogenetics of tacrolimus. Selective serotonin reuptake inhibitors (SSRIs) The literature search revealed several case-control and cohort studies pertaining to the clinical validity of genotyping patients to predict their response to SSRIs. No studies were identified that addressed analytic validity or clinical utility. In general, studies of clinical validity were limited by inadequate power, poor and intermediate metabolizers were analyzed together, studies grouped different SSRIs together or with other classes of antidepressant medications, and studies did not provide information on variables such as diet, other medications, race/ethnicity, and other genetic factors that may influence SSRI efficacy and tolerability. The majority of studies evaluating the clinical validity of genotyping patients to predict their response to SSRIs found no association between genotype and adverse drug reactions (Murphy 2003, Roberts 2004, Suzuki 2006, Peters 2008). One study did find an association between genotype and the occurrence of adverse events; however, there were only 8 (29%) poor metabolizers and 3 (19%) UM included in the study (Rau 2004). Conclusion**:** There is insufficient evidence to determine the analytic validity, clinical validity, or clinical utility of genotyping for the following indications: Atomoxetine (dosing), Codeine (deciding whether to prescribe codeine for nursing mothers), Efavirenz (dosing), *Helicobacter pylori* (managing treatment), Immunosuppressant for organ transplantation (dosing), Selective serotonin reuptake inhibitors (selection or dosing)
Articles: There is limited evidence pertaining to the analytic validity, clinical validity, and clinical utility of CYP450 genotyping. The majority of studies identified were small observational studies that addressed the association between CYP450 genotype and intermediate outcomes. A prospective cohort study that evaluated the effect of CYP3A5 genotype on tacrolimus exposure, dose, and incidence of acute rejection, and a meta-analysis that looked at the association between CYP2C19 polymorphisms and H. pylori eradication rates were selected for review. The following studies were critically appraised: Zhao F, Wang J, Yang Y, et al. Effect of CYP2C19 genetic polymorphisms on the efficacy of proton pump inhibitor-based triple therapy for Helicobacter pylori eradication: a meta-analysis. Helicobacter 2008; 13:532-541. See Evidence Table Hesselink DA, van Schaik RHN, van Agteren M, et al. CYP3A5 genotype is not associated with a higher risk of acute rejection in tacrolimus-treated renal transplant recipients. Pharmacogenetic Genomics 2008; 18: 339-348. See Evidence Table

The use of in the evaluation of Atomoxetine, Codeine for nursing mothers, Efavirenz, Proton pump inhibitors (PPI) for treating Helicobacter pylori, Immunosuppressants for organ transplant, and selective serotonin reuptake inhibitors (SSRIs) metabolization does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

02/13/2012: MTAC REVIEW
Cytochrome P450 Genotyping Test Drug Metabolizing
Evidence Conclusion: Analytic validity No published studies on the accuracy of commercially available tests for detecting CYP2C19 variants were identified. Clinical validity Results from the 2010 MTAC review were based on a meta-analysis that included 7 cohort studies. Results from the meta-analysis showed that the presence of CYP2C19*2 allele was associated with an increased risk of a subsequent cardiovascular event (RR 1.96, p=0.02) and stent thrombosis (RR 3.82, p<0.01); however, there was significant heterogeneity between the studies. Studies varied with regard to clopidogrel dose, duration of follow-up, and patient type. Because of this, it was determined that there was insufficient evidence to determine whether the presence of CYP2C19 variant genotypes predict clinical outcomes (Sofi 2011). Results from both of the most recent meta-analyses suggest that there is no significant association between major cardiovascular events and CYP2C19 genotype. Both studies also found some evidence that the loss of function genotype may be associated with stent thrombosis; however, the quality of this evidence is weak due to evidence of publication bias. Meta-analyses are only as good at the studies that they include. The majority of the studies included in these analyses were small, there was variation between the studies with regard to the components of the primary endpoint, and misclassification is possible as not all alleles were typed (Bauer 2011, Holmes 2011).Clinical Utility No published studies were identified that prospectively compared patient outcomes managed with and without CYP2C19 genotyping.
Articles: The literature consisted mainly of cohort studies and genetic sub-studies of randomized controlled trials. No studies were identified that examined the analytic validity of CYP2C19 genotyping. Several meta-analyses were identified that evaluated the association between CYP2C19 and the clinical efficacy of clopidogrel. However, only 2 of these analyses included additional studies that were not included in the 2010 MTAC review. Both of these meta-analyses were selected for review. Several studies were identified that looked at the effect of higher doses of clopidogrel or other medications on platelet reactivity in patients with the CYP2C19 loss of function genotype; however, since platelet reactivity is an intermediate marker, none of these studies were selected for review. No studies were identified that looked at the effect of CYP2C19 genotyping on long term clinical outcomes such as major cardiovascular events. The following studies were critically appraised:
Bauer T, Bouman HJ, van Werkum JW, Ford NF, ten Berg JM, Taubert D. Impact of CYP2C19 variant genotypes

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on clinical efficacy of antiplatelet treatment with clopidogrel: systematic review and meta-analysis. *BMJ.* 2011;343:d4588. See Evidence Table Holmes MV, Perel P, Shah T, Hingorani AD, Casas JP. CYP2C19 genotype, clopidogrel metabolism, platelet function, and cardiovascular events: a systematic review and meta-analysis. *JAMA.* 2011;306:2704-2714. See Evidence Table

The use of in the evaluation of Plavix and Tamoxifen metabolization does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

EndoPredict

BACKGROUND

Breast cancer is the most common cancer diagnosed and the second most common cause of cancer death in women in the United States. Patients with breast cancer can present with a variety of symptomatology that originates from heterogeneous molecular pathology (Dowsett et al., 2010). Breast cancer can be staged using the Tumor, Node, Metastases classification (TNM). The treatment of invasive breast cancer is based on the stage and involves radiation, surgery, and adjuvant therapy. The management based on adjuvant therapy derives from many factors such as the TNM characteristics, the grade, the presence or absence of estrogen and progesterone receptors, and the human epidermal growth factor 2 (HER2) receptor. However, some patients are still mistreated. Molecular tests that can predict the prognosis and the response to adjuvant therapy might accurately evaluate the recurrence risk and impact disease management. The literature has described several molecular tests including the EndoPredict test. Based on the manufacturer, a tumor section from the FFPE block is needed to perform the test. The tissue collected is treated and the RNA is isolated. The reverse transcription and quantitative PCR are performed, and the levels of gene expression are measured. These genes include eight disease-genes and four reference genes. Results are exported from the EP device into the EP software which generates EP scores and classifies patients into low or high risk of distant metastasis within 10 year. The EP score is a number that ranges from 0 to 15; EP score ≤ 5 is indicative of low distant recurrence risk under endocrine therapy; EP score > 5 indicates high distant recurrence risk. The molecular features are coupled with clinicopathological parameters including tumor size and nodal status to determine the EPclin score. The test is believed to predict distant metastasis in ER-positive, HER2-, node negative or node positive breast cancer treated with endocrine treatment alone (Kronenwett et al., 2012). It is also believed that it can be performed in decentralized laboratories (Denkert et al., 2012; Kronenwett et al., 2012).

06/05/2017: MTAC REVIEW

EndoPredict

Evidence Conclusion: Analytical validity: Three studies were identified (Denkert et al., 2012; Kronenwett et al., 2012; Varga et al., 2013). Two were validation studies and one was a retrospective comparison between EndoPredict and the Oncotype Dx. Patients were ER+, HER2-. Sample size ranged from 10 to 34. The majority of the sample was node negative in two studies; node status is unknown in the second study. The studies show that EndoPredict test is reproducible (correlation coefficient: 0.994 to 0.995). The test is also reliable (variance of EP scores 0.15 for proficiency test to 0.18 in an independent lab). Sensitivity and specificity were evaluated in one study and were 100% (Denkert et al., 2012). Analytical accuracy was evaluated in one study (Kronenwett et al., 2012) and found that the difference between reference EP scores and reported EP scores was less than 1.0 EP units for 9 out of 10 samples with mean deviation of 0.15. The study that compared EndoPredict to Oncotype Dx showed moderate positive linear correlation and concordance between these tests.
Nevertheless, the results should be interpreted with caution due to the small sample size, and financial ties between authors and Sividon, the reference laboratory. In light of these limitations, the studies provide low to moderate evidence to support the reproducibility and reliability of the test. **Clinical validity:** Seven studies (Bertucci, Finetti, Viens, & Birnbaum, 2014; Buus et al., 2016; Dubsky, Filipits, et al., 2013; Filipits et al., 2011; Fitzal et al., 2015; Martin et al., 2014; Martin et al., 2016) were identified. The studies were retrospective-prospective in design. Patients were ER+, HER2-, LN- or LN+, treated with endocrine therapy alone or chemotherapy or chemotherapy followed by endocrine therapy. Sample size was up to 1702 patients and age ranged from 23-80 years. Patients were postmenopausal women in four studies. Most of these studies were conducted in Europe. The primary outcome was the assessment of prognostic performance of EndoPredict test. The prognostic performance was evaluated by assessing distant recurrence, or metastasis-free survival (MFS), or distant-relapse free survival (DRFS). One study (Bertucci et al., 2014) assessed the predictive value of the test; another study compared EP versus Oncotype Dx (Buus et al., 2016). These studies demonstrate that the EndoPredict test is highly prognostic of distant recurrence or metastasis-free survival. Based on Simon et al. 2009 (Simon, Paik, & Hayes, 2009), the studies provide level IB

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evidence. However, limitations include one or more of the following: lack of data on premenopausal women, lack of assessment of the predictive value of the test, low to moderate quality trials, clinicopathological factors varied between studies, small sample size, financial ties with manufacturer, and low events suggesting an overestimation of the prognostic performance. **Clinical utility:** One retrospective study (Muller et al., 2013) with 167 patients reported that EP may change treatment decision in ER+, HER2-, LN+/LN- breast cancer patients. The change in treatment decision occurred in 38% of patients with 25% changed to endocrine treatment alone. The main limitations include the retrospective nature of the study.

Other studies:

Author, year	Findings
(Dubsky, Brase, et al., 2013)	HR: 2.80 (1.81–4.34) P<0.001 first 5 years HR: 3.28 (1.48–7.24) P=0.002 after 5 years EP is highly prognostic of distant recurrence
(Muller et al., 2012)	Correlation r=0.92 between biopsies and surgical specimens

Conclusion

- Analytic validity: Three studies with low to moderate evidence show that EndoPredict may be reproducible and reliable in ER+, LN-, or LN+ breast cancer patients.
- Clinical validity: Seven studies with level IB evidence show that EndoPredict test may be prognostic of distant recurrence in ER+, LN-, or LN+ breast cancer patients. In addition, studies assessing the predictive value of the test are lacking and women who benefit from chemotherapy are unknown.
- Clinical utility: One study, that provides low evidence, assessed the impact of EndoPredict on treatment decision; thus there is insufficient evidence to recommend for or against the clinical utility of the test.
- Based on one study, EP may be more prognostic than Oncotype Dx.

Articles: PubMed was searched through March 28, 2017 with the search terms EndoPredict with variations. The search was limited to English language publications and human populations. The reference lists of relevant studies were reviewed to identify additional publications. A total of 14 studies were identified; however, 12 studies were reviewed. The main findings of the two remaining were included under other studies.

The use of in the evaluation of EndoPredict test for breast cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Epidermal Growth Factor Receptor (EGFR)

BACKGROUND

Lung cancer is one of the most common causes of cancer death, accounting for over 1 million deaths annually. Non-small-cell lung cancer (NSCLC) accounts for approximately 80% of lung cancers and the majority of cases present at an advanced stage. For patients with good performance status, platinum-based chemotherapy constitutes standard first-line treatment. However, a therapeutic plateau has been reached with conventional chemotherapy for NSCLC patients. Advances in the knowledge of molecular mechanisms of carcinogenesis has led to the development of new molecular-targeted agents. Current research efforts focus on a number of promising agents targeted against the epidermal growth factor receptor (Yoshida 2010, Campbell 2010). The epidermal growth factor receptor (EGFR) is normally present on the surface of epithelial cells, and plays an important role in regulating cellular processes such as proliferation, differentiation, survival, and maintenance of normal epidermal tissues. Researchers observed that when the function of EGFR becomes deregulated, it contributes to the growth and survival of cancer cells (Huang 2004, Ettinger 2006). The role of EGFR in carcinogenesis led to the development of several therapeutic agents which specifically target growth factor pathways that are deregulated in tumor cells. Tyrosine kinase inhibitors (TKIs) are one of these agents. Results of clinical trials on TKIs are conflicting and show a significant variability in response and survival rates. Some trials showed an improved survival when used after first or second-line chemotherapy, while others failed to show significant response and/or survival benefit. The investigators attributed the lack of benefit to the lack of patient selection in the trials, i.e. the inclusion of unselected NSCLC population in the studies. This was based on the observation that cancer cell lines and tumors are selectively susceptible to inhibition of the EGFR pathway. Results of subgroup analysis of data from observational studies suggest that the response to TKIs is also associated with a number of clinical and biological factors including gender, ethnic origin, smoking status,

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and histology of the cancer. More recently in 2004, the clinical responsiveness to the TKIs gefitinib and erlotinib were correlated to specific somatic EGFR mutations in the TK domain in NSCLC. The two most common activating mutations seen in patients are exon 19 deletions, and the exon 21 mutation L858R. Data from retrospective studies suggested that these mutations occurred more frequently among females, non-smokers, patients from East Asia, and those with adenocarcinoma histology (Linardou 2009). Extensive research is underway to identify the optimal molecular or genetic biomarkers that can predict the efficacy of a therapeutic agent for treating NSCLS and other malignancies. Predictive biomarkers include EGFR protein expression, gene copy number, mutation status, and others. A qualitative immunohistochemical (IHC) kit for EGFR gene expression testing (the Dako Cytomation EGFR pharmaDx ^{TM} assay) was approved by the FDA in 2004 as an aid to identify colorectal cancer patients eligible for treatment with the cancer drug cetuximab. In June 2005, the FDA issued an alert that new patients should not be given gefitinib, and limited its use to cancer patients who have already taken the medicine and whose doctor believe it is helping them. Erlotinib is another TKI that was approved by the FDA for treatment of locally advanced or metastatic non- small-cell lung cancer (NSCLC) after failure of at least one prior chemotherapy regimen. In June, 2005 the FDA issued an alert that new patients should not be given gefitinib, and limited its use to cancer patients who have already taken the medicine and whose doctor believes it is helping them. Erlotinib is another TKI that was approved by the FDA for treatment of locally advanced or metastatic non-small-cell lung cancer (NSCLC) after failure of at least one prior chemotherapy regimen.

08/04/2008: MTAC REVIEW
Epidermal Growth Factor Receptor (EGFR)
Evidence Conclusion: In order to identify the optimal molecular or genetic biomarkers that predict the efficacy of a therapeutic agent, the biomarker should have a plausible relationship with the biology of the disease, and should have a standardized reproducible test, as regards the reagent, performance, analysis and interpretation. There also should be standards for the tumor sample size and fixation. Several potential biomarkers have been identified, but none was validated in randomized controlled trials, to date. Moreover, as the literature indicates, there is no standardized methodology for tissue sampling, nor a standardized reproducible assay for EGFR- expression that would allow a direct comparison of the results obtained from different laboratories. The majority of the published trials on EGFR testing and the use of TKIs in patients with NSCLC were small prospective and retrospective case series. There were variations in the inclusion criteria, time of taking and fixation f the tumor tissue samples, as well as other differences in the study designs, which could be potential sources of bias and confounding. In several studies, biomarker assessment was done among a small proportion of patients due to lack of tissue availability. The studies used different tests and arbitrary cut-offs for identifying EGFR mutations as well as unvalidated techniques with no standardized criteria for quantification, processing, scoring, and reporting of the results. Most importantly TKI therapy was not compared to an alternative therapy. Without an appropriate control it is not possible to differentiate between the predictive and prognostic significance of a biomarker.* Moreover, the published trials retrospectively correlated the response to TKIs treatment and/or survival with the EGFR status based on tumor specimens collected at initial diagnosis. This may confound the correlation analysis of EGFR mutations and response as additional mutations could have occurred during therapy. In conclusion, the role of EGFR expression testing as a predictive factor is not well defined. There is insufficient evidence from the published studies, to determine whether EGFR mutation is a predictive marker of clinical benefit from treatment with TKIs or only a prognostic biomarker of better survival, independent of TKI treatment. * A prognostic marker is defined as a characteristic associated with prognosis or outcome, usually in terms of relative hazard, whereas a predictive marker is defined as a characteristic that is associated with, and predicts, treatment response. **Articles:** The literature search revealed over 800 articles on epidermal growth factor receptor (EGFR) and TKIs. There were 4 meta-analyses of observational studies, and a number of phase II and phase III clinical trials that studied the effects of specific TKIs and retrospectively correlated the outcomes with EGFR. The phase III trial (Tsao 2005) that compared erlotinib (a TKI) to placebo retrospectively correlated the outcome to EGFR mutation. The three most recent meta-analyses were critically appraised. Nakamura H, Kawasoki N, Taguchi, et al. Survival impact of epidermal growth factor receptor overexpression in patients with non-small cell lung cancer: a meta- analysis. *Thorax* 2006;61:140-145. See Evidence Table Costa DB, Kobayashi S, Tenen DG, et al. Pooled analysis of the prospective trials of gefitinib monotherapy for EGFR-mutant non-small cell lung cancers. Lung cancer 2007;58:95-103. See Evidence Table Wu y-L, Zhong W-Z, Li L-Y, et al. Epidermal growth factor receptor mutations and their correlation with gefitinib therapy in patients with non-small cell lung cancer: A meta-analysis based on updated individual patient data from six medical centers in Mainland China. *J Thorac Oncol* 2007;2:430-
439. See Evidence Table

The use of Epidermal growth factor receptor (EGFR) testing in the treatment of NSCLC to Tyrosine Kinase

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Inhibitors (TKIs) does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

10/18/2010: MTAC REVIEW
Epidermal Growth Factor Receptor (EGFR) Evidence
Conclusion: Analytic validity
There are a variety of methods used to detect EGFR mutations. Each of these assays has its advantages and limitations. Rapid detection of EGFR mutations with multiplex PCR and primer was found to be highly accurate compared to direct sequencing. In a sample of 81 tumors the two methods identified the same 26 mutations (Lin 2010). Clinical validity The Iressa Pan-Asian Study (IPASS) was a phase 3, multicenter, randomized, open-label trial comparing gefitinib with carboplatin plus paclitaxel as first-line treatment in 1217 clinically selected patients in East Asia with advanced non-small-cell lung cancer. In the overall population, the median progression-free survival (PFS) was 5.7 months in the gefitinib group and 5.8 months in the carboplatin plus paclitaxel group. The probability that a patient would be free of disease progression was greater with carboplatin-paclitaxel in the first 6 months and greater with gefitinib in the following 16 months. The objective response rate was significantly higher with gefitinib that with carboplatin plus paclitaxel. Overall survival did not differ between the two treatment groups; however, there were less than 100 events in each group. A preplanned subgroup analysis by EGFR mutation status was also performed. EGFR mutation status could be determined for 437 subjects (35.9%). Patients with sensitive EGFR mutations who received gefitinib had longer PFS, higher response rates, and a lower rate of adverse events compared to patients with sensitive EGFR mutations taking carboplatin plus paclitaxel. However, results should be interpreted with caution as EGFR status could only be evaluated for 35.9% of the original study population and patients were not randomized based on EGFR status. The results from this study are generalizable to patients of Asian ethnicity, who were nonsmokers or former light smokers, and had adenocarcinoma of the lung. Another limitation of this study lies in the analysis. The Cox proportional-hazards model is based on the assumption that the hazard ratio of the two treatments is constant overtime. Since the curves cross, this assumption is violated. However, in the subgroup analysis (patients with EGFR mutations) this assumption is not violated (Mok 2009). The results from a preplanned subgroup analysis of the INTEREST trial, a RCT comparing gefitinib to docetaxel in a Western pretreated population, were consistent with the results from the IPASS trial.
However, only 44 subjects in the study were EGFR mutation-positive (Douillard 2010). Clinical utility Two RCT recently evaluated the efficacy of gefitinib compared to chemotherapy in patients with sensitive EGFR mutations and non-small-cell lung cancer. The first trial compared gefitinib to carboplatin plus paclitaxel chemotherapy. Patients treated with gefitinib had significantly longer progression-free survival than patients treated with carboplatin plus paclitaxel (median 10.8 vs. 5.4 months, P<0.001) and higher response rates (73.7% vs. 30.7%, P<0.001). There was no difference in overall survival between the two groups; however, the incidence of severe toxic effects was significantly higher in the chemotherapy group than in the gefitinib group (71.1% vs. 41.2%, P<0.001). The results from this trial are generalizable to nonsmoking patients from Asia who had not previously received chemotherapy (Maemondo 2010). The second RCT assessed the efficacy of gefitinib compared to cisplatin plus docetaxel chemotherapy in patients with sensitive EGFR mutations. Findings from this trial are similar to the afore mentioned trial with progression-free survival being longer (9.2 vs. 6.3 months, P<0.001) and response rate being higher (61.2% vs. 32.2%, P<0.001) in patients treated with gefitinib compared to patients treated with cisplatin plus docetaxel. Results for overall survival could not be determined as data were immature and follow-up is still ongoing. Results from this study are generalizable to patients of Asian origin (Mitsudomi 2010). Conclusion: Analytic validity: There is fair evidence that rapid detection of EGFR mutations with multiplex PCR and primer extension produce good results compared to direct sequencing. However, there is insufficient evidence concerning the reproducibility of this test. Clinical validity: There is fair evidence that for patients with EGFR mutations the use of the tyrosine kinase inhibitors gefitinib and erlotinib is associated with an improvement in progression-free survival and response rate. Clinical utility: There is fair evidence that patients managed with the genetic test had better outcomes than patients managed without the genetic test.
Articles: There were several articles that addressed analytic validity. One of the most recent articles was selected for review. Several trials assessed the clinical validity and clinical utility of EGFR testing. Trials were selected for review if they were published after the 2008 review and addressed the safety or efficacy of TKI in patients with EGFR mutations.

The use of Epidermal growth factor receptor (EGFR) testing in the treatment of NSCLC to Tyrosine Kinase Inhibitors (TKIs) does meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Genetic Testing for IL28B Polymorphisms in Patients with Hepatitis C
BACKGROUND
Hepatitis C virus (HCV) is a single-stranded, enveloped RNA virus that is spread through contact with the blood of

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an infected person. In the United States, roughly 4.1 million Americans have been infected with the HCV, making it one of the most common blood borne pathogens. After acute infection with HCV, approximately 70-80% of infected individuals will go on to develop chronic HCV, which is a leading cause of cirrhosis, liver cancer, and liver transplant in the western world (Armstrong 2006, CDC 2009, Rosen 2011). For patients with chronic HCV infection, treatment includes a combination of pegylated interferon (PEG-INF) plus ribavirin given for 24 or 48 weeks depending on genotype. Results from recent RCTs also suggest that treatment for patients with HCV genotype 1, the most common isolate in the United States, may also include a protease inhibitor in conjunction with PEG-INF plus ribavirin. Treatment success, referred to as sustained viral response (SVR), is defined as the absence of virus 24 weeks after treatment completion. Less than 50% of patients HCV genotype 1 respond to therapy with PEG-INF plus ribavirin compared to around 80% of patients with HCV genotype 2 and 3. Besides genotype, female gender, white ethnicity, age less than 45 years, low HCV RNA levels at baseline, and lack of cirrhosis are considered to be predictors of viral response. Treatment for HCV is expensive and associated with numerous side effects such as anemia and neutropenia, which can lead to dose reduction or premature termination, thus increasing the risk of treatment failure. Research is currently underway to identify factors that could help patients and clinicians make more informed decisions regarding the risk and benefit of treatment and the likelihood of treatment response. Recent studies suggest that polymorphisms in the IL28B gene may be a useful predictor of treatment response (Clark 2011, Ghany 2009, Mangia 2011, Rauch 2010, Rosen 2011).
The IL28B gene encodes interferon (INF) lambda, a cytokine that shares the same intercellular pathway of INF alpha, the drug currently used in combination with ribavirin for the treatment of chronic HCV. Genome wide association studies suggest that polymorphisms in the IL28B gene may be associated with response to antiviral treatment with PEG-INF plus ribavirin in patients with HCV genotype 1. However, it is important to note that IL28B polymorphisms do not explain all treatment failure, and patients with the non-responder genotype may still respond to therapy (Ahlenstiel 2010, Mangia 2011).

10/17/2011: MTAC REVIEW
Genetic Testing for IL28B Polymorphisms in Patients with Hepatitis C
Evidence Conclusion: Analytic validity
No studies were identified that evaluated the analytic validity of genetic testing for IL28B polymorphisms in patients with chronic hepatitis C infections. Clinical validity A recent genome-wide association study (GWAS) identified seven single nucleotide polymorphisms (SNPs) around the IL28B gene that were associated with SVR in patients with chronic genotype 1 HCV infection. The most strongly associated SNP was rs12979860 followed by rs8099917. Results from this study suggest that the rate of viral response in European-Americans and Hispanics with the CC genotype was twofold higher compared to patients with the TT genotype. The rate of viral response in African Americans was threefold higher compared to patients with the TT genotype. No replication cohort was performed (Ge 2009). Two other GWAS in different populations also found that polymorphisms on the IL28B gene locus were associated with SVR. The first study found that the rs8099917 SNP on the IL28B gene was associated with SVR in Australian patients with chronic HCV infection. These results were replicated in an independent cohort of Europeans from the United Kingdom, Germany, Italy, and Australia (Suppiah 2009). The second study found that in Japanese patients with genotype 1 HCV, SNPs near the IL28B chromosome (rs8099917 and rs12980275) were associated with SVR. These results were replicated in an independent cohort on Japanese patients with HCV infection (Tanaka 2009). Clinical utility No studies were identified that evaluated the clinical utility of genetic testing for IL28B polymorphisms in patients with chronic hepatitis C infections. Conclusion:
Analytic validity: No studies were identified that evaluated analytic validity of genetic testing for IL28B polymorphisms in patients with chronic hepatitis C infections. Clinical validity: Results from several GWAS suggest that SNPs around the IL28B gene may be associated with SVR in patients with chronic genotype 1 HCV infection. Clinical utility: No studies were identified that evaluated the clinical utility of genetic testing for IL28B polymorphisms in patients with chronic hepatitis C infections.
Articles: The literature search identified several genome-wide association studies that identified polymorphisms near the IL28B gene locus as predictors of response to treatment in patients with chronic hepatitis C infection. The largest study was selected for review. No studies were identified that evaluated the analytic validity or clinical utility of genetic testing for IL28B polymorphisms in patients with chronic hepatitis C infection. The following study was critically appraised: Ge D, Fellay J, Thompson AJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature.* 2009;461:399-401. See Evidence Table

The use of IL28B polymorphisms does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

KRAS Mutation Testing for Predicting Response to Treatment in Patients with Advanced Colon Cancer
BACKGROUND

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Nearly a million new cases of colorectal cancer (CRC) are diagnosed worldwide each year, and about half a million people die from CRC annually. In the United States, CRC is the most common form of cancer in people aged 75 and older (Boyle and Leon, 2002). The length of survival of people with metastatic colorectal cancer has increased from approximately 12 months to 20 months in the past decade. This improvement has been attributed largely to the introduction of new treatments, including chemotherapeutic agents and novel targeted drugs (Di Fiore et al., 2007). Novel therapies include those that target the epidermal growth factor receptor (EGFR) signaling pathway which is believed to be involved in colorectal carcinogenesis. EGFR expression has been found in 60-80% of colorectal tumors (Heinemann et al., 2008). Two new monoclonal antibody inhibitors, cetuximab (Merck) and panitumumab (Amgen), are designed to block EGFR, thereby preventing the activation of downstream signaling pathways and inhibiting tumor cell proliferation. The new targeted therapies are costly and potentially increase the toxicity of treatment. It is thus desirable to select the patients most likely to respond to these treatments. Research is underway to identify biomarkers that predict response to the EGRF inhibitors. One biomarker under investigation is mutations in the K-ras gene (KRAS). KRAS mutations occur in approximately 20-50% of CRC tumors. It is believed that, in patients with mutant KRAS genes, treatment with the new monoclonal antibody inhibitors does not prevent signaling of EGFR, and consequently that the therapies should only be given to patients with wild-type (i.e. non-mutant) KRAS genes (Heinemann et al., 2008). Research first suggested that KRAS mutation selection might be useful for metastatic CRC patients who failed initial chemotherapy and are considering second-line treatment with cetuximab, as monotherapy, or in combination with irinotecan. KRAS mutation selection is also being proposed for first-line treatment with FOLFIRI, with or without cetuximab.
A genetic test is available to determine whether the KRAS gene contains mutations. Response Genetics (Los Angeles) has a PCR-based test. KRAS mutation testing for colorectal cancer patients has not been previously reviewed by MTAC.

02/02/2009: MTAC REVIEW
KRAS Mutation Testing for Predicting Response to Treatment in Patients with Advanced Colon Cancer
Evidence Conclusion: Analytic validity: No published articles on the accuracy of commercially available tests for detecting KRAS mutations were identified. Clinical validity: The three retrospective cohort studies evaluated (Lievre et al. 2008; DeRoock et al., 2008; DiFiore et al., 2007) all found that second-line treatment with cetuximab monotherapy or combination treatment was not effective in any of the patients with mutant KRAS genes (0% treatment response). The response rate in patients without mutations varied from 28-44%. Two of the three studies found a significantly higher rate of progression-free survival in patients with wild-type KRAS versus mutant forms. Only two studies reported overall survival; both found a significantly higher rate in patients with wild-type versus mutant KRAS. Limitations common to the three studies is that the analyses were retrospective, and subject to confounding--there may have been other differences between patients with wild-type and mutant KRAS genes that affected outcome. In addition, the vast majority of patients in the cohort studies received combination therapy as second-line treatment. Thus, one cannot disentangle the effectiveness of cetuximab from the irinotecan-based chemotherapy. This makes it difficult to make conclusions about what treatment patients should receive. Even if one concluded that KRAS mutation status impacts treatment outcomes, it is not possible from these studies to conclude that a monoclonal antibody inhibitor is necessary for treatment success. The Bokemeyer RCT provides some evidence on the added impact of treatment with cetuximab, as first-line treatment. Overall, there was no significant difference in response rate when cetuximab was added to FOLFOX-4 compared to FOLFOX-4 alone. However, in the sub-analysis by KRAS mutation status, there was a better response when cetuximab was added to chemotherapy for patients with wild-type KRAS genes. Clinical utility: No published articles were identified that prospectively managed patients with and without KRAS mutation testing were identified.
Articles: No published articles were identified on the accuracy of any commercially available test for detecting KRAS mutations. There were several retrospective cohort studies that evaluated the statistical association between KRAS mutation status and clinical outcomes with second-line treatment. Three studies (Lievre et al. 2008; DeRoock et al., 2008; DiFiore et al., 2007) were critically appraised. In addition, there was one published RCT evaluating first-line treatment, with a secondary analysis by KRAS mutation status (Bokemeyer et al., 2008), and this was critically appraised. Two unpublished RCTs were also identified that included analyses of outcomes by KRAS status. Both trials were presented as abstracts at the 2008 annual meeting of American Society of Clinical Oncology. The CRYSTAL study (Van Cutsem et al., 2008) evaluated patients receiving first-line treatment and the EVEREST study (Tejpar et al., 2008) evaluated second-line treatment. In terms of clinical utility of KRAS mutation testing for treatment selection, the ideal study would randomize patients to be managed with and without KRAS testing. For those managed with KRAS mutation testing, only patients with wild-type KRAS genes would receive cetuximab (second-line treatment) or FOLFIRI with or without cetuximab (first-line treatment). No randomized or non-randomized controlled trial that prospectively conducted KRAS testing was identified.

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Citations for the studies that were reviewed are as follows: Bokemeyer C et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. J Clin Oncol 2008 (Epub ahead of print). See Evidence Table. Lievre A et al. KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. J Clin Oncol 2008; 26: 374-379. See Evidence Table DeRoock W et al. KRAS wild-type state predicts survival and is associated to early radiological response in metastatic colorectal cancer treated with cetuximab. Ann Oncol 2008; 19: 508-515. See Evidence Table DiFiore F et al. Clinical relevance of KRAS mutation detection in metastatic colorectal cancer treated by cetuximab plus chemotherapy. Br J Cancer 2007; 96: 1166-1169. See Evidence Table

The use of KRAS mutation testing for predicting response to treatment in patients with advanced colon cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

08/16/2010: MTAC REVIEW

KRAS Mutation Testing for Predicting Response to Treatment in Patients with Advanced Colon Cancer

Evidence Conclusion: Analytic validity No studies were identified that directly compared the Response Genetics test to another test. A recent study compared four different methods of *KRAS* mutation testing–Sanger sequencing, array analysis, melting curve analysis, and pyrosequencing. The study included samples from 263 patients with colorectal cancer. Results from this study indicate that there was very good agreement between the four methods (κ >0.9). As to date there is no reliable, predetermined gold standard method for comparison, direct estimates of the sensitivity and specificity of the respective methods is not possible (Weichert 2010). Clinical validity Treatment regimens differed across the studies; however, there was a consistent message that for patients with mutant *KRAS* tumors the addition of the monoclonal antibodies cetuximab and panitumumab did not increase progression-free, overall survival, or response rate compared to mutant *KRAS* tumor patients who were not treated with a monoclonal antibody. *First-Line* Three RCTs conducted retrospective subgroup analyses to investigate the influence of *KRAS* mutation status on progression-free survival (PFS), overall survival (OS), and response rate. The Von Cutsem study analyzed data from the CRYSTAL trial. This trial was a randomized, open- label, multi-centered study that compared 14-day cycles of cetuximab plus FOLFIRI to FOLFIRI alone. For patients with mutant *KRAS* tumors, there was no difference between response rate, PFS, or OS between the two treatment groups. When patients with wild-type *KRAS* tumors were compared to patients with mutant *KRAS* tumors there was no difference between the groups for PFS or OS; however, the response rate was higher for patients with wild-type tumors (Von Custem 2009). Tol et al analyzed data from the CAIRO2 trial. This was an open-label randomized trial that evaluated the addition of cetuximab to capecitabine, oxaliplatin, and bevacizumab as first-line treatment in patients with metastatic colorectal cancer. Patients with mutant *KRAS* tumors who did not take cetuximab had significantly longer PFS and OS and higher response rates compared to patients who took cetuximab. Compared to patients with mutant *KRAS* tumors taking cetuximab, patients with wild-type *KRAS* tumors taking cetuximab had longer PFS, OS, and higher response rates. There was no significant difference in PFS, OS, or response rates for between mutant and wild-type patients not taking cetuximab (Tol 2009). Hecht and colleagues used data from the PACCE trial that evaluated panitumumab added to bevacizumab and oxaliplatin- based chemotherapy (cohort 1) or irinotecan-based chemotherapy (cohort 2). There was no significant difference in PFS or OS for patients with mutants *KRAS* tumors in either cohort (Hecht 2008). *Second-Line* No new information was identified since the 2008 MTAC review. Evidence for the 2008 MTAC review: The three retrospective cohort studies evaluated (Lievre 2008; DeRoock 2008; DiFiore 2007) all found that second-line treatment with cetuximab monotherapy or combination treatment was not effective in any of the patients with mutant *KRAS* genes (0% treatment response). The response rate in patients without mutations varied from 28- 44%. Two of the three studies found a significantly higher rate of progression-free survival in patients with wild- type *KRAS* versus mutant forms. Only two studies reported overall survival; both found a significantly higher rate in patients with wild-type versus mutant *KRAS* tumors. *Third-Line* Two RCTs conducted retrospective subgroup analyses to investigate the influence of *KRAS* mutation status on progression-free survival (PFS), overall survival (OS), and response rate. Amado and colleagues used data from a trial that that evaluated panitumumab monotherapy versus best supportive care (BCS) for patients with chemotherapy-refractory metastatic colorectal cancer. In this trial, patient in the BSC arm could receive panitumumab after disease progression. The effects of panitumumab on PFS were significantly greater for patients with wild-type tumors compared to patients with mutant tumors. As this was a crossover study, reliable overall survival measures cannot be obtained. Response rate data were missing for 19% of the population (13% wild-type *KRAS* and 26% mutant *KRAS*). For patients with wild-type *KRAS* taking panitumumab 17% had a partial response; no responders were identified in any other group (Amado 2008). Karapetis and colleagues used data from a phase 3 trial that examined the effects of cetuximab on patients with chemotherapy-refractory colorectal cancer versus BSC. There was no difference in PFS or OS for patients with mutant *KRAS* tumors between the treatment groups. The effects of cetuximab on PFS and OS were

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significantly greater for patients with wild-type tumors compared to patients with mutant tumors. In the cetuximab group, the response rate was 12.8% for wild-type *KRAS* tumors and 1.2% for mutant *KRAS* tumors. None of the patients in the BSC group had an objective tumor response (Karapetis 2008). All analyses were retrospective and therefore are subject to confounding – other differences between patients with wild-type and mutant *KRAS* genes could have affected the outcome. Patients in the RCTs were not randomized based on their *KRAS* mutation status. A subset of subjects from the RCT was used for analysis. Samples could only be obtained from 45%-92% of the primary analysis populations. Not all *KRAS* mutations were assessed. Mutations in codon 62 would have been missed even though this is a less prevalent mutation (~3% of mutations) it still may result in misclassification. The trials received industry funding. In the study conducted by Hecht and colleagues, censoring could have altered the PFS results. Additionally, response rate data was missing from 19% of the subject in the Amado study. Clinical utility
No studies were identified that specifically addressed clinical utility. However, identifying patients who will not respond to therapy will avoid the administration of an ineffective treatment and its associated toxicities.
Conclusion: A medical technology review from Blue Cross Blue Shield (BCBS) in conjunction with Kaiser Permanente from 2008 was identified. BCBS found sufficient evidence to approve the use of *KRAS* mutation analysis to predict non-response to the anti-EGFR monoclonal antibodies cetuximab and panitumumab based on retrospective genetic sub-studies from randomized controlled trials. Analytic validity: There is fair evidence that there is very good agreement between Sanger sequencing, array analysis, melting curve analysis, and pyrosequencing for the detection of a KRAS mutation. However, there is insufficient evidence concerning the sensitivity, specificity, and reproducibility of these tests. Clinical validity: There is fair evidence that for patients with *KRAS* mutations the use of the monoclonal antibodies cetuximab and panitumumab in not associated with an improvement in overall or progression-free survival. Clinical utility: There is insufficient evidence to determine that patients managed with the genetic test had better outcomes than patients managed without the genetic test.
However, identifying patients who will not respond to therapy will avoid the administration of an ineffective treatment and its associated toxicities.
Articles: A number of studies comparing different methods of *KRAS* mutation detection were identified. The trial with the largest sample size was selected for review. Several randomized controlled trials were identified that included a retrospective subset analysis of treatment efficacy in relations to *KRAS* mutation status. No studies were identified that addressed the clinical utility of *KRAS* mutation testing. A recent retrospective cohort study that evaluated the efficacy of cetuximab in patients with chemotherapy-refractory metastatic colorectal cancer treated with cetuximab plus chemotherapy was not included in this review as the study population was heterogeneous with regard to treatment regimen and line of chemotherapy. Additionally, approximately one third of the study population was included in previous reports.

The use of KRAS mutation testing for predicting response to treatment in patients with advanced colon cancer does meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Oncotype DX

BACKGROUND

Breast Cancer- Breast cancer is the most common cancer diagnosed and the second most common cause of cancer death in women in the United States. Patients with breast cancer can present with a variety of symptomatology that originates from heterogeneous molecular pathology (Dowsett, Cuzick et al. 2010). Breast cancer can be staged using the Tumor, Node, Metastases classification (TNM). The treatment of invasive breast cancer is based on the stage and involves radiation, surgery, and adjuvant therapy. The management based on adjuvant therapy derives from many factors such as the TNM characteristics, the grade, the presence or absence of estrogen and progesterone receptors, and the human epidermal growth factor 2 (HER2) receptor. However, some patients are still mistreated. Molecular tests that can predict the prognosis and the response to adjuvant therapy might accurately evaluate the recurrence risk and impact disease management. The literature has described several molecular tests including the oncotype Dx breast cancer assay. The oncotype Dx breast cancer assay is a molecular diagnostic test used in patients with early stage invasive breast cancer. In addition to standard measurements used to make treatment decision, the assay provides three advantages including the assessment of gene expression, the determination of recurrence, and the prediction of chemotherapy benefit. Scientists at Genomic Health, the manufacturer of the assay, utilize the reverse-transcriptase polymerase chain reaction (RT-PCR) to analyze a set of 21 genes in several samples and developed a mathematical formula that led to the breast recurrence score result. The score is also known as the recurrence score (RS). A lower score is indicative of a lower chance of recurrence or a smaller chemotherapy benefit. A higher score suggests a higher likelihood of recurrence or a significant chemotherapy benefit. In general, RS less than 18 suggests a low RS; a RS between18-30 indicates an intermediate RS and RS more than or equal to 31 indicates a high RS.

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Eligible patients are patients who are medically eligible for chemotherapy and have been diagnosed with stage I, II or IIIa invasive breast cancer, and whose breast cancer is estrogen-receptor positive (ER+) and Human Epidermal growth factor Receptor-negative (HER2-). The oncotype DX breast cancer assay was initially developed in patients with estrogen receptor-positive (ER+) and lymph node-negative (LN-) early invasive breast cancer. However, the test is believed to predict recurrence and chemotherapy benefit on candidates with lymph node-positive breast cancer. The test is being assessed for the first time on Medical Technology Assessment Committee (MTAC) and has been exempt from FDA clearance. **Colorectal Cancer -** Nearly a million new cases of colorectal cancer (CRC) are diagnosed worldwide each year and about half a million people die from CRC annually. In the United States, CRC is the most common form of cancer in people aged 75 and older (Boyle 2002). The length of survival of people with metastatic colorectal cancer has increased from approximately 12 months to 20 months in the past decade. This improvement has been attributed largely to the introduction of new treatments, including chemotherapeutic agents and novel targeted drugs (DiFiore 2007). Several randomized controlled trials (RCT) have shown that adjuvant chemotherapy improves overall survival in patients with stage III disease; however, a clear benefit for patients with stage II disease has not been established. Findings from the QUASAR trial, a RCT designed to determine the effects of 5-FU/LV (fluorouracil/leucovorin) compared to observation in patients with predominantly stage II colorectal cancer, suggest that stage II patients may benefit from 5-FU-based adjuvant therapy. However, since the majority of patients with stage II disease can be cured with surgery alone it is important to identify patients who are likely to develop metastasis and who will benefit from adjuvant chemotherapy (Gangadhar 2010). Currently, the risk of recurrence in stage II disease is clinically determined by histologic staging, extended to include evidence of lymphatic or vascular invasion, tumor grade, and the number of lymph nodes identified and examined in the surgical specimen (Midgley 2010). Biomarkers could also be useful in this assessment. Recently, a quantitative multigene expression assay has been developed with the aim of improving treatment decision-making in the setting of stage II colon cancer and is now being marketed as the Oncotype DX® colon cancer assay (Genomic Health Inc., Redwood City, CA). The Oncotype DX® colon cancer assay was derived from an initial set of 761 candidate genes to create a 12-gene panel assay that uses real-time PCR to measure the expression of 7 genes prognostic for relapse-free survival 5 reference genes used for normalization. The assay is performed on excised tumors and yields a prognostic recurrence score that ranges from 0 to 100. The recurrence score is used to improve patient selection criteria for adjuvant chemotherapy (Kerr 2009).

04/04/2005: MTAC REVIEW
Oncotype DX
Evidence Conclusion: Oncotype Dx is a test that is used to predict risk of distant recurrence in women with node-negative and estrogen-receptor-positive breast cancer. There is one published validation study (Paik, 2004) in which Oncotype test results were divided into three risk categories (low, intermediate or high) and the risk categories were correlated with the likelihood of distant recurrence over 10 years. Significantly fewer patients who were categorized as low-risk experienced distant recurrence compared to those categorized as high-risk (6.8% vs. 30.5%). The risk score contributed information on recurrence beyond that provided by age and tumor size. The Paik study included only patients who were treated with tamoxifen. The primary authors of the published study have substantial financial links to the Genomic Health Inc., the company that developed Oncotype Dx. There are no published data on the use of Oncotype Dx on women who are not treated with tamoxifen. There is no evidence that the recommendation for chemotherapy would change based on Oncotype Dx results or that changing treatment based on Oncotype Dx results would improve health outcomes.
Articles: The search yielded 43 articles. Many were on technical aspects of developing genetic assays. There was one published article on methods used to develop the test; this was not evaluated further because it did not address test accuracy. One published validation study was identified and this was critically appraised. There were also several unpublished abstracts and posters, including presentations at the 27th San Antonio Breast Cancer Symposium (SABCS) in December 2004. One of the SABCS posters reported on a case-control study conducted at Kaiser, Northern California to evaluate the Oncotype Dx recurrence score (Habel et al, unpublished manuscript). The study includes both women treated with and without tamoxifen. In the presentation, findings were primarily presented on the group treated with tamoxifen. The unpublished abstracts and posters do not meet the Kaiser Permanente criteria for evaluable evidence. *The reference for the published validation study is as follows:* Paik S, Shak S, Tang G. et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *NEJM* 2004; 351: 2817-2826. See Evidence Table

The use of Oncotype Dx in the evaluation of the likelihood of distal recurrence in patients with estrogen-dependent, node-negative breast cancer does not meet the *Kaiser Permanente Medical Technology*

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Assessment Criteria.

10/18/2010: MTAC REVIEW
Oncotype DX
Evidence Conclusion: There is insufficient evidence to determine the analytic validity, clinical validity, and clinical utility of the *Oncotype DX®* colon cancer assay.
Articles: No articles were identified that addressed the analytic validity, clinical validity, or clinical utility or the *Oncotype DX®* colon cancer assay. Conclusion: There is insufficient evidence to determine the analytic validity, clinical validity, and clinical utility of the *Oncotype DX®* colon cancer assay.

The use of Oncotype Dx in the evaluation of the colorectal cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

04/16/2010: MTAC REVIEW
Oncotype DX
Evidence Conclusion: Analytic validity No studies were identified that assessed the sensitivity and specificity of the *Oncotype DX®* colon cancer assay. Clinical validity A recent retrospective analysis of the Quick Simple and Reliable (QUASAR) trial evaluated whether the Oncotype® DX assay can provide clinically relevant information to assist treatment decision making in patients with resected stage II colon cancer. The assay yields a prognostic recurrence score that ranges from 0 to 100 and a treatment score. Results from this trial suggest that recurrence score (RS) was significantly associated with the risk of recurrence even after controlling for other factors such as tumor location, T stage, grade, nodes examined, lymph vascular invasion, and MMR deficient. The estimated recurrence risk at 3 years was 12% for the low recurrence risk group (RS<30), 18% for the intermediate recurrence risk group (RS 30-40), and 22% for the high recurrence risk group (RS≥40). The treatment score was not predictive of chemotherapy benefit (Gary 2011). Clinical utility No studies were identified that assessed the clinical utility of the *Oncotype DX®* colon cancer assay.
Conclusion: Analytic validity: There is insufficient evidence to determine the analytic validity of the *Oncotype DX®* colon cancer assay. Clinical validity: Results from a retrospective analysis suggest that the *Oncotype DX®* colon cancer assay recurrence score may be associated with recurrence risk in patients with stage II colon cancer. Results from this study also suggest that the *Oncotype DX®* colon cancer assay treatment score was not predictive of chemotherapy benefit. Clinical utility: There is insufficient evidence to determine the clinical utility of the *Oncotype DX®* colon cancer assay.
Articles: Screening of articles: No studies were identified that addressed the analytic validity or clinical utility of the Oncotype DX® colon cancer assay. The following study was selected for critical appraisal: Gray RG, Quirke P, Handley K, et al. Validation study of a quantitative multigene reverse transcriptase-polymerase chain reaction assay for assessment of recurrence risk in patients with stage II colon cancer. J Clin Oncol. 2011;29:4611-4619.
See Evidence Table

03/20/2017: Oncotype DX
Evidence Conclusion: Analytic Validity: There was insufficient evidence to determine the analytic validity of Oncotype DX breast cancer assay in lymph node-positive breast cancer patients. **Clinical validity:** (Albain et al., 2010) (Evidence table 1) performed a retrospective assessment of the phase 3 trial SWOG-8814. Women with node-positive breast cancer were treated with cyclophosphamide, doxorubicin, fluorouracil followed with tamoxifen (CAF-T) or tamoxifen alone. Patients were postmenopausal women with node positive, ER positive breast cancer. Recurrence score (RS) was found to be highly prognostic (Disease free survival) in the tamoxifen group (HR 2.64, 95% CI, 1.33 – 5.27; p=0.006). The same trend was found for overall survival (OS); HR 4.42 (95% CI 1.96, 9.97; p<0.001). Furthermore, there was no chemotherapy benefit in the low RS; however, disease-free survival was improved with high RS, independent of the number of positive nodes (HR 0.59, 95% CI, 0.35- 1.01; p=0.033). For DFS (disease free survival) as well as OS (overall survival), trend was similar; this means that RS significantly predicted chemo benefit (p=0.053 for DFS and p=0.026 for OS). However, this effect was not constant after 5 years (except for higher RS). The cumulative chemotherapy benefit persisted to 10years. Limitations included a specific population consisting of postmenopausal women limiting extrapolation of finding in premenopausal women. In addition, the sample size was small and some co-authors had ties with the manufacturer. (Dowsett et al., 2010) investigated whether the Recurrence Score (RS) provided information on the risk of distant recurrence (DR) in the tamoxifen and anastrozole arms of the Arimidex, Tamoxifen, alone or in Combination (ATAC) Trial. Outcomes were time to distant recurrence (TTDR), time to recurrence (TTR) and overall survival (OS).Three hundred and six (306) lymph node-positive (LN+) breast cancer in post-menopausal women were examined out of 1231 evaluable

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patients; the median follow-up was 8.5 years. Seventy-four (74) distant recurrences occurred in LN+ patients. In LN+ patients, 52%, 31% and 17% had an RS of <18, 18-30, and ≥31 respectively. The authors reported that the RS was predictive of TTDR in LN+ (HR=3.47, 95% CI = 1.64-7.38; **P=0.002**). After adjusting for clinical variables, the HRs between high and low RS and low to intermediate RS were 2.7% and 1.8% respectively. The 9-year DR rates in LN+ were 17%, 28%, and 49% in the RSs <18, 18-30 and ≥31 respectively. The same trend was observed for OS. The risk of DR was linearly associated with increasing RS. The risk of DR was higher for LN+ than LN- patients. RS was predictive of DR in the same way in patients treated with tamoxifen or anastrozole. Limitations included the small sample size, a specific population consisting of postmenopausal women and the lack of assessment of the chemotherapy benefit. Some authors had financial interest with the manufacturer of the oncotype DX assay. Mamounas (Mamounas et al., 2012) evaluated the association between RS and Paclitaxel (Pac) benefit. The sample used in the current study derived from a study that assessed doxorubicin/cyclophosphamide (AC) with AC followed by Pac (AC→Pac); patients were also treated with tamoxifen. This current study enrolled 1065 patients with ER+, LN+ breast cancer; the median follow-up was 11.2 years. 36%, 34% and 30% had low, intermediate and high RSs respectively. The authors found that RS was significantly predictive of loco-regional recurrence (LRR), disease free survival, distant recurrence and death in patients treated with AC as well as AC→Pac (findings can be seen in the table below).

10-year cumulative incidence (%) of LRR, DFS, DR and death

	Low RS	Intermediate RS	High RS	Log-rank p
LRR				
AC	3.4 (1.4 – 70)	8.3 (4.8 – 13.3)	13.2 (8.3 – 19.1)	**0.004**
AC→Pac	3.1 (1.4 – 6.3)	6.2 (3.3 – 10.4)	11.4 (7.0 – 17.0)	**0.037**
	HR 1.19 (0.45 – 3.16)	HR 0.75 (0.34 – 1.65)	HR 0.80 (0.42 – 1.52)	
DFS				
AC	24.5 (18.8- 31.5)	46.6 (39.5 – 54.4)	54.7 (47 – 62.8)	**<0.001**
AC→Pac	23.9 (18.5 – 30.6)	39.6 (32.8-47.1)	49.5 (42 – 57.5)	**<0.001**
	HR 1.01 (0.69 – 1.47)	HR 0.84 (0.62 – 1.14)	HR 0.81 (0.60 – 1.10)	
DR & death				
Similar trend				

LRR, Loco-Regional Recurrence; RS, Recurrence Score; DFS, Disease Free Survival; DR, Distant recurrence

Furthermore, patients with high or intermediate RS benefited the most from Paclitaxel indicating that chemotherapy may not be warranted in patients with low RS.

On-going trial:
NCT01272037: A Phase III, Randomized Clinical Trial of Standard Adjuvant Endocrine Therapy +/- Chemotherapy in Patients with 1-3 Positive Nodes, Hormone Receptor-Positive and HER2-Negative Breast Cancer with Recurrence Score (RS) of 25 or Less. RxPONDER: A Clinical Trial Rx for Positive Node, Endocrine Responsive Breast Cancer

Clinical Utility: Summary of evidence Eight observational studies were identified. The studies were retrospective or prospective in design and evaluated the impact of the oncotype DX assay recurrence score on treatment recommendations, patient decisional conflict, patient satisfaction and physician confidence in recommending treatment. Sample sizes were small and ranged from 20 to 282 patients with lymph node-positive, ER+, HER2- breast cancer. Most of the included patients received hormonal therapy or chemo hormonal therapy. These studies showed a change in the treatment recommendations after the oncotype Dx assay was performed. The proportion of the change ranged from 26% to 51%. The principal change was the removal of chemotherapy from the initial treatment recommendation. This suggests that the oncotype DX testing may impact decision-making or treatment plan and reduces the adverse effects caused by chemotherapy. Other findings included patient satisfaction, reduction of decisional conflict. Limitations included the small sample size, the difference between the groups with respect to characteristics of the tumors, and the financial ties between the manufacturer and some authors.
In addition, the retrospective analysis of RCT (evidence table 1) included in the clinical validity section (Albain et al., 2010) found that the addition of anthracycline-based chemotherapy improved disease-free survival (0.59 (0.35 – 1.01); P=0.033) and overall survival (P=0.0271) in patients with high recurrence score.
In conclusion, well-design studies with larger sample size are warranted to assess the patients reported outcomes which evaluate the clinical utility of molecular tests.

Studies assessing clinical utility (Bargallo et al., 2015) in a prospective study (evidence table 2) evaluated the

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impact of the recurrence Score result on the adjuvant therapy decision-making process. The authors reported that for LN+, the change occurred for 41% of the patients. Similarly, treatment recommendations changed for 32% for all patients irrespective of lymph node status and with the use of the oncotype DX assay. A retrospective study (Stemmer et al., 2013) (evidence table 3) compared treatment decisions in N1+/ER+/ HER2-negative breast cancer patients who underwent the oncotype DX assay with a control group composed of patients for whom treatment decisions were solely based on clinicopathologic criteria. Both groups received hormonal therapy with or without chemotherapy. Data of 282 patients who underwent the assay and 669 controls were analyzed. Some differences were noted on the tumor characteristics with patients on oncotype DX group with smaller tumor, lower frequencies of grade 3 tumors and number of positive nodes. The authors reported a lower utilization of chemotherapy in patients who were tested with the assay compared to the control (24.5 vs. 70.1%). In addition, the assay testing was significantly associated with a lower chance of receiving chemotherapy (OR 0.16; P<0.0001) after adjusting for age, tumor size, tumor grade, and nodal status. Nevertheless, limitations included the dissimilarity among groups and the change in adjuvant treatment recommendations for this population. A prospective German study (Eiermann et al., 2013) of 366 patients, of whom 122 were LN+ and 244 were LN- reported a change in treatment decision in 39% of women with LN+ (for LN-, A change of 30% was observed) after performing the oncotype Dx assay. The principal change was from chemo hormonal therapy (CHT) to hormonal therapy (HT) in 28% of all LN+ patients. Similarly, a reduction in chemotherapy was observed. Patient decisional conflict was also reduced by 6% and for both LN- and LN+ patients. Physician confidence in recommending treatment was increased in 45% for both LN- and LN+ patients. However, this was an industry funded study; therefore results should be interpreted with caution. (De Boer, Baker, Speakman, & Mann, 2011) reported that in 50 patients of LN+ patients, a change in treatment decision occurred in 26% of patients. The main change was from chemo hormonal therapy to hormonal therapy alone. Another study (Oratz et al., 2011) showed that 51% (70/138) patients with LN+ early breast cancer had their treatment recommendations changed after undergoing the oncotype Dx assay. The main change included the elimination of chemotherapy from the initial recommendation. A retrospective analysis of a sample of 40 patients with LN+ breast cancer (Nguyen et al., 2014) showed that the oncotype Dx assay was linearly associated with the use of chemotherapy. However, the small sample size constituted a limitation. A prospective study (Yamauchi et al., 2014) of the effect of the 21-gene assay on adjuvant clinical decision-making in Japanese women with hormone-receptor positive, LN- and LN+ breast cancer reported that of the 20 LN+ patients, 65% (95% CI, 41 -85%) had their recommendations changed. 87% (13/15) of LN+ patients had their initial recommendation for chemo hormonal therapy changed to hormonal therapy after performing the oncotype Dx assay. No patients, out of 5 LN+ patients, had their initial recommendations for hormonal to combined chemo hormonal. The results should be interpreted with caution because of the small sample size.

Conclusion:

- Analytic validity: There was insufficient evidence to determine the analytic validity of Oncotype DX breast cancer assay in lymph node-positive breast cancer patients.
- Clinical validity: Moderate evidence shows that the oncotype DX assay predicts recurrence in lymph- node positive breast cancer patients. However, the evidence was insufficient for the predictive effect. Studies with larger sample size are needed to optimally determine who will benefit from chemotherapy (particularly among patients with low or moderate recurrence score).
- Clinical utility: The oncotype DX assay may improve outcomes; however well design studies with larger sample size are warranted.

The use of Oncotype DX for breast cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Invader UGT1A1 Molecular Assay

BACKGROUND

The Invader UGT1A1 molecular assay tests variations in a gene called UGT1A1 that produces the enzyme UDP-glucuronosyltransferase. The UDP enzyme is active in the metabolism of certain drugs, including irinotecan, a chemotherapy agent commonly used to treat colorectal and lung cancer. The active metabolite of irinotecan, SN-38, is glucuronidated by hepatic UGTs. The main dose-limiting toxicity of irinotecan treatment is diarrhea, which is believed to be secondary to the biliary excretion of SN-38. Diarrhea associated with irinotecan-treatment can be serious and often does not respond to conventional antidiarrheal agents. The diarrhea may be due to direct enteric injury caused by the active metabolite of irinotecan, SN-38. A phase 1 clinical trial found an inverse relationship between SN-38 glucuronidation rates and severity of diarrheal incidence in patients treated with increasing doses of irinotecan. This suggests that decreased glucuronidation of SN-38 increases the risk of

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irinotecan-induced toxicity. Differential rates of SN-38 glucuronidation may help explain individual variation in toxicity rates among cancer patients treated with irinotecan. There may be a genetic predisposition to the metabolism of irinotecan.
Research has found that the UGT1A1 gene is responsible for SN-glucuronidation. Patients with low UGT1A1 activity, such as those with Gilbert's syndrome, may be at increased risk of irinotecan-induced toxicity. The Invader UGT1A1 molecular assay is marketed as a test to aid physicians in making individualized decisions about treatment and medication dosage. By detecting variations in the UGT1A1, the Invader UGT1A1 molecular assay might be able to predict which patients are at an increased risk of toxicity from irinotecan. The Invader UGT1A1 molecular assay was approved by the FDA in 2005 as substantially equivalent to the AmpliChip cytochrome P450 genotyping test. Both are genetic tests that detect single nucleotide polymorphisms. Since it was approved as substantially equivalent to an existing test, the manufacturer was not required to data on clinical sensitivity and specificity to the FDA. (References: Innocenti and Ratain, 2003; Iyer et al., 1998; Rouits et al. 2004; FDA documents).

06/05/2006: MTAC REVIEW
Invader UGT1A1 Molecular Assay
Evidence Conclusion: There is insufficient evidence to draw conclusions on the diagnostic accuracy of the Invader UGT1A1 molecular assay. No published peer-reviewed studies were identified. The only article with empirical data is a letter to the editor of Clinical Chemistry. The authors of the letter reported that findings from the Invader assay had a high rate of agreement with direct DNA sequencing for detecting UGT1A1 polymorphisms in 60 patients. Diagnostic accuracy studies that are published and peer-reviewed are needed. There is insufficient evidence that more appropriate therapy is used after application of the Invader assay than would be used if the test were not available. There was no published evidence on the impact on health outcomes of using UGT1A1 genotype information from the Invader test to adjust irinotecan treatment. There is some evidence that the UGT1A1 genotype is associated with irinotecan-induced toxicity. The studies reviewed found statistically significant associations between UGT1A1 genotype and irinotecan-induced toxicity. Two of the three studies (Marcuello et al., 2004; Ando et al., 2000) used multivariate analysis. In general, limitations of the studies were that they had relatively small sample sizes and estimates may be imprecise. Their findings provide preliminary data suggesting that information on UGT1A1 genotype may help physicians make better treatment decisions. Results of the studies reviewed cannot necessarily be generalized to use of the Invader assay to identify UGT1A1 polymorphisms, since this test was not used in any of the studies.
Articles: Accuracy of Invader UGT1A1 molecular assay: No published peer-reviewed studies were identified on the accuracy of the invader test for identifying variations in the UGT1A1 gene. There was a letter to the editor that presented data on test accuracy. Letters to the editor do not meet MTAC criteria for acceptable evidence because the scientific methods are not peer reviewed. Does adjusting the dose of irinotecan treatment based on UGT1A1 genotype identified using the Invader assay result in improved health outcomes? No published studies that directly address this question were identified. However, several studies were identified that examined the association between UGT1A1 variants and rates of toxicity related to irinotecan treatment. If there is a significant association between UGT1A1 genotypes and irinotecan-induced toxicity, then using information on UGT1A1 genotypes to inform irinotecan dosing decisions has the potential for improving health outcomes. The three largest studies evaluating the association between UGT1A1 genotype and toxicity (two cross-sectional studies and one case-control study) were critically appraised. *The studies reviewed were:* Marcuello E, Altes A, Menoyo A et al. UGT1A1 gene variations and irinotecan treatment in patients with metastatic colorectal cancer. Br J Cancer 2004; 91: 678-682. See Evidence Table Rouits E, Boisdron-Celle M, Dumont A et al. Relevance of different UGT1A1 polymorphisms in irinotecan-induced toxicity. Clin Can Res 2004; 10: 5151-5159. See Evidence Table Ando Y, Saka H, Ando M et al. Polymorphisms of UDP-Glucuronosyltransferase gene and irinotecan toxicity: A pharmacogenetic analysis. Can Res 2000; 60: 6921-6926. See Evidence Table

The use of Invader UGT1A1 molecular assay in the treatment of polymorphisms in the UGT1A1 gene does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Platelet Function Testing (VerifyNow P2Y12 Assay)
BACKGROUND
In the Unites States, cardiovascular disease is the leading cause of death in both men and women (Heron 2009). Clinical trials have shown that clopidogrel (Plavix), an anti-blood clotting medication, reduces the morbidity and mortality associated with several cardiovascular diseases. However, there is a significant amount of inter-individual variability in clopidogrel responsiveness, which leads some patients to experience decreased platelet inhibition

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(poor response) with clopidogrel (Momary 2010).
Studies suggest that approximately 4% to 30% of patients treated with clopidogrel do not have adequate antiplatelet response. The mechanism for poor response is not fully understood; however, poor compliance, drug interaction, clinical factors such as increased body mass index and diabetes, as well as genetic factors such as polymorphisms in the enzymes that metabolized clopidogrel into its active metabolite are all proposed mechanisms of clopidogrel non-responsiveness (Fileti 2011).
Platelet function testing is a way to monitor response to clopidogrel. It has been hypothesized that monitoring platelet reactivity and then tailoring treatment accordingly may improve clinical outcomes such as major adverse cardiovascular events. There are several different laboratory-based and point-of-care testing systems used to measure platelet response. These methods all have different definitions of high on-treatment platelet reactivity and are known to correlate poorly with each other. All of these methods have advantages and limitations. This review will focus on the VerifyNow P2Y12 Assay (Acumetrics Inc., San Diego, California), which is a fast, standardized point-of-care testing system that does not require special training to perform. The VerifyNow P2Y12 Assay evaluates platelet aggregation of fibrinogen-coated beads in response to adenosine diphosphate (ADP) and prostaglandin E1. Results are expressed as P2Y12 Reaction Units (PRU) with a common cutoff of ≥240 PRU for indicating suboptimal response to clopidogrel. However, one of the limitations of this test is that the cutoff for suboptimal response has not been firmly established (Sambu 2011, Smock 2011). The VerifyNow P2Y12 Assay has received approval from the FDA.

02/13/2012: MTAC REVIEW
Platelet Function Testing (VerifyNow P2Y12 Assay)
Evidence Conclusion: Analytic validity Light transmission aggregometry (LTA) is considered by many to be the gold standard in platelet function testing; however, even though this method is the gold standard it is not without limitations. It is time consuming, it has poor reproducibility, and it requires experienced technicians (Sambu 2011). A recent study evaluated the correlation between platelet function tests to measure clopidogrel-mediated platelet inhibition in 80 patients on dual antiplatelet therapy after percutaneous intervention with stent implantation. The cut-off value for defining residual ADP-platelet aggregation despite treatment with clopidogrel was maximal aggregation ≥62% for LTA and PRU ≥273 for the VerifyNow P2Y12 Assay. There was significant correlation between the two assays (r=0.61). When using LTA as the gold standard, the VerifyNow P2Y12 Assay had a sensitivity of 55% and a specificity of 85% (Gremmel 2009). Clinical validity Results from a recent meta-analysis that included 3,058 subjects suggest that that high on-treatment platelet reactivity (PRU ≥ 230) after percutaneous coronary intervention was associated with cardiovascular events. However, the results of this analysis should be interpreted with caution due to methodological limitations. For example, study quality was not reported and confidence intervals were wide due to the small number of events (Brar 2011).Clinical utility A recent RCT evaluated the effect of high-dose compared with standard-dose clopidogrel in 2,214 patients with high on- treatment platelet reactivity after percutaneous coronary intervention (PCI). Results from this study suggest that the use of high-dose clopidogrel in patients with high on-treatment platelet reactivity after PCI did not reduce the incidence of death from cardiovascular causes, nonfatal myocardial infarction, or stent thrombosis compared to standard-dose clopidogrel. Due to the fact that fewer events occurred than anticipated, a treatment effect of high- dose clopidogrel cannot be excluded (Price 2011). Conclusion: Analytic validity: Results from a recent study suggest that when using LTA as the gold standard, the VerifyNow P2Y12 assay has a sensitivity of 55% and a
specificity of 85%. Clinical validity: Results from a recent meta-analysis with methodological limitations suggest that high on-treatment platelet reactivity may be associated with cardiovascular events. Clinical utility: Results from a recent RCT suggest that high-dose compared to standard-dose clopidogrel in patients with high on-treatment platelet reactivity may not reduce cardiovascular events.
Articles: The literature search revealed several studies and review articles addressing the analytic validity of platelet function testing. Results of a recent study are presented below. Several observational studies and meta-analyses were identified that addressed the clinical validity of platelet function testing with the VerifyNow P2Y12 Assay. Studies were excluded if they were: retrospective, did not look at clinical outcomes, were not powered to evaluate clinical outcomes, or did not measure platelet function using the VerifyNow P2Y12 Assay. A meta- analysis of studies using the VerifyNow P2Y12 Assay to measure platelet reactivity was selected for review. Two randomized controlled trials (RCTs) were identified that looked at the clinical utility of VerifyNow P2Y12 Assay to measure platelet reactivity. One trial was excluded because it had a short duration of follow-up and the results combined patients who were poor responders to clopidogrel with patients who were poor responders to aspirin and patients who were poor responders to both aspirin and clopidogrel. The GRAVITAS trial, which evaluated the effect of high-dose compared with standard-dose clopidogrel in patients with high on-treatment platelet reactivity, was selected for review. The following studies were critically appraised: Brar SS, ten Berg J, Marcucci R, et al.
Impact of platelet reactivity on clinical outcomes after percutaneous coronary intervention. A collaborative meta-

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analysis of individual participant data. *J Am Coll Cardiol.* 2011; 58:1945-1954. See Evidence Table Price MJ, Berger PB, Teirstein PS, et al. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. *JAMA.* 2011; 305:1097-1105. See Evidence Table

The use of Platelet function testing (VerifyNow P2Y12 Assay) does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Warfarin Sensitivity DNA Test

BACKGROUND

Warfarin, an anticoagulant, is used to help prevent and treat blood clots. It is commonly used to treat patients with deep vein thrombosis, atrial fibrillation, stroke, and artificial heart valves. Blood clots are potentially dangerous because they can detach and travel in the bloodstream, where they can get wedged in a blood vessel and block the blood supply to a vital organ such as the lungs, heart or brain (Yin 2007). Blood clots are initiated when platelets clump together at the site of bleeding and produce chemicals that activate clotting factors in the blood. Vitamin K is essential for the production of these clotting factors. Warfarin prevents blood clots by inhibiting the action of vitamin K, thereby preventing the activation of clotting factors. The anticoagulant effect of warfarin is measured in terms of the prothrombin time, the time taken for blood clotting to occur in a sample of blood to which calcium and thromboplastin have been added. This time is expressed as the International Normalized Ratio (INR). The higher the INR, the longer time it takes for blood to clot. If the INR is too high, there is an increased risk of bleeding. If it is too low, there may be an increased risk of clot formation. The goal is to adjust the dose of warfarin so that the INR reaches and stays within a narrow therapeutic range. The initial dose of warfarin is an approximation, generally based on a standard protocol or dosing algorithm. Over the first several weeks on the medication, the patient's INR is tested regularly, and the dose adjusted. The risk of anticoagulant-related bleeding is highest at the beginning of therapy (Tan 2010). Warfarin dosing is influenced by a variety of factors such as sex, age, smoking status, medications, diet, height, and weight. Another factor that may be associated with the optimal dose of warfarin is the presence of certain genetic variants (Jonas 2009). Two relevant genes have been identified: Vitamin K epoxide reductase (VKORC1) is a gene which codes for the enzyme that warfarin targets for its effect. Patients with the sensitive AA halotype generally require a lower dose of warfarin than average. Patients with the BB halotype generally require larger doses. The common halotype is AB. The sensitive AA variant of VK0RC1 is estimated to occur in approximately 35-37% of Caucasians, 10-23% of African Americans, and in up to 89% of Asians. Cytochrome P450 (CYP) 2C9 (called CYP2C9) is a gene which codes for the specific liver enzyme that is largely responsible for metabolizing the most active component of warfarin. Some patients have a genetic variation in the CYP2C9 enzyme that causes them to metabolize warfarin more slowly. Patients with this genetic variation generally require a lower dose of warfarin. The usual variant of CYP2C9 that is associated with normal enzyme activity is CYP2C9*1. The variants associated with slower metabolism of warfarin are CYP2C9*2 and CYP2C9*3. The prevalence of these variants varies considerably by ethnic group with Caucasians having the highest prevalence (Tan 2010). In 2007, the FDA approved new labeling for warfarin indicating that patients with variations in CYP2C9 and VCORC1 may respond differently to the drug. Due to the fact that warfarin has a narrow therapeutic window and over- or underdosing of warfarin can lead to catastrophic hemorrhagic or thrombotic complications there has been increasing interest in warfarin genotyping to aid in optimizing initial and maintenance warfarin dosing. There are several FDA-approved warfarin sensitivity genotyping test kits; all of them test for mutations in both the CYP2C9 and VKORC1 genes.

10/06/2008: MTAC REVIEW

Warfarin Sensitivity DNA Test

Evidence Conclusion: Analytic validity: No published evidence was identified.

Clinical validity: A meta-analysis of observational studies (Sanderson et al., 2005) found a statistically significant association between variants of the CYP2C9 gene and both a lower dose of warfarin and lower risk of bleeding. The meta-analysis did not study the VKORC1 gene. Two cohort studies published after the meta-analysis (Schwartz et al., 2008; Wadelius et al., 2008) found significant associations between genetic variants of VKORC1 and efficacy outcomes (time to therapeutic INR or dose of warfarin). Associations with genetic variants of CYP2C9 were significant in one study but not the other. Both cohort studies were underpowered to assess the association between bleeding and genetic variants. Clinical utility: Two RCTs, one pilot study (Hillman et al., 2005) and one completed trial (Anderson et al., 2007) compared outcomes in patients managed with pharmacogenetic-guided dosing and those managed with standard dosing. The Anderson et al., 2007 study did not find a significant difference in the primary outcome, the per-patient percentage of out-of-range INR (30.7% in pharmacogenetic-

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guided dosing, and 33.1% in standard dosing). There was also no significant between-group difference in the secondary outcomes, achieving a therapeutic INR by day 5 or day 8, or the proportion of patients with adverse events. There were, however, significantly fewer dose adjustments (mean of 3.6 vs. mean of 3.0) with pharmacogenetic-guided dosing. The Hillman et al., 2005 focused on the feasibility of pharmacogenetic-guided dosing in a clinical setting, which was found to be feasible. The study also described clinical outcomes but did not do statistical testing. Outcomes (e.g. percent time INR in range and percent of patients with maximum INR>4) were similar in the two groups and the number of adverse effects was somewhat higher in the standard-dosing group. In conclusion: There is no published evidence on the accuracy or reliability of commercially available kits for identifying variants in the CYP2C9 and VKORC1 genes. There is fair evidence that variants of the genes are associated with warfarin-related intermediate outcomes (dosing, time to therapeutic INR). There is insufficient evidence due to lack of statistical power that genetic variants are related to risk of bleeding. There is insufficient evidence to determine that managing patients using pharmacogenetic-guided dosing improves outcomes. To date, there is one published completed RCT (Anderson et al., 2007), and this study did not find significant differences in the primary outcome, percentage of out-of-range INR and most secondary outcomes. Several additional RCTs are underway.

Articles: Analytic validity: No published studies were identified that discuss the accuracy or reliability of commercially available test kits for measuring genetic variants in the CYP2C9 and VKORC1 genes. Clinical validity: There is a meta-analysis of studies evaluating the association between CYOP269 genetic variants and bleeds and drug dosing (Sanderson et al., 2005). This study, and the two largest prospective studies evaluating VKORC1 (Wadelius et al., 2008; Schwartz et al., 2008) were critically appraised. Clinical utility: There is one published RCT that compares outcomes in patients managed with pharmacogenetic-guided dosing versus standard dosing (Anderson et al., 2007). In addition, there is an earlier published pilot RCT examining the feasibility of using pharmacogenetic-guided dosing (Hillman et al., 2005). These two studies were critically appraised. The Hillman study was included because, although its primary purpose was examining feasibility, it also included some clinical outcome variables. Several additional randomized controlled trials are underway examining health outcomes in patients starting warfarin therapy who are managed with pharmacogenetic-guided dosing compared to standard methods of dosing. These include the prospective evaluation comparing initiation of warfarin strategies (PRECISE) trial, a study of patients receiving total hip or knee replacement, and a Creighton University study comparing these two types of dosing (ClinicalTrials.gov). *The following studies were critically appraised:* Sanderson S, Emery J, Higgins J. CYP2C9 gene variants, drug dose and bleeding risk in warfarin-treated patients: A HuGEnet systematic review and meta-analysis. Genet Med 2005; 7: 97-104. See Evidence Table. Schwarz UI, Ritchie MD, Bradford Y et al. Genetic determinants of response to warfarin during initial anticoagulation. NEJM 2008; 358: 999-1008. See Evidence Table. Wadelius M, Chen LY, Lindh JD et al. The largest prospective warfarin-treated cohort supports genetic forecasting. Blood 2008. June 23 (E-pub ahead of print). See Evidence Table. Anderson JL, Horne BD, Stevens SM et al. for the Couma-Gen investigators. Randomized trial of genotype-guided versus standard warfarin dosing in patients initiating oral anticoagulation. Circulation 2007; 116: 2563-2570. See Evidence Table. Hillman MA, Wilke RA, Yale SH et al. A prospective, randomized pilot trial of model-based warfarin dose initiation using CYP2C9 genotype and clinical data. Clin Med & Res 2005; 3: 137-145. See Evidence Table.

The use of a DNA sensitivity test to determine the optimal dosing of warfarin does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

10/18/2010: MTAC REVIEW
Warfarin Sensitivity DNA Test

Evidence Conclusion: Analytic Validity There are several genotyping assays available to detect polymorphisms in the CYP2C9 and VKORC1 genes. King and colleagues compared the accuracy of four commercially available assays. All four methods evaluated had high accuracy compared to bi-directional sequencing (King 2009). Clinical Validity In 2008, based on the results from a meta-analysis and two cohort studies warfarin sensitivity DNA testing was found to have adequate clinical validity. Information from the 2008 review: A meta-analysis of observational studies found a statistically significant association between variants of the CYP2C9 gene and both a lower dose of warfarin and lower risk of bleeding. The meta-analysis did not study the VKORC1 gene (Sanderson 2005). Two cohort studies published after the meta-analysis (Schwartz 2008, Wadelius 2008) found significant associations between genetic variants of VKORC1 and efficacy outcomes (time to therapeutic INR or dose of warfarin). Associations with genetic variants of CYP2C9 were significant in one study but not the other. Both cohort studies were underpowered to assess the association between bleeding and genetic variants. New information since the 2008 review: A recent retrospective cohort study compared the accuracy of three different warfarin dosing

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algorithms. Results from this study suggest that the pharmacogenetic algorithm that included information on CYP2C9 and VKORC1 genotype produced initial warfarin dose recommendations that were significantly closer to the stable therapeutic dose than the clinical or fixed-dose algorithms. This analysis did not address whether a precise initial dose of warfarin would improve clinical endpoints, such as a reduction in the time needed to achieve a stable therapeutic INR, fewer INRs that are out of range, or a reduced incidence of bleeding (Klein 2009).Clinical Utility A recent cohort study compared the six month incidence of hospitalization in patients receiving warfarin genotyping versus historical controls. Compared to historic controls, patients who were genotyped for warfarin sensitivity had 31% fewer hospitalizations (P<0.001). Results from this study should be interpreted with caution. Patients were taking warfarin for a median of 32 days before the physician received the lab results. As there was no further communication with the physician after the lab results were sent, it is unknown if the genotyping results were used to inform treatment. The main limitation of this study is the use of a historical control group. Because a contemporary control group was not selected the possibility that the benefits of genotype-guided warfarin therapy may be exaggerated due to confounding, either in the vigilance by the treating physicians or in the kinds of patients who agreed to participate, cannot be ruled out. Other limitations include the fact that the genotype of the control group was unknown and baseline differences in the prevalence of hypertension and diabetes between the control and intervention group (Epstein 2010). Conclusion: Analytic validity: There is fair evidence that the commercially available assays for determining warfarin genotype are accurate compared to bi-directional sequencing. However, there is insufficient evidence concerning the reproducibility of these tests. Clinical validity: Based on information for the 2008 review, the warfarin sensitivity DNA test was found to have adequate clinical validity. Clinical utility: There is insufficient evidence to determine whether patients managed with the genetic test had better outcomes compared to patients managed without the genetic test.

Articles: The literature search revealed several articles that addressed the analytic validity of warfarin genotyping assays. The study by King and colleagues was selected for review as it assessed the accuracy of four different commercial systems. In the 2008 review, warfarin sensitivity DNA testing passed criterion 3 (clinical validity), since then several studies were identified that evaluated the clinical validity of genetic testing to predict warfarin dose. One of the larger cohort studies was selected for review. The study by Epstein and colleagues was the only study identified that addressed the clinical utility of the warfarin sensitivity DNA test. The following studies were critically appraised: King CR, Porsce-Sorbet RM, Gage BF, et al. Performance of commercial platforms for rapid genotyping of polymorphisms affecting warfarin dosing. *Am J Clin Pathol 2008;* 129:876-883. See Evidence Table. Klein TE, Altman RB, Ericksson N, et al. Estimation of the warfarin dose with clinical and pharmacogenetic data. *N Engl J Med 2009;* 360:753-764. See Evidence Table. Epstein RS, Moyer TP, Aubert RE, et al. Warfarin genotyping reduced hospitalization rates. *J Am Coll Cardiol 2010;* 55:2804-2812. See Evidence Table.

The use of a DNA sensitivity test to determine the optimal dosing of warfarin does not meet all of the *Kaiser Permanente Medical Technology Assessment Criteria.*

Prosigna Breast Cancer Prognostic Gene Signature Assay

BACKGROUND

Breast cancer is the most common cancer diagnosed and the second most common cause of cancer death in women in the United States. Patients with breast cancer can present with a variety of symptomatology that originates from heterogeneous molecular pathology (Dowsett, Cuzick et al. 2010). Breast cancer can be staged using the Tumor, Node, Metastases classification (TNM). The treatment of invasive breast cancer is based on the stage and involves radiation, surgery, and adjuvant therapy. The management based on adjuvant therapy derives from many factors such as the TNM characteristics, the grade, the presence or absence of estrogen and progesterone receptors, and the human epidermal growth factor 2 (HER2) receptor. However, some patients are still mistreated. Molecular tests that can predict the prognosis and the response to adjuvant therapy might accurately evaluate the recurrence risk and impact disease management. The literature has described several gene expression-based tests including Prosigna breast cancer prognostic gene signature assay.

Prosigna is a genomic test that evaluates the activity of 58 genes and categorizes a patient's tumor into a subtype based on the signature (luminal A, luminal B, HER-2 enriched or basal-like) (Gordon-Craig et al., 2020). It is a gene expression-based test founded on the prediction analysis of microarray 50 (PAM50) gene (Jensen et al., 2018). The PAM50 gene is a gene expression-based test that categorizes the risk of breast cancer. It predicts distant recurrence by defining inherent breast cancer subtypes (Walden et al., 2015). It is reported that Prosigna assay has been validated as a prognostic indicator in postmenopausal patients with ER-positive early-stage breast cancer treated with endocrine therapy and who are low-risk (Alvarado et al., 2015).

Prosigna predicts the risk of distant recurrence. It determines the prognosis for postmenopausal patients with early-

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stage breast cancer who are estrogen receptor (ER)+ (Jensen et al., 2018). However, it is not clear whether Prosigna predicts chemotherapy benefit (Alvarado, et al., 2015). It is indicated in postmenopausal breast cancer women with stage I or stage II, lymph node-negative, stage II with one to three positive nodes, hormone-receptor-positive, invasive and have undergone surgery and hormonal therapy (https://www.veracyte.com/our-products/prosigna; https://www.breastcancer.org/symptoms/testing/types/prosigna).
Prosigna assesses the activity of 58 genes and produces an estimation of distant recurrence risk of breast cancer within 10 years (after diagnosis). Prosigna produces two outcomes: 1) risk of recurrence score (ROR), a numerical score (1 to 100 scale) that corroborates with the 10-year distant recurrence risk, and 2) an improved risk classification which utilizes predetermined cutoff points associated with clinical outcomes. The risk classification is reported as low, moderate, and high in cancers with negative node, and low or high for patients with positive node. Cancers with negative node are classified as low (0-40), intermediate (41-60), or high (61-100) risk whereas cancers with positive node are classified as low (0-40) or high (41-100) risk (https://www.breastcancer.org/symptoms/testing/types/prosigna).

10/12/2020: MTAC REVIEW

Evidence Conclusion:

- Analytic validity
  - Evidence is insufficient
- Clinical validity
  - Low evidence shows that Prosigna can significantly prognosticate 10-year distant recurrence in post-menopausal patients with ER+, HER2-, LN- or LN+, early breast cancer.
  - Evidence comparing Prosigna and other genomic tests are limited. Two low quality studies showed that Prosigna (ROR) has better prognostic value than Oncotype Dx (RS). According to one low quality study comparing Prosigna, BCI, EPclin, RS, Clinical tx score, immunohistochemical score, Prosigna, BCI, and EPclin provide the most prognostic information in LN- cancers during 0 to 10 years and late recurrence. In LN+, all the signatures are weakly prognostic. Similar and more comparative studies are needed to determine the best genomic test.
  - There is insufficient evidence for or against the predictive effect (chemotherapy benefit) of Prosigna.
- Clinical utility:
  - Although, two low quality studies demonstrated the utility of Prosigna, more high-quality studies are warranted to draw a strong conclusion.

Articles:

PubMed was searched through September 16, 2020 with the search terms Prosigna OR PAM50 OR Prosigna Breast Cancer Prognostic Gene Signature Assay with variations. The search was limited to English language publications and human populations. Validation studies, RCTs, and observational studies were included. The reference lists of relevant studies were reviewed to identify additional publications. See Evidence Table.

The use of Prosigna Breast Cancer Prognostic Gene Signature Assay does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

***Note:** Codes listed in the criteria above may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check.**

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Date Created	Date Reviewed	Date Last Revised
04/04/2005	06/04/2013[MPC] 08/06/2013[MPC], 06/03/2014[MPC], 04/7/2015[MPC], 01/05/2016[MPC], 11/01/2016[MPC] ’09/05/2017[MPC], 07/10/2018[MPC], 07/09/2019[MPC], 07/07/2020[MPC], 07/06/2021[MPC], 07/05/2022[MPC], 07/11/2023[MPC]	09/05/2023

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MPC Medical Policy Committee

Revision History	Description
06/14/2016	Platelet function testing – VerifyNow changed to “medical review no longer required”. CPT code 85576
06/30/2015	Added additional Medicare LCD links and PROOVE® panels
09/08/2015	Revised LCD CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing L36311 and L35472, GeneSight® Assay for Refractory Depression (L36324), Genetic Testing L34101, Cytogenic Studies L34067
03/01/2016	Added Abacavir as a new test, added NRAS as an additional tumor marker, updated criteria for BRAF v600E Mutation
04/04/2017	Added MTAC review for Oncotype Assay for Lymph Node Positive Breast Cancer
08/01/2017	Added MTAC review for Breast Cancer Index and EndoPredict
04/24/2018	Added Oncotype DX Breast criteria revision
04/24/2018	Move BRAF testing to Genetic Screening Policy
06/02/2020	Added section: “Preferred Lab for Genetic Testing for Kaiser Permanente non-Medicare enrollees” Requires 60-day notice, effective date 10/01/2020.
10/06/2020	MPC approved the MCG 24th ed. guidelines for Opioid Pharmacogenetics - CYP450 Polymorphisms, OPRM1 Gene, and GeneSight Analgesic Panel: A-0992, Statin Pharmacogenetics - SLCO1B1 Gene: A-0981; added exception for NGS for Advanced Cancer (CellNetix lab) to Invitae as preferred lab section
12/01/2020	Added MTAC review for Breast Cancer Index and Prosigna Breast Cancer Prognostic Gene Signature Assay. MPC approved to adopt non-coverage policy.
05/04/2021	Updated lists of tests, criteria, and applicable codes in Medicare and Non-Medicare sections. MPC voted to adopt MCG* A-0859 for psychotropic medications – this requires 60-day notice, effective date October 1, 2021.
10/27/2022	Updated lab vendor to include Prevention and align with other genetic criteria.
11/18/2022	Updated Medicare Links
12/06/2022	MPC approved to update criteria for ALK (81401), EGFR (81235) and KRAS (CPT 81275, 81276, 0111U) and/or NRAS (CPT 81311, 0111U) testing to no longer require review. MPC also approved to move BRAF testing from the Genetic screening/testing criteria page to the pharmacogenomic criteria page. Requires 60-day notice. Effective 05/01/2023.
08/01/2023	Added MTAC review for Breast Cancer Index
09/05/2023	MPC approved medical necessity coverage indications for Breast Cancer Index. MPC approved to adopt Azathioprine and 6-Mercaptopurine Pharmacogenetics - NUDT15 and TPMT Genes, MCG A-0628. Requires 60-day notice, effective February 1, 2024.

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Clinical Review Criteria
Photodynamic Therapy (PDT)

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Ocular Photodynamic Therapy (OPT) (80.2) Verteporfin (80.3.1)
Local Coverage Determinations (LCD)	None
Local Coverage Article	Ocular Photodynamic Therapy (OPT) with Verteporfin (A52769) RETIRED
Kaiser Permanente Medical Policy	Due to the absence of an active NCD, LCD, or other coverage guidance related to non-ocular conditions, Kaiser Permanente has chosen to use their own Clinical Review Criteria for medical necessity determinations**. For all non-ocular conditions, use the Non-Medicare criteria below**.

For Non-Medicare Members

Service	Criteria Used
PDT with Visudyne for Pathologic Myopia PDT for Advanced Esophageal Cancer and Barrett's Esophageal Disease PDT for Age-Related Wet Macular Degeneration PDT for Actinic Keratosis	Medical necessity review no longer required
Photodynamic Laser Therapy for Tracheobronchial Cancer	Covered when the patient has obstructive tracheobronchial cancer as a palliative treatment.
PDT for Brain Tumors PDT for Rosacea	There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Photodynamic therapy (PDT) is a cancer treatment that destroys cancer cells selectively by an interaction between absorbed light and a retained photosensitizer. It is a two-part treatment using a photosensitizing drug, and red non-thermal laser light. The photosensitizing agent is a light activated chemical that selectively

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concentrates in malignant tissue. This agent is usually injected intravenously, and two days later it is activated by exposing the tissue to a laser light energy of a specific wavelength. For Photofrin, the FDA approved photosensitizer, the wavelength of light used for activation is 630 nm. The photosensitizer will absorb the light energy and produce toxic oxygen radicals that destroy the tumor and result in its necrosis in about 24 to 48 hours. The depth of penetration and tumor necrosis after PDT is limited to approximately 5-10 mm. This shallow depth of light penetration in the tumor provides a safety factor against perforation, but on the other hand it is a limiting factor to the effectiveness of the therapy for deeper tumors.

Photodynamic therapy is an outpatient procedure, performed with the patient sedated. It can be used together with other treatments and can be repeated several times. It does not require anesthesia or pre-dilation of the esophagus.

The side effect most commonly associated with PDT is photosensitivity. This is usually manifested as sunburn or periorbital edema. Patients are advised to avoid direct light for at least 4 weeks, after the treatment.

Evidence and Source Documents

Photodynamic Therapy (PDT) for Advanced Esophageal Cancer and Barrett's Esophageal Disease
Photodynamic Therapy for Brain Tumors
Photodynamic Laser Therapy for Tracheobronchial Cancer
Photodynamic Therapy with Visudyne for Pathologic Myopia
Visudyne with Photodynamic Therapy for Age-Related Wet Macular Degeneration

Medical Technology Assessment Committee (MTAC)

Photodynamic Therapy (PDT) for Advanced Esophageal Cancer and Barrett's Esophageal Disease

BACKGROUND

Esophageal carcinoma is the seventh most common malignancy worldwide. Its incidence is increasing rapidly in the western world mainly due to adenocarcinoma of the lower third of the esophagus and gastro-esophageal junction, which usually arises from areas of Barrett's metaplasia (Lee 2001). Approximately 13,100 new cases of adenocarcinoma were diagnosed in the United States in 2002. The overall survival rate from esophageal cancer is 5-10% (Litle 2003). Most patients present with dysphagia, which usually occurs at an advanced stage of the disease. At that time, the lumen of the esophagus is often reduced by at least 50% of its diameter among most of the patients. Radical esophageal resection is still considered the therapeutic gold standard in patients with high-grade dysplasia or early cancer. For those not legible for surgical resection, treatment is palliative to reduce the esophageal obstruction and reduce the dysphagia. Different forms of palliative treatment include external beam radiation therapy, brachytherapy, pneumatic dilatation, esophageal stenting, Nd: YAG laser, and photodynamic (PDT) therapy. Some of these therapies e.g. external radiation therapy may take several weeks to relieve the dysphagia, others like esophageal bypass have a longer recovery time, and still others are associated with severe side effects as stricture, perforation, reflux, fistula formation and others. PDT is a two-part treatment using a photosensitizing drug, and red non-thermal laser light (green light has been used in some studies). The photosensitizing agent is a light- activated chemical that is selectively retained in tumor cells, and interstitial tissue of the tumor. (McCaughan, 1996). This agent is usually injected intravenously, and two days later it is activated by exposing the tissue to a laser light energy of a specific wavelength. For Photofrin, the FDA approved photosensitizer, the wavelength of light used for activation is 630 nm. The photosensitizer will absorb the light energy and produce toxic oxygen radicals that destroy the tumor and result in its necrosis in about 24 to 48 hours. The depth of penetration and tumor necrosis after PDT is limited to approximately 5-10 mm. This shallow depth of light penetration in the tumor provides a safety factor against perforation, but on the other hand it is a limiting factor to the effectiveness of the therapy for deeper tumors. Photodynamic therapy is an outpatient procedure, performed with the patient sedated. It can be used together with other treatments and can be repeated several times. It does not require anesthesia or pre-dilation of the esophagus. Sensitivity of the patient body tissues to light always occurs once the agent is injected, and the patients should avoid direct light for at least four weeks. An important adverse effect of PDT is the potential formation of esophageal strictures due to fibrosis and scarring during the healing process. Barrett's esophagus is a condition where the squamous epithelium of the lower esophagus is substituted by specialized columnar mucosa. It is estimated to affect 700,000 adults in the United States (FDA 2003) and is believed to occur as a response to esophageal reflux of gastric contents especially gastric acid. Barrett's esophagus is regarded as a premalignant condition and is the most important risk factor for the development of adenocarcinoma (Spechler 2002). Non-dysplastic metaplasia can progress to low-grade dysplasia, high-grade dysplasia, and finally to invasive cancer (Conio 2005). Several investigators reported that the relative risk of the adenocarcinoma depends on several negative prognostic factors among which are metaplasia extension, length of the involved segment, dysplasia grading, and timing of diagnosis (Pagoni 2003).

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Esophageal adenocarcinoma is often diagnosed at an advanced stage of the disease, and thus has a poor prognosis with 5-year survival rates below 20% (Enzinger 2003). The increased availability of endoscopy and awareness of Barrett's esophagus and its associated cancer risk have led to the increased detection of the condition in premalignant or early malignant stages. Partial or total esophagogastrectomy are considered the therapeutic gold standard in patients with high-grade dysplasia or early cancer. Surgical resection may however, be associated with high morbidity and mortality rates especially in low-volume surgical centers (Birkmeyer 2002). Moreover, some patients may be unfit for surgery. Other possible strategies have been proposed to destroy Barrett's mucosa. Among these techniques are photodynamic therapy (PDT), ablation therapy with Nd-YAG laser, Argon Plasma Coagulation (APC), and endoscopic mucosal resection (EMR). The objective of all these treatments is the complete destruction of the abnormal mucosa to reduce the cancer risk. The ideal treatment would destroy columnar metaplasia and achieve regeneration of the squamous epithelium. PDT is a two-part treatment using a photosensitizing drug and red non-thermal laser light (green light has been used in some studies). The photosensitizing agent is a light- activated chemical that selectively concentrates in malignant tissue. This agent is usually injected intravenously, and two days later it is activated by exposing the tissue to a laser light energy of a specific wavelength. The photosensitizer will absorb the light energy and produce toxic oxygen radicals that destroy the esophageal mucosa in about 24 to 48 hours. Photodynamic therapy is an outpatient procedure, performed with the patient sedated. It can be used together with other treatments and may be repeated several times. It does not require anesthesia or pre-dilation of the esophagus. Sensitivity of the patient body tissues to light always occurs once the agent is injected, and the patients should avoid direct sunlight or any bright light for at least four weeks. An important adverse effect of PDT is the potential formation of esophageal strictures due to fibrosis and scarring during the healing process. Porfimer sodium (photofrin) was approved by the FDA in December 1995, to use in PDT for the palliation of patients with completely obstructing esophageal cancer, or patients with partially obstructing esophageal cancer who cannot be satisfactorily treated with Nd:YAG laser therapy. More recently, in August 2003 it was also approved for the ablation of precancerous lesions in Barrett's esophagus patients who do not undergo esophagectomy (FDA 2003).

02/06/2000: MTAC REVIEW
Photodynamic Therapy for the Treatment of Advanced Esophageal Cancer
Evidence Conclusion: Photodynamic therapy when compared to Nd:YAG thermal ablation for palliation of dysphagia from advanced esophageal cancer provides equivalent improvement in dysphagia, improved objective tumor response as measured by esophageal lumen diameter (ARR of 12% at one month in "complete response + partial response" P <0.05), and increased mild to moderate complications including sunburn in 19% of patients treated with PDT. Perforations from laser treatments or associated dilatations occurred in 1% of patients following PDT and 7% of patients following Nd:YAG treatment. (p<0.05) Termination of laser sessions due to adverse events occurred in 3% of patients receiving PDT and 19% receiving Nd:YAG. While this is an RCT, the high dropout rate and lack of blinding limit our ability to understand the difference in clinically important outcomes between Nd:YAG thermal ablation and PDT.
Articles: Articles were sorted on the basis of study type. Case series and cohort studies were not selected. Two randomized controlled trials were selected for review. One randomized controlled trial was selected (study by Heier SK et al. *Gastroenterology.* 1995; 109:63-72) was excluded because of small study size: N=44; 20 in PDT group, 22 in Nd:YAG group). An evidence table was created for the best available evidence (Lightdale CJ, et al. *Gastrointestinal Endoscopy.* 1995; 42:507-12.) Reference**:** Lightdale CJ, Heier SK, Marcon NE, et al. Photodynamic therapy with porfimer sodium versus thermal ablation therapy with Nd: YAG laser for palliation of esophageal cancer: a multicenter randomized trial. *Gastrointestinal Endoscopy.* 1995; 42:507-12. See Evidence Table.

The use of photodynamic therapy in treatment of esophageal cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*

02/11/2004: MTAC REVIEW
Photodynamic Therapy for the Treatment of Advanced Esophageal Cancer
Evidence Conclusion: Barrett's esophagus: Ackroyd's study was a small RCT with valid methodology. It is randomized, controlled, double blind, and with sufficient power to detect the difference in the treatment response between the two groups despite the small sample size. The trial however compared PDT to placebo and not to an alternative treatment. The photosensitizer used was ALA not the commonly used porphyrin-based agent, and the laser light used was the green light, not the red light described in the literature. Effect of the treatment on survival was not studied. Overall, the results of the trial show that patients treated with PDT showed significantly more macroscopic and microscopic evidence of regression and reduction in Barrett's area, compared to those who received a placebo treatment. The response to treatment observed was maintained for the follow-up duration of 24 months. The other study reviewed (Overholt 2003) was a case series with long-term follow-up. The study, like

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all case series, has potential threats to its internal validity, and lacks a comparison or control group. Its results show that PDT was associated with a success rate (no dysplasia with or without Barrett's) ranging from 44.4% for cases with early stage carcinoma to 92.9% for cases with low-grade hyperplasia. PDT was not compared to an alternative treatment. In addition, it was supplemented with Nd: YAG laser photoablation and continuous use of omeprazole, which may be responsible in part for the treatment success. Advanced esophageal cancer:
Only case series data were available. The dysphagia scores seem to significantly improve after PDT treatment in the two-series reviewed. There are no studies comparing the PDT with other treatments, so the relative effectiveness cannot be determined. Moreover, the case series studies are subject to selection and observation bias. A RCT (Lightdale, et al, 1995) with 218 patients randomized to receive either PDT or Nd:YAG was reviewed for MTAC in February 2000. It was not blinded, and had a high dropout rate, and did not provide sufficient evidence to determine the effect of the PDT on the treatment of esophageal cancer.
Conclusion: There is some weak evidence from one small RCT that PDT using ALA photosensitizer has more than a placebo effect on the regression of Barrett's area. There is insufficient evidence on the effect of PDT in the palliative treatment of advanced, and/ or inoperable esophageal cancer.
Articles: Barrett's esophagus: The search revealed 125 articles. The majority were reviews and tutorials. There was one RCT comparing the procedure to placebo, two others small RCTs comparing different methods for performing PDT, and several case series or case reports. The RCT and the case series with a relatively large sample size, and long-term follow-up were selected for critical appraisal. Ackroyd R, Brown JN, Davis MF, et al. Photodynamic therapy for dysplastic Barrett's oesophagus: a prospective, double blind, randomized, placebo-controlled trial. *Gut* 2000; 47:612-617. See Evidence Table. Overholt BF, Panjehpour M, Halberg D, et al. Photodynamic therapy for Barrett's oesophagus with dysplasia and/or early stage carcinoma: Long-term results. *Gastrointest Endosc* 2003; 58:183-188. See Evidence Table. Advanced esophageal cancer: The search on esophageal cancer in general revealed 94 articles, and that on advanced esophageal cancer revealed 21 articles the great majority of which were review articles. There were no RCTs comparing PTD to other modes of treatment. There were three case series with more than 50 patients each. One of these series compared PDT given in addition to radiotherapy. The other two were critically appraised. Luketich JD, Christie Na, Buenavantura PO, et al. Endoscopic photodynamic therapy for obstructive esophageal cancer. *Surg Endosc* 2000; 14:653-657. See Evidence Table. Moghissi K, Dixon K, Thorpe JA, et al. The role of photodynamic therapy (PDT) in inoperable oesophageal cancer. *Eur J Cardiothorac Surg* 2000; 17:95-100. See Evidence Table.

The use of photodynamic therapy in treatment of esophageal cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

06/06/2005: MTAC REVIEW
Photodynamic Therapy in Treatment of Barrett's Disease
Evidence Conclusion: Kelty et al's RCT compared photodynamic therapy (PDT) and argon plasma coagulation (APC) for the ablation of Barrett's esophagus. The outcomes were the number of treatments required to achieve ablation, and the complete macroscopic reversal of the columnar epithelium. All patients had a biopsy proven Barrett's epithelium, but none had any evidence of dysplasia. Thirty-four patients were randomized to each treatment group and followed for up to two years (range 6-24, median 12 months). 50% of the patients in the PDT group showed complete response to PDT, and 50% had only a partial regression. The APC therapy had significantly better outcomes with a complete response rate of 97%. Hage et al's trial was a smaller study (N=40) that also compared PDT with APC, and the primary outcome was the endoscopic reduction of the Barrett's esophagus surface. All patients had no or a low-grade dysplasia. They were randomized to receive APC therapy, single illumination (PDT 100), or a fractionated illumination (PDT 20+100), and followed for up to two years. The results of the trial show that patients who received a single illumination of PDT had a significantly lower rate of Barrett's esophagus surface reduction when compared to the PDT 20+100 group or the APC group (51%, 86% and 93% respectively). The difference between the latter two groups was insignificant. The two studies used 5-aminolevulonic acid (5-ALA); a more recent sensitizing agent and not the FDA approved photofrin (porfimer sodium). Both trials had generally valid methodology. However, they had relatively small sample sizes, and the follow-up duration of 2 years might be insufficient to study the effect of the therapy on reducing the risk of cancer. The outcome in these trials was the effect of the therapy on the reversal of the columnar epithelium and not on patient survival. Moreover, all study subjects had no or low-grade dysplasia, which might limit generalization of the results. The 2004 MTAC review only found weak evidence from one small RCT that PDT using ALA photosensitizer had more than a placebo effect on the regression of Barrett's area. The therapy failed the committee evaluation criteria. In conclusion, the studies reviewed provide some evidence that PDT may achieves complete clearance of Barrett's epithelium in at least 50% of the patients with no or low-grade dysplasia. They do not provide evidence on the effect of the therapy on higher-grade dysplasia, or its impact on cancer risk, and patient survival. Larger trials with long-term follow-up may be needed to establish these effects.

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Articles: The search revealed 26 articles. The majority were review articles or opinion pieces. There were two randomized controlled trials and two case series. The two RCTs were selected for critical appraisal: Kelty CJ, Ackroyd R, Brown JN, et al. Endoscopic ablation of Barrett's esophagus: a randomized controlled trial of photodynamic therapy vs. argon plasma coagulation. *Aliment Pharmacol Ther* 2004; 20:1289-1296. See Evidence Table. Hage M, Siersema PD, van Dekken H, et al. 5-Aminolevulinic acid photodynamic therapy versus argon plasma coagulation for ablation of Barrett's oesophagus: a randomized trial. *Gut* 2004; 53:785-790. See Evidence Table.

The use of photodynamic therapy in treatment of Barrett's disease does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Photodynamic Therapy for Brain Tumors

BACKGROUND

Photodynamic therapy (PDT) refers to the use of photosensitizing agents to treat tumors. The only FDA-approved photosensitizing agent is porfimer sodium (Photofrin). The PDT process involves the infusion of photosensitizing agents intravenously that are selectively retained within tumor cells. The photosensitizing agents are activated by exposure to light and cause oxidative damage to tumor tissues in which the drug has been retained.

The use of PDT to treat cerebral gliomas (brain tumors) was first investigated in 1972 using hematoporphyrin activated by white light on glioma cells in vitro and in rat tumors. Animal models have demonstrated the selective uptake of photosensitizers into cerebral gliomas. The first examination of PDT to treat human gliomas was reported by Perria in 1980. The ideal dose of photosensitizer and light for cerebral tumors has yet to be determined (Popovic). Other treatments for cerebral gliomas include surgical resection, postoperative whole-brain irradiation and chemotherapy. The effectiveness of these treatments is limited by inadequate local control of disease. It is hoped that PDT can improve local disease control and increase survival (Rosenthal).

02/13/2002: MTAC REVIEW

Photodynamic Therapy for Brain Tumors

Evidence Conclusion: There is insufficient evidence to determine the effect of PDT on health outcomes for patients with brain tumors. Much of the research appears to focus on developing the best methods for applying PDT to the treatment of brain tumors. Few clinical data are available. Popovic reported on a series of 120 patients; few methodological details were given, and the intervention may not have been consistent. They found that the median survival among 38 patients with glioblastoma multiforme was 24 months; in a historical control group subject to selection bias, median survival in patients with a similar diagnosis was 8 months.
Articles: The search yielded 69 articles, most of which were review articles, laboratory studies, dealt with technical aspects of the procedures or addressed other, similar treatments. There were no randomized controlled trials or meta-analyses. There were several small case series, many of which did not report clinical outcomes. A recent review article with some case series data was reviewed: Popovic EA, Kaye AH, Hill JS. Photodynamic therapy of brain tumors. J of Clin Laser Med & Surg 1996; 14: 251-261. See Evidence Table.

The use of photodynamic therapy in the treatment of brain tumors does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Photodynamic Laser Therapy for Tracheobronchial Cancer

BACKGROUND

Lung cancer is the leading cause of cancer deaths. It usually originates from bronchial cells, and grows in the bronchial lumen or peribronchially, thus, the term bronchial cancer is used synonymously with lung cancer. Resectional surgery is considered the treatment of choice, and the therapy with potential cure or long survival. However, the majority of patients diagnosed with lung cancer are at an advances stage, and only 15-20% are surgical candidates at the time of diagnosis (Fry, 1996). There are several methods used for palliative treatment for bronchial obstruction including Nd: YAG laser therapy, brachytherapy, electrocautery, balloon dilatation, stent insertion, and photodynamic therapy (PDT). PDT is a cancer treatment that destroys cancer cells selectively by an interaction between absorbed light and a retained photosensitizer. It is a two-part treatment using a photosensitizing drug, and red non-thermal laser light. The photosensitizing agent is a light activated chemical that selectively concentrates in malignant tissue. This agent is usually injected intravenously, and two days later it is activated by exposing the tissue to a laser light energy of a specific wavelength. For Photofrin, the FDA approved photosensitizer, the wavelength of light used for activation is 630 nm. The photosensitizer will absorb the light energy and produce toxic oxygen radicals that destroy the tumor and result in its necrosis in about 24 to 48 hours. The depth of penetration and tumor necrosis after PDT is limited to approximately 5-10 mm. This shallow depth of light penetration in the tumor provides a safety factor against perforation, but on the other hand it

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is a limiting factor to the effectiveness of the therapy for deeper tumors. Of the potential advantages of the procedure is that may be technically easier and potentially safer than other procedures, and that it is repeatable and appears to be compatible with other treatments. The procedure does not require general anesthesia, and only requires a prolonged bronchoscopy. The side effect most commonly associated with PDT is photosensitivity. This is usually manifested as sunburn or periorbital oedema. Patients are advised to avoid direct light for at least 4 weeks, after the treatment. The risk of serious bronchial hemorrhage, which may be fatal is another important complication associated with the PDT therapy used for treating tumors invading bronchial walls, and big vessels. Other complications include cough, dyspnea, bronchitis, and pneumonia. PDT is approved by the FDA for the palliation of airway obstruction caused by malignant tumors in patients with advanced obstructive endobronchial disease, and as an alternative to surgery in selected patient with early-stage lung cancer. PDT use in the treatment of tracheobronchial cancer was reviewed by MTAC in February 2002 and failed the committee evaluation criteria.

02/11/2004: MTAC REVIEW
Photodynamic Laser Therapy for Tracheobronchial Cancer
Evidence Conclusion: There is insufficient new evidence to determine the effectiveness of photodynamic therapy in the treatment of tracheobronchial cancer.
Articles: The search yielded 25 articles. The majority were reviews and tutorials. There was a small longitudinal study (32 patients) on all bronchoscopic treatments of occult lung cancer, another retrospective study on all palliative measures for malignant airways including 8 patients receiving PDT treatment or stents, and a small trial with 16 patients comparing 2 photosensitizers used in PDT for the treatment of malignant bronchial stenosis. None of the studies was critically appraised.

The use of photodynamic therapy in the treatment of bronchial cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

02/13/2002: MTAC REVIEW
Photodynamic Laser Therapy for Tracheobronchial Cancer
Evidence Conclusion: Early-stage lung cancer: Only case series data were available. A large proportion of the patients studied appear to have complete remission following PDT (approximately 80%); there are no studies comparing remission rates with other treatments, so the relative effectiveness cannot be determined. The case series reports are subject to selection and observation bias. The long-term effectiveness is difficult to determine because patients were permitted to have other treatments after PDT. Advanced lung cancer: The highest grade of evidence was an RCT. Diaz-Jimenez compared Nd-YAG to PDT in 31 patients. They found that patients who received PDT had a median of 12 days longer before treatment failure for any reason (50 vs. 38 days) and survived for a mean of 170 days longer (265 vs. 95 days) than the group receiving Nd-YAG. Because this is a small RCT, selection bias is likely. A greater proportion of patients assigned to the Nd-YAG group had advanced lung cancer that could at least partially explain the shorter time to treatment failure and shorter survival time. The existing evidence is insufficient to determine the effect of PDT on advanced lung cancer.
Articles: The search yielded 57 articles, many of which were review articles, opinion piece, dealt with technical aspects of the procedures or addressed other, similar treatments. Early-stage lung cancer: There were no randomized controlled trials (RCTs) or meta-analyses. The highest grade of evidence available was case series. The two largest case series were critically appraised: Furuse K, Fukoka M, Kato H, Horai T, Kubota K, Kodamo N et al. A prospective Phase II study on photodynamic therapy with photofrin II for centrally located early-stage lung cancer. J Clin Oncol 1993; 11: 1 852-57. See Evidence Table. Kato H, Okunaka T, Shimatani H. Photodynamic therapy for early stage bronchogenic carcinoma. J Clin Laser Med & Surg 1995; 14: 235-238. See Evidence Table Advanced lung cancer: There were two RCTs. The remaining empirical articles were case series. One RCT had included only 11 patients and did not compare outcomes in the two randomized groups in analysis. One RCT was critically appraised: Diaz-Jimenez JP, Martinez-Ballerin JE, Llunell A, Farrero E, Rodriguez A, Castro MJ. Efficacy and safety of photodynamic therapy versus Nd-YAG laser resection in NSCLC with airway obstruction. Eur Respir J 1999; 14: 800-805. See Evidence Table.

The use of photodynamic therapy in the treatment of bronchial cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Photodynamic Therapy with Visudyne for Pathologic Myopia
BACKGROUND
Choroidal neovascularization (CNV) in patients with pathologic myopia is a condition in which there is an abnormal growth of blood vessels under the retina due to an elongation of the back of the eye associated with severe myopia. This condition can result in a progressive and serious loss of vision. There have not been

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effective treatments for this disease. Photodynamic therapy using Visudyne (verteporfin for injection) involves intravenous injection of verteporfin, a light activated or "photosensitive" drug. After infusion, verteporfin is activated by illumination with laser light shone into the patient's eye from a slit lamp of a microscope. The wavelength used corresponds to the wavelength at which peak absorption occurs but is not so strong as to cause thermal damage. The light is directed to the area of neovascularization and damage to the retina is minimized. In April 2000, the FDA approved Visudyne for the treatment of the wet form of age-related macular degeneration. In August 2001, photodynamic therapy with Visudyne was additionally approved for the treatment of subfoveal choroidal neovascularization (CNV) due to pathologic myopia. Visudyne for age-related macular degeneration was found to meet MTAC review criteria in June 2000.

02/13/2002: MTAC REVIEW
Photodynamic Therapy with Visudyne for Pathologic Myopia
Evidence Conclusion: One well done randomized controlled trial (VIP study group) was reviewed. This study provides evidence that photodynamic therapy with verteporfin is effective at decreasing vision loss 12 months after treatment. 28% of patients in the verteporfin group compared to 56% in the placebo group had at least an eight-letter loss at 12 months, the study's primary outcome ($p<0.01$, NNT=4). This finding is likely to be clinically as well as statistically significant. The treatment appears to be safe. Ideally, the findings would be replicated in other studies and there would be longer-term follow-up. 24-month follow-up data will be available from the VIP study.
Articles: The search yielded 26 articles, many of which were review articles, opinion pieces, dealt with technical aspects of the procedures or addressed other, similar treatments. There was 1 randomized controlled trial (n=120) with and 1 case series (n=13). The case series included patients with choroidal neovascularization due to several conditions, e.g. pathologic myopia, ocular histoplasmosis syndrome, angiod streaks and idiopathic causes. *The RCT was critically appraised:* Verteporfin in photodynamic therapy (VIP) study group. Photodynamic therapy of subfoveal choroidal neovascularization in pathologic myopia with verteporfin: 1-year results of a randomized clinical trial: VIP report no. 1. Ophthalmol 2001; 108: 841-52. See Evidence Table

The use of photodynamic therapy in the treatment of pathologic myopia passed the *Kaiser Permanente Medical Technology Assessment Criteria*.

Visudyne with Photodynamic Therapy for Age-Related Wet Macular Degeneration
BACKGROUND
Age-related macular degeneration (AMD) is the most common and most severe cause of vision loss in the U.S. and many developed countries. With increasing life expectancy, the prevalence of AMD (currently about 25%) in people aged 65 years and older will increase significantly, with an enormous social and financial cost. In spite of the significance of this problem, AMD's pathogenesis remains unclear and is essentially untreatable.
AMD is characterized by two forms: the "dry" and more severe "wet" form. The latter accounts for 15% of all AMD cases, but is responsible for 90% of the severe vision loss associated with this condition. Visual acuity loss usually results from choroidal neovascularization (CNV), the ingrowth of new vessels from the choriocapillaris. These new vessels are accompanied by fibrous tissue that can destroy central visual function over months to years. Standard treatment of CNV has been with a thermal laser. The drawback of this laser is that in addition to destroying the CNV it destroys the surrounding retinal tissue with immediate vision loss. Photodynamic Therapy (PDT) utilizing verteporfin (Visudyne; CIBA Vision Corp, Duluth, GA) is a new technology which completed Phase III clinical trials last year and was recently recommended for FDA approval by the Ophthalmic Drugs Subcommittee of the FDA. Verteporfin therapy involves an intravenous administration of verteporfin, a light activated drug. Laser light at the specific wavelength absorbed by Visudyne is then directed to the area of neovascularization and causes preferential closure of these vessels while sparing the overlying retina.
The articles described below evaluate PDT as a treatment for choroidal neovascularization (CNV), the type of late AMD that is the most frequent cause of visual loss.

06/14/2000: MTAC REVIEW
Visudyne with Photodynamic Therapy for Age-Related Wet Macular Degeneration
Evidence Conclusion: The prospect of verteporfin (Visudyne) as a new therapy for subfoveal wet AMD is very promising, in light of the fact AMD is an important public health problem with no currently available treatment that spares destruction of the fovea itself. However, the efficacy and safety of verteporfin cannot be fully determined from the limited evidence provided by these two studies, which were conducted by the same investigators. The findings from the case series are threatened by small sample size and possible observation and selection biases. The findings from both studies are threatened by short length of follow-up, concerns about the generalizability of the findings, and the fact that the investigators would benefit financially from FDA approval of the drug. Further studies, preferably blinded, randomized controlled trials, such as the Verteporfin in Photodynamic Therapy (VIP)

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Trial (to be completed this Fall), will provide further evidence regarding whether photodynamic therapy with verteporfin can safely and effectively reduce the risk of vision loss in patients with age-related macular degeneration.

Articles: Miller JW, Schmidt-Erfurth U. Sickenberg M; Piurnaras CJ et al. Photodynamic Therapy with verteporfin for Choroidal Neovascularization caused by age-related Macular Degeneration. *Archives of Ophthalmology 1999; 117:1167-1173.* See Evidence Table. TAP Study Group. Photodynamic Therapy of subfoveal choroidal neovascularization in age-related Macular Degeneration. *Archives of Ophthalmology 1999; 117:1329-1345.* See Evidence Table.

The use of Visudyne with Photodynamic Therapy in the treatment of Age-related Macular Degeneration does meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

Verteporfin

CPT® or HCPC Codes	Description
J3396	Injection, verteporfin, 0.1 mg

Photodynamic Therapy

CPT® or HCPC Codes	Description
96567	Photodynamic therapy by external application of light to destroy premalignant lesions of the skin and adjacent mucosa with application and illumination/activation of photosensitive drug(s), per day
96570	Photodynamic therapy by endoscopic application of light to ablate abnormal tissue via activation of photosensitive drug(s); first 30 minutes (List separately in addition to code for endoscopy or bronchoscopy procedures of lung and gastrointestinal tract)
96571	Photodynamic therapy by endoscopic application of light to ablate abnormal tissue via activation of photosensitive drug(s); each additional 15 minutes (List separately in addition to code for endoscopy or bronchoscopy procedures of lung and gastrointestinal tract)
96573	Photodynamic therapy by external application of light to destroy premalignant lesions of the skin and adjacent mucosa with application and illumination/activation of photosensitizing drug(s) provided by a physician or other qualified health care professional, per day
96574	Debridement of premalignant hyperkeratotic lesion(s) (ie, targeted curettage, abrasion) followed with photodynamic therapy by external application of light to destroy premalignant lesions of the skin and adjacent mucosa with application and illumination/activation of photosensitizing drug(s) provided by a physician or other qualified health care professional, per day

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed	Date Last Revised
12/1998	04/06/2010 MDCRPC, 02/10/2011 MDCRPC, 12/06/2011 MDCRPC, 10/02/2012 MDCRPC, 8/06/2013 MPC, 11/05/2013 MPC, 09/02/2014MPC, 07/07/2015MPC, 05/03/2016MPC, 03/07/2017MPC, 01/09/2018MPC, 12/04/2018MPC, 12/03/2019MPC, 12/01/2020MPC,12/07/2021MPC,12/06/2022MPC, 12/09/2023MPC	12/21/2023

MDCRPC Medical Director Clinical Review and Policy Committee

MPC Medical Policy Committee

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Revision History	Description
06/02/2015	Added Actinic Keratosis
10/11/2016	Added Medicare coverage article A52769
09/03/2019	MPC approved to add PDT for Rosacea to the non-covered list
12/21/2023	Added NCD Verteporfin (80.3.1)

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KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
PLAC Test

- Predicting the Risk of Coronary Heart Disease (Lp-PLA2)

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	MolDX: Biomarkers in Cardiovascular Risk Assessment (L36362) *This test is not covered when included in a CV risk assessment panel per Medicare LCD.*
Local Coverage Article	Billing and Coding: MolDX: Biomarkers in Cardiovascular Risk Assessment (A57055)

For Non-Medicare Members

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage

Background

Recent research suggests that inflammation plays a role in the development and progression of atherosclerosis. This observation, together with the advances in inflammatory biomarkers research, has led to the emergence of dozens of novel biomarkers that may potentially aid in predicting an individual's risk for cardiovascular disease. Among these novel biomarkers are C-reactive proteins, lipoprotein associated phospholipase A2 (Lp-PLA2), homocysteine, fibrinogen, plasminogen, interleukin-6 (IL-6), IL-18, and many others (Anderson 2008, Khakpour 2009, Packard 2009).

A novel biomarker for cardiovascular risk has clinical utility if it independently provides risk information above and beyond that provided by conventional risk factors, is easy to obtain and interpret in a primary care setting, is highly specific, accurately reproducible and contributes to patient management particularly through more accurate risk stratification and guidance in the choice of therapy (Oldgren 2007, Lerman 2008, Khakpour 2009).

Lp-PLA2, also known as platelet activating factor acetyl-hydrolase, has been proposed to be a more specific marker for vascular inflammation. It is an enzyme secreted by macrophages, monocytes, T-lymphocytes, and mast cells. Over two thirds of Lp-PLA2 circulate in the bloodstream bound to low-density lipoprotein cholesterol, and the rest travels bound to high-density and very low-density lipoproteins. For several years there has been a lot of debate on whether the enzyme has a pro- or anti-atherogenic mechanism. One viewpoint suggests that it plays a role in the production of proinflammatory mediators including oxidized free fatty acids and lysophosphatidylcholine, and another view implies that that the enzyme could be protective by reducing

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inflammation and predisposition to thrombosis in blood through its hydrolysis of platelet activating factor (Anderson 2008, Wilensky 2009).

The diaDexus PLAC test is a second generation of the enzyme-linked immunoassay (ELISA) test used in many of the population studies that investigated the association of Lp-PLA2 with cardiovascular diseases. It is based on the standard principle of a sandwich enzyme immunoassay using two specific high affinity monoclonal antibodies directed against Lp-PLA2 that show no cross-reactivity with other phospholipases. A set of Lp-PLA2 calibrators is used to plot a standard curve of absorbance (y-axis) versus Lp-PLA2 concentration in ng/ml (x-axis) from which the Lp-PLA2 concentration in the test sample can be determined. This concentration of the enzyme in each sample and control is then interpolated from the standard curve using a point-to-point curve fit with appropriate calibration curve fitting software. The test has a minimum detection limit of 1.3 ng/ml and the expected Lp-PLA2 concentrations are 120-342 ng/ml for females and 131-376 ng/ml for males. PLAC test is classified under the Clinical Laboratory Improvement Amendments (CLIA) 88 as a high-complexity test and must be run in CLIA-certified-high-complexity laboratories (Hoogerveen 2005, FDA Website).

PLAC test, diaDexus, Inc, San Francisco, CA, was cleared by the FDA in 2003, for the quantitative determination of Lp-PLA2 in human plasma to be used in conjunction with clinical evaluation and patient risk assessment as an aid for predicting risk for coronary heart disease, and ischemic stroke associated with atherosclerosis (FDA website).

Medical Technology Assessment Committee (MTAC)

PLAC Test in Detecting Risk of Coronary Heart Disease

02/11/2004: MTAC REVIEW

Evidence Conclusion: Ballantyne et al's study was nested in a large prospective study. It included both men and women 45-64 years of age. In this sub-study CHD patients were compared to a random sample of 785 subjects (minus 45 cases with CHD), and not to the whole study population. The authors do not provide explanation why they selected such a design. There were several significant differences in the base-line characteristics between the cases, and non- cases. Adjustments were made for several of these variables, not for all. Other variables not adjusted for in the analysis may be potential confounders. Overall, it showed that the highest tertile of Lp-PLA_2 enzyme was associated with a higher CHD risk among patients with LDL cholesterol level <130 mg/dL. Packard's study was a case control nested in the WOSCOPS study. Participants were men 45-64 years of age, with baseline LDL cholesterol level 174 –232 mg/dL. Cases were those who developed a coronary event, and controls were men from the same cohort who did not develop a coronary event during the follow-up. Overall the results showed that lipoprotein-associated phospholipase A_2 was significantly associated with coronary events, independent of the other variables studied. Blake's study on the other hand did not detect a significant association between the enzyme and the risk of cardiovascular events among women. It was also a case control nested in a large trial, "Women's Health Study" that only enrolled women 45 years of age or older. The case control study was small, and the power might have been insufficient to detect a significant association. The different findings between the two studies may also indicate that lipoprotein-associated phospholipase levels may be predictive of coronary events in men but not women. The three studies reviewed examined Lp-PLA_2 as a marker or risk predictor for coronary events but did not study the implication of identifying this risk factor on the management of the patients or in improving the net health outcome.

Articles: The search yielded 25 articles, the majority of which were news, review articles, and tutorials. The search did not reveal any RCTs. The studies embedded in larger prospective cohort studies were identified. All three were critically appraised: Ballantyne CM, Hoogeveen RC, Bang H, et al. Lipoprotein-associated phospholipase High sensitivity C-reactive protein, and risk incident coronary heart disease in middle-aged men and women in the atherosclerosis risk in communities (ARIC) study. *Circulation* 2004; 109:837-842. See Evidence Table. Packard CJ, O'Reilly DS, Caslake MJ, et al. Lipoprotein- associated phospholipase A_2 as an independent predictor of coronary heart disease. N Engl J Med 2000; 343:1148-1155. See Evidence Table. Blake GJ, Dada N, Fox JC, et al. A prospective evaluation of lipoprotein- associated phospholipase A_2 levels and the risk of future cardiovascular events in women. J Am Coll Cardiol 2001; 38:1302-1306**.** See Evidence Table.

The use of PLAC Test in detecting risk of coronary heart disease does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

10/05/2009: MTAC REVIEW

PLAC Test in Detecting Risk of Coronary Heart Disease

Evidence Conclusion: *Lp-PLA2 as a marker for predicting future CVD risk* in the last decade, a number of epidemiologic studies investigated the association between plasma Lp-PLA2 and the cardiovascular disease risk.

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The majority were nested case-cohort studies, and the blood samples were taken only once at baseline and stored at ~ -70oC for up to 10 years before its analysis. The results were mainly presented in hazard ratios comparing the lowest with the highest tertile, quartile or quintile values. Several studies including West of Scotland Coronary Prevention Study (WOSCOPS), the Atherosclerosis Risk in Communities (ARIC) Study, and MONICA study found an association between elevated levels of Lp-PLA2 and increased risk for cardiovascular events in certain groups of patients. In the ARIC study however, the relative risk associated with the upper tertile of Lp-PLA2 became statistically insignificant when adjustments were made for traditional risk factors. Other studies including the Women's Health Study, GUSTO and FRISC did not show a significant association between Lp-PLA2 and CVD risk. A meta-analysis (Garza 2007) that pooled the results of 14 studies, showed a significant independent association between Lp-PLA2 and CVD risk. The results, however, do not provide evidence that measurement of Lp-PLA2 levels would improve risk stratification for CVD or add to the predictive value of the traditional risk factors and scoring systems used e.g. Framingham Risk Score. An analysis of the ARIC study (Folsom 2006) showed that the addition of Lp-PLA2 to the basic risk model increased the area under the receiver operating curve (AUC) from 0.774 to 0.780. Due to the large sample size, this small difference was statistically significant, but is of minor clinical significance. A statistically significant, independent association of a marker to CVD does not necessarily indicate that it improves the risk prediction beyond the traditional variables. Lp-PLA2 as therapeutic target There are no long-term published RCTs to date provide evidence that measuring LP-PLA2 would lead to meaningful changes in patient management, or improvement in clinical outcomes. In a multicenter placebo-controlled trial, Mohler and colleagues 2008 investigated the effect of darapladib, a selective Lp-PLA2 inhibitor, on the enzyme activity as well as on another panel of biomarkers. The study randomized 959 participants with stable CHD or risk equivalent, to receive a placebo or one of three doses of darapladib (40, 80, or 160mg daily), for 12 weeks, together with atorvastatin 20 or 80mg/day. The trial did not have hard clinical outcomes, instead Lp-PLA2 and other select biomarkers were used as surrogates of atherosclerosis risk, to assess the efficacy of the therapy. The results showed that darapladib given together with atorvastatin was associated with lower Lp-PLA2 activity, which appeared to be dose-dependent (darapladib 40,80, and 160 mg significantly inhibited Lp-PLA2 activity by 43%, 55%, and 66% respectively compared to placebo). This was observed in the two atorvastatin groups but without affecting the LDL levels. The study duration was too short to determine the long-term adverse events of the therapy, and its effect on CVD risk. (i.e. whether inhibition of Lp-PLA2 leads to accumulation of proinflammatory or prothrombotic factors). Intervention trials investigating the effect of LP-PLA2 inhibitors on coronary disease events are in progress. These include STABILITY trial on the effect of darapladib on CHD and FRANCIS-ACS trial that evaluates varespladib in patients with acute coronary syndrome. Diagnostic accuracy of PLAC test: The literature did not identify any study that examined the diagnostic accuracy, predictive values, or likelihood ratios of PLAC test in measuring LP-PLA2 among patients at different levels of cardiovascular disease risk. *Conclusion:* The current evidence suggests that Lp-PLA2 may be associated with vascular disease risk, but it is insufficient to show the association is causal, that measuring the enzyme level improves risk stratification for CVD, would have any impact on managing patients at high risk, or that inhibition therapy of Lp-PLA2 enzyme would improve health outcomes.

Articles: The search yielded around 33 articles. There was a meta-analysis, and a number of case control studies examining the association between Lp-PLA2 and CVD. The search also identified one randomized controlled trial on the effect of a selective Lp-PLA2 inhibitor of the enzyme activity (darapladib) in patients with CHD or risk equivalent, and another small RCT on the effect of the drug on the atherosclerotic plaque. The literature search did not reveal any published studies on the clinical benefits of screening for Lp-PLA2 in optimizing therapy and reducing cardiovascular risk, and/or events. There were also no studies on the diagnostic accuracy of PLAC test in assessing the Lp-PLA2 levels. The meta-analysis on the association between Lp-PLA2 and CVD risk, the ARIC study (FDA approval), and the RCT on the effect of darapladib on the enzyme activity in patients with CHD or risk equivalent were selected for critical appraisal: Garza CA, Montori VM, Connell JP, et al. Association between lipoprotein-associated phospholipase A2 and cardiovascular disease: a systematic review . Mayo Clin Proc.2007; 82:159-165. See Evidence Table. Ballantyne CM, Hoogeveen RC, Bang H, et al. Lipoprotein-associated phospholipase High sensitivity C-reactive protein, and risk incident coronary heart disease in middle-aged men and women in the atherosclerosis risk in communities (ARIC) study. Circulation 2004; 109:837-842. See Evidence Table. Mohler ER, Ballantyne CM, Davidson MH, et al. The effect of darapladib on plasma lipoprotein -associated phospholipase A2 activity and cardiovascular biomarkers in patients with stable coronary heart disease or coronary heart disease equivalent. The results of a multicenter, randomized double-blind, placebo-controlled study. J Am Coll Cardiol 2008; 51:1632-1641. See Evidence Table.

The use of PLAC Test in detecting risk of coronary heart disease does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

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Considered Not Medically Necessary:

CPT® or HCPC Codes	Description
83698	Lipoprotein-associated phospholipase A2 (Lp-PLA2)

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Dates Reviewed	Date Last Revised
02/11/2004	Initiated annual review because of Medicare criteria 04/04/2011 MDCRPC, 02/07/2012 MDCRPC, 12/04/2012 MDCRPC,10/01/2013 MPC, 08/05/2014 MPC, 06/02/2015MPC, 04/05/2016MPC, 02/07/2017MPC, 12/05/2017MPC, 11/06/2018MPC, 11/05/2019MPC, 11/03/2020MPC, 11/02/2021MPC, 11/01/2022MPC, 11/07/2023MPC	09/08/2015

MDCRPC Medical Director Clinical Review and Policy Committee
MPC Medical Policy Committee

Revision History	Description
08/04/2015	Changed Medicare links
09/08/2015	Revised LCD L34886 and L35008 Non-Covered Services

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Clinical Review Criteria
Platelet Rich Plasma

- Autologous Platelet Derived Wound Healing Factors for Non-Healing Cutaneous Wounds (Autologel, Procuren, SafeBlood)
- Injections for the Treatment of Non-Healing Fractures and Tendinopathy
- Platelet Rich Plasma for Knee Osteoarthritis
- Platelet Rich Plasma for Plantar Fasciitis

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Blood-Derived Products for Chronic Non-Healing Wounds (270.3)
Local Coverage Determinations (LCD)	Platelet Rich Plasma Injections for Non-Wound Injections (L39060)
Local Coverage Article	Billing and Coding: Platelet Rich Plasma Injections for Non-Wound Injections (A58790)

For Non-Medicare Members

Kaiser Permanente has elected to use the Platelet Rich Plasma (A-0630) MCG* for medical necessity determinations. The use of platelet rich plasma is not covered for any indications by MCG guidelines. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.

__The MCG are proprietary and cannot be published and/or distributed__. However, on an individual member basis, Kaiser Permanente can share a copy of the specific criteria document used to make a utilization management decision. If one of your patients is being reviewed using these criteria, you may request a copy of the criteria by calling the Kaiser Permanente Clinical Review staff at 1-800-289-1363 or access the MCG Guideline Index using the link provided above.

If requesting review for this service, please send the following documentation:

- Last 6 months of clinical notes from requesting provider &/or specialist (Orthopedics, sports medicine, physiatrist)

Service	Criteria
• Platelet Rich Plasma for Plantar Fasciitis • Platelet Rich Plasma for Knee Osteoarthritis	There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies

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Background

Platelets are rich in growth factors that play an essential role in tissue healing. Platelet-rich plasma (also known as platelet-enriched plasma, platelet-rich concentrate, autogenous platelet gel, or platelet releasate) is used to enhance bone and soft tissue healing by placing supraphysiologic concentrations of autologous platelets at the site of tissue damage. Platelet-rich plasma has been tried for a wide variety of clinical applications, including orthopedics, otolaryngology, and oral and maxillofacial, plastic, gynecologic, cardiac, and general surgeries. Platelet-rich plasma can be prepared from blood collected in the immediate pretreatment period using standard cell separators and salvage devices. After activation, platelet-rich plasma is usually administered by either direct application or injection into the affected area. There is little consensus regarding the production and characterization of platelet-rich plasma.

Bone Fracture Healing (GEM 21STM)

Bone fracture healing is a biological process that involves both local and systemic acute phase reactants. The physiological events occurring at the site of injury include hematoma formation, recruitment and transformation of mesenchymal cells, induction of angiogenesis, and the production and remodeling of the extracelluar matrix. Radiographic healing of a bone fracture is normally achieved in 4-13 months depending on type and location of the fracture. The rate of bone union also depends on several other factors as patient's health, compliance, nutritional status, stability of the fracture and others. Disruption of any of these factors would lead to delayed or non-union of the fracture. It was reported that approximately 10% of the bone fractures in the US are complicated by impaired healing, which has a high impact on the quality of life and burden of health costs. Several compounds and technologies have been and are being developed to enhance fracture healing and accelerate repair. These include prostaglandins, gene therapy, growth hormone, parathyroid hormone, and growth factors. Among the growth factors studied are the bone morphologic proteins, transforming growth factor B, vascular endothelial growth factor, and platelet derived growth factor (PDGF) (Axelrad 2007, Hollinger 2008).

In vitro and animal studies indicate that PDGF has the potential of accelerating the bone healing process. The experimental studies showed that PDGF receptors increase in osteoblasts as they mature, but that the response varies inversely to the number of receptors. This indicates that there is an optimal concentration and time during bone regeneration to deliver the PDGF in order to be effective (Axelrad 2007).

The GEM 21STM a device for bone grafting material containing a therapeutic tri- calcium phosphate or PDGF was approved by the FDA for periodontally related defects in November 2005.

Tendinopathy

Painful tendon disorders are common among professional and recreational athletes, and also among sedentary individuals. It is estimated that 30-50% of all sports-related injuries are painful tendon injuries. These injuries are classified as tendinitis during the acute inflammatory process and tendinosis when healing becomes chronically impaired. Clinicians are increasingly using the term tendinopathy to refer to tendon disorders without implying a specific pathology, and chronic tendinopathy for cases that are refractory to conventional treatment. If the triad of pain, swelling, and reduced load bearing capacity are present, then the correct term for the diagnosis is tendinopathy, which is a clinical and not a histopathological diagnosis. The pathophysiology of chronic tendinopathy involves the presence of degenerative changes, including disorganized collagen fibers, increased granular substance and neovascularity. Tendinopathy leads to reduction in activity levels and sometimes cessation of all sports activities. The three most common sites affected are the Achilles, patellar, and rotator cuff tendons. Other tendons affected include those around the elbow (medial and lateral epicondylitis), wrist extensors, supraspinatus tendon, and plantar fasciopathy (Maffulli 2003, de Vos 2010, Creaney 2011, Mautner 2013).

Tendinopathies are difficult to treat, and the healing response differs between load-bearing tendons such as the patellar and Achilles tendons, and non-load-bearing tendons such as the wrist extensors. Traditionally tendinopathy have been treated with oral and injectable anti-inflammatory medications, bracing, physical therapy, and heavy load eccentric training programs. The rationale for anti-inflammatory therapies for tendinopathy has been questioned recently, and currently heavy load eccentric training programs are being used by many practitioners as a first-line therapy. These training programs require high levels of patient motivation and are not always successful. When conservative therapies fail, surgery may be recommended (Krogh 2013, Mautner 2013).

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Recently, research focused on the use of complex growth factor preparations derived from the patient's blood to drive the body's own tissue healing mechanisms. The use of autologous growth factors is thought to lead to tendon repair through collagen regeneration and stimulation of angiogenesis. This concept of delivering humoral mediators to promote normal tendon healing was first reported in 2003. Platelets are the major player; in addition to their central role in the clotting cascade, they are involved in the normal healing response. The exact mechanism by which platelets promote tendon healing is unclear; however, it is theorized that the growth factors and cytokines contained in the platelets speed tissue regeneration and healing. Platelets contain alpha granules and dense granules, which when stimulated release platelet-derived growth factor, transforming growth factor (TGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), insulin-like growth factor (IGF) I and II, and fibroblast growth factor. These factors play an important role in cellular proliferation, chemotaxis, cellular differentiation, extracellular matrix production, and angiogenesis. The dense granules contain adenosine, serotonin, histamine, and calcium, which play a role in tissue modulation and regeneration (Foster 2009, Maffulli 2010, Thanasas 2011).

There is no standard technique for harvesting growth factors for administration, and several preparations are described in the literature as the autologous blood injection (ABI), and platelet rich plasma (PRP). PRP is defined as autologous blood with concentration of platelets higher than its physiologic concentration found in healthy whole blood. PRP contains a 2- to 8-fold increase in platelets concentration (150,000-350,000µL in blood and at least 1,000,000µL in PRP), and 1- to 25-fold growth factor concentration depending on which factor is examined. PRP is commonly prepared in the laboratory, operating suite, outpatient sports medicine clinic, or at a radiology setting. It begins with venipuncture and collection of autologous whole blood from the patient into a syringe containing anticoagulant at the point of care. The collected blood is then centrifuged in a tabletop centrifuge machine. This separates the whole blood into three layers: red blood cells, platelet poor plasma, and platelet concentrate that contains white blood cells. Typically, the red blood cells are discarded after the first spin, and a second spin yields a more concentrated platelet layer. The PRP amount is approximately 10% of the volume of whole blood collected. PRP can be categorized according to its leukocyte content into leukocyte depleted pure PRP (P-PRP) in which leucocytes are purposely eliminated, or PRP that contains a high concentration of leukocytes (L-PRP). Once prepared the PRP is maintained in a sterile environment and used immediately for the procedure (Foster 2009, de Vos 2010, Maffulli 2010, Creaney 2011, Gosens 2011, Thanasas 2011, Lee 2013).

Earlier use of PRP included its application in maxillofacial surgery, plastic surgery, cardiac bypass surgery, and orthopedics. The positive effects observed in these surgical applications have stimulated its use in sports medicine outpatient clinic setting. The use or PRP is accepted by the patients because it is produced from their own blood and the risk of adverse effects is minimal. Different types of centrifuge machines used vary in their ability to separate red blood cells from platelets which affects the platelet concentration, separating leukocytes from platelets, or shearing platelets during the centrifuge process that may cause premature platelet activation and degranulation. The variation in centrifuge machines and PRP preparation techniques cannot provide a consistently similar or standardized final product. There is also no clear definition for the optimal dose of PRP or the number of injections needed. Most physicians perform one injection, although sometimes PRP injections are given as a series of injections over several weeks. Some physicians may choose to add an activating agent (thrombin or calcium chloride) to PRP before its injection, while others only inject just the platelets based on the assumption that they can be slowly activated with the exposure to thrombin or tendon collagen. Potential risks related to PRP injection include infection, hemorrhage, and soft tissue injury. Concerns have also been raised about the potential harms of PRP in delaying tissue remodeling, excessive growth, and excessive scarring (de Vos 2011, Lee 2013),

To date, platelet rich plasma for the treatment of tendinopathy has not received FDA approval. The FDA has cleared several devices used in the preparation of PRP and has standards for the procedure of preparation of PRP.

Medical Technology Assessment Committee (MTAC)

Autologous Platelet Derived Wound Healing Factors for Non-Healing Cutaneous Wounds (Procuren)

BACKGROUND

Wound healing is a dynamic process that involves a complex interaction of several cellular and biochemical events. Tissue repair begins with a clot formation and platelet degranulation which release the growth factors necessary for wound repair. Generally, the process of normal healing takes few days to 2 weeks and involves three phases that may overlap in time: 1. inflammatory phase, 2. proliferative phase, and 3. remodeling phase. If any of these phases is compromised, healing will be delayed. Treatment of chronic non-healing

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cutaneous wounds has challenged health care providers for generations, and various strategies including devices, biologics and drug have been used to accelerate the healing process. These agents are designed to affect one of processes involved in healing (Robson 1999). Advances in biology of wound healing, showed that macrophages and platelets are the chief regulatory cells in the repair process. Platelets are known for their role in haemostasis where they help prevent blood loss at site of vascular injury. They adhere, aggregate, and form a procoagulant surface leading to thrombin generation and fibrin formation. Activated platelets release potent locally acting growth factors substances that initiate division and migration of fibroblasts and formation of new capillaries promoting wound healing (Knighton 1986, Fu 2005). Becaplermin, a topical treatment with platelet derived growth factor as its active ingredient was approved by the FDA in 1997 to treat diabetic foot and leg ulcers that extend into the subcutaneous tissue or beyond and have adequate blood supply. Platelet derived growth factor (Procuren) for the treatment of non-healing cutaneous wounds was reviewed by MTAC in February 1999, and failed MTAC evaluation criteria due to the lack of scientific evidence to determine its safety and efficacy. It is being re-reviewed based on requests for coverage from Eastern WA. ***Bone Fracture Healing (GEM 21STM)*** Bone fracture healing is a biological process that involves both local and systemic acute phase reactants. The physiological events occurring at the site of injury include hematoma formation, recruitment and transformation of mesenchymal cells, induction of angiogenesis, and the production and remodeling of the extracelluar matrix. Radiographic healing of a bone fracture is normally achieved in 4-13 months depending on type and location of the fracture. The rate of bone union also depends on several other factors as patient's health, compliance, nutritional status, stability of the fracture and others. Disruption of any of these factors would lead to delayed or non-union of the fracture. It was reported that approximately 10% of the bone fractures in the US are complicated by impaired healing, which has a high impact on the quality of life and burden of health costs. Several compounds and technologies have been, and are being developed to enhance fracture healing and accelerate repair. These include prostaglandins, gene therapy, growth hormone, parathyroid hormone, and growth factors. Among the growth factors studied are the bone morphologic proteins, transforming growth factor B, vascular endothelial growth factor, and platelet derived growth factor (PDGF) (Axelrad 2007, Hollinger 2008). In vitro and animal studies indicate that PDGF has the potential of accelerating the bone healing process. The experimental studies showed that PDGF receptors increase in osteoblasts as they mature, but that the response varies inversely to the number of receptors. This indicates that there is an optimal concentration and time during bone regeneration to deliver the PDGF in order to be effective (Axelrad 2007). The GEM 21STM a device for bone grafting material containing a therapeutic tri- calcium phosphate or PDGF was approved by the FDA for periodontally related defects in November 2005.
Tendinopathy Tendinopathy is a general term that is used to describe a tendon injury. It is characterized by pain, stiffness, and loss of strength in the affected area. Treatments for tendinopathy include, but are not limited to: rest, anti-inflammatory medication, analgesia, orthotics, physical therapy, and local steroid injections. Another more recent technology that has been proposed for the treatment of tendinopathy is platelet rich plasma injections into the ailing tendon (Kampa 2010). Platelets are small nonnucleated bloods cells that are involved in wound healing. The exact mechanism by which platelet rich plasma promotes tendon healing is unclear; however, it is thought that the growth factors and cytokines contained in the platelets speed tissue regeneration and healing. Platelets contain alpha granules and dense granules, which when stimulated release growth factors and cytokines. The alpha granules release: platelet-derived growth factor, transforming growth factor-beta, vascular endothelial growth factor, epidermal growth factor, insulin-like growth factor I and II, and fibroblast growth factor. These factors play an important role in cellular proliferation, chemotaxis, cellular differentiation, extracellular matrix production, and angiogenesis. The dense granules contain adenosine, serotonin, histamine, and calcium, which play a role in tissue modulation and regeneration (Foster 2009, Maffulli 2010). Platelet rich plasma is derived from anti-coagulated autologous whole blood, which is centrifuged to concentrate platelets in plasma. Normal platelet counts in the blood range from 150,000-350,000 µL. The goal of the devices used to create platelet rich plasma is to raise the concentration to at least one million platelets per µL. After separation, the platelet rich plasma must be clotted to allow for delivery to the desired site. This clotting leads to platelet activation, resulting in the release of growth factors and cytokines. Bovine thrombin, calcium chloride, and type I collagen are different agents used to stimulate platelet activation (clotting) (Foster 2009). One of the advantages of this approach is that because the platelet rich plasma is derived from the patient's own blood there is a low chance of rejection. However, the optimal dose range has not been defined. The injection of platelet rich plasma is a procedure and therefore not regulated by the FDA. However, several devices used in the preparation of platelet rich plasma have received FDA approved.

Platelet Derived Growth Factors
02/10/1999: MTAC REVIEW

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Evidence Conclusion: The published evidence on the effect of Procuren for treating non-healing cutaneous wounds consists of two small randomized controlled trials, one of which reports improvements in wound healing for Procuren as compared to placebo and the other trial reports worse outcomes with Procuren. The available evidence does not allow any conclusion about the effects of Procuren on non-healing cutaneous wounds.
Articles: Knighton DR, et al. Stimulation of repair in chronic, nonhealing cutaneous ulcers using platelet-derived wound healing formula. Surgery, Gyn, Obstet 1990;170:56-60.

There is insufficient scientific evidence that Procuren is medically effective and therefore does not meet *Kaiser Permanente Medical Technology Assessment Criteria*.

06/17/2003: MTAC REVIEW
Autologous Platelet Derived Wound Healing Factors in the treatment of Tendinopathy
Evidence Conclusion: *Achilles tendinopathy* De Vos and colleagues' study (2010), reviewed by MTAC earlier in 2010, is a double-blind, placebo-controlled, randomized, controlled trial that compared the effect of injecting platelet rich plasma (PRP) versus isotonic saline (placebo) in 54 patients with chronic midportion Achilles tendinopathy. After PRP injection, patients in the two study groups underwent standardized rehabilitation program including a daily eccentric exercise program for 12 weeks. The primary outcome was pain and activity level as measured with the Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire. The first publication of the trial (de Vos et al, 2010) reported on the clinical outcomes at 24 weeks, and the second (de Vos, et al 2011) reported on the effect of PRP on ultrasonographic tendon structure and neovascularization at 24 weeks. This was followed by another report (de Jonge, et al 2011) on the one-year clinical and ultrasonographic outcomes for the same group of patients (evidence table 1). The results of the trial showed significant improvement in pain and activity level among patients in both the PRP group and the placebo group at 24 weeks and at one year compared to baseline values. There were no statistically significant differences for these outcomes between the two study groups. The 24-weeks follow-up also showed a significant increase in the neovascularization scores among patients in the two treatment groups when compared to baseline, but with no between-group differences at any point of time (6,12,24 weeks, or 1 year). The one-year follow-up also showed that the ultrasonographic tendon structure improved significantly in both groups with no significant difference between them. Overall, the results of the trial indicate that adding PRP injection therapy to eccentric exercises for patients with midportion Achilles tendinopathy was not superior to the addition of saline injection as regards clinical outcomes, tendon structure, or neovascularization. The trial did not compare PRP head to head with eccentric exercises, nor did it include a comparison group that received PRP without exercises, which makes it hard to determine the effect of PRP used alone, and whether the eccentric exercises have a dominating positive effect that overshadows the benefit of PRP therapy. In addition, saline injection in the tendon may have had more than a placebo effect as either or both the trauma of introducing a needle (needling) into the tendon, and the volume increase due to saline injection into the tendon may initiate a healing response as noted by several investigators. *Lateral epicondylitis (tennis elbow)*
The few published RCTs on the use of PRP injections for the treatment of lateral epicondylitis, had their limitations and showed conflicting results. In these trials PRP was compared to the injection of corticosteroids, whole autologous blood, or saline. No comparisons were made to standardized eccentric muscle strengthening exercises used alone or to watchful waiting. Patients were included in the trials if they had symptoms of epicondylitis for at least 3 or 6 months (depending on study), not allowing for the natural healing of the condition (Peerbooms 2010 indicated that the "Natural history of lateral epicondylitis predominantly results in healed patients [80%] in one year). The studies used different definitions for success as well as different tools and questionnaires for measuring the outcomes. All, except for one trial, did not use ultrasonography to evaluate the effect of PRP therapy on tissue healing. Peerbooms (2010), Gosens (2011) and colleagues (Evidence table 2) conducted a double-blind RCT to compare the efficacy of a platelet rich plasma injection versus corticosteroid injection for the treatment of lateral epicondylitis in 100 patients who had failed non-operative treatment. Patients in the two treatment groups also participated in an eccentric exercise program. The primary outcome of the trial was the difference in successful outcomes (25% reduction in the pain according to VAS score or disabilities of the arm, shoulder, and hand according to DASH Outcome Measure), without a re-intervention after one year and 2 years of follow-up. The one-year follow-up results of the trial showed a statistically significant greater improvement in pain and function in the PRP group versus the corticosteroid group. Patients in the corticosteroid group experienced a decline in function after an initial short-term improvement. The 2-year follow-up results of the trial (Gosens et al 2011) showed that the mean improvement in the pain and function scores continued to favor the PRP group. The study had valid design and analysis, however, PRP was compared to corticosteroid, the use of which in tendinopathy is currently controversial as is known to have a short-term pain relief effect and may lead to permanent adverse changes in the tendon (according to the authors). The study did not include a placebo arm to determine whether the improvement observed with the PRP was due to the treatment or to the natural course of the lateral epicondylitis. The authors indicated that the natural history of lateral epicondylitis usually results in

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healed patients (80%) within 1 year, but they included patients with lateral epicondylitis for as short as 6 months. Ultrasound evaluation was not used to determine the effect of PRP on tissue healing. There was a discrepancy in the figures and numbers presented in the two published articles reporting on the 1-year and 2-year follow-up results. Creaney and colleagues (2011) compared the injection of blood versus PRP in 150 patients who had elbow tendinopathy for at least 6 months and had failed conservative therapy including physical therapy exercises (stretches and eccentric loading). The authors did not clearly indicate whether all patients had undergone a standardized muscle strengthening eccentric exercises. Study participants were randomly assigned to receive 2 injections (one month apart) of either PRP or autologous blood injection (ABI). The primary outcome was improvement in patient-related tennis elbow-evaluation (PRTEE) score at 6 months (PRTEE is a 0- 100 composite scale that measures pain and physical function). 20 patients (13%) were lost to follow-up at six months. Analysis of the results of the remaining 130 patients (authors considered it ITT analysis) showed a higher but statistically insignificant success rate in the ABI group (72%) vs. the PRP group (66%). Success was defined as an improvement in the PRTEE score of 25 points at 6 months. The study was randomized and controlled, but it compared two forms of growth factor preparations and did not include a placebo or sham therapy group that did not undergo tendon penetration, nor did it compare growth factor injection versus a standardized program of eccentric muscle exercises that are known to have a beneficial effect. The needling effect or placebo effect of injection cannot be ruled out. The investigators were not blinded, and no ultrasound evaluation was used to determine the effect of PRP on tissue healing. In addition, the trial does not allow studying the natural course of lateral epicondylitis, and its short follow-up duration does not allow studying the long-term effects or harms associated with the therapy. In a small trial Thanasas and colleagues (2011) also compared PRP versus autologous whole blood injection (ABI) for the treatment of lateral epicondylitis. In this trial the injection of either 3 mL PRP or 3 mL whole blood was given only once under ultrasound guidance and followed by a standardized eccentric muscle strengthening. The trial had only six months of follow-up and the primary outcome was improvement in pain (using VAS score) and function (using the Liverpool elbow score). The results of the study showed that PRP was more effective that ABI in reducing pain at 6 weeks, but not at 3 or 6 months. There was no significant difference between the two treatment groups in the functional score of Liverpool. Similar to Creaney and colleagues' trail, the study does not determine whether any benefit observed was due to the injected substance, needling procedure, or the natural course of the disease. The authors of a network meta-analysis (Krogh 2012) of RCTs that assessed the comparative effectiveness and safety of injection therapies in patients with lateral epicondylitis, concluded that autologous blood products either as whole blood or PRP may have benefits over placebo, only one trial (Peerbooms 2010) was considered to be at low risk of bias, and that further high quality RCTs are needed to evaluate these therapies before any recommendation can be made. A more recent double-blind RCT (Krogh et al 2013, evidence table 3) compared the effect of a single injection of PRP to the injection of corticosteroid or saline for the treatment of lateral epicondylitis in 60 patients. The primary outcome was pain reduction at 3 months (a change from 12 months in the initial protocol due to the high dropout rate resulting from unsatisfactory pain reduction). The study had other limitations including but not limited to the inclusion of patients who were not naïve to corticosteroids (58% of the participants had received corticosteroid therapy, and 35% had received more than one injection at study entry). The study also included patients with lateral epicondylitis symptoms for as short as 3.8 months (not allowing for natural healing of the condition), and as long as 232 months and combined them in the analysis. Saline injection may not have been the appropriate placebo as it was applied through 5-7 tendon perforations. Needling and/or volume increase due to saline injection could initiate a healing process. It is reported that needling, also known as microtenotomy, involves treating a chronic tendon injury, by attempting to change a chronic injury to an acute lesion that may have greater healing potential. The disruption of the tendinosis or scar tissue by needling and consequent bleeding is thought to release tissue growth factors that stimulate a healing response (Rha et al 2012). The authors of the trial also indicated that they did not test the actual platelet content but relied on the manufacturer's description. Overall, the results of the trial show that the effect of PRP or glucocorticoids on pain was not superior to saline injection, and that steroid injection was superior to PRP and saline in reducing color Doppler activity and tendon thickness.

Rotator cuff

A published RCT (Rha et al, 2012) compared the therapeutic effect of platelet rich plasma with dry needling in 38 patients with rotator cuff disease. The trial was randomized and blinded, but had a small size, included patients with tendon tear or tendinosis, had a short follow-up of six months, and a 25% dropout rate. The study participants were randomized to receive either two PRP injections or two dry needling procedures at 4-week intervals. The primary outcome measure was Shoulder Pain and Disability Index (SPADI). This was measured at baseline, two weeks after the first injection, immediately before the second injection, two weeks after the second injection, and at the 3- and 6-month follow-up visits. The authors did not indicate whether the analysis performed was intention to treat or completer analysis. Overall, the results indicated that patients in the two treatment groups showed a significant reduction in the Shoulder Pain and Disability Index and improvement of range of motion during follow-up. The PRP injections provided more symptomatic relief and functional improvement than dry needling at six months, but there was no difference in range of motion improvement between the two groups.

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These results should be interpreted with caution due to the limitations of the trial. *Plantar Fasciitis* Aksahin and colleagues (2012) compared the effect of corticosteroids and platelet rich plasma in 60 patients diagnosed with plantar fasciitis who had failed conservative therapy. The trial was not randomized which is a potential source of selection bias. The first 30 consecutive patients received corticosteroid injections and the second 30 patients received PRP injections. All participants were followed up for 6 months and the primary outcome was improvement in the mean VAS heal pain scores. The results showed significant improvement in each of the two groups compared to baseline, but there were no significant differences between the two groups. *Conclusion:* There is some evidence that the adding PRP injection therapy to eccentric exercises for patients with Achilles tendinopathy is **not** more effective than injecting the tendon with saline also in addition to eccentric exercises. There is insufficient evidence to determine that PRP injections given alone are effective at reducing pain and improving function in patients with lateral epicondylitis. There is insufficient evidence to determine the effect of PRP injections on rotator cuff disease, plantar fasciitis or other tendinopathies. The published studies do not allow making any conclusion on whether the effect of PRP injections is due to the therapy or due to healing initiated with needling of the tendons. There is insufficient evidence to determine the effect of PRP on tissue healing. There is insufficient evidence to determine whether there is an optimal PRP dose, concentration, or number and interval of injection that would potentially reduce pain and improve function in patients with tendinopathy. There are variations among the studies as regards the preparation of PRP products, platelet concentration, presence of white blood cells, and number of injections uses, which would limit generalization of the negative or positive results of the trials published to date. Definition of treatment success varied between studies. Larger RCTs with longer follow-up duration are needed to determine the efficacy and safety of PRP in tendinopathy.
Articles: The literature search for studies published after the last MTAC review of platelet rich plasma for the treatment of tendinopathy revealed 4 randomized controlled studies on PRP injections for lateral elbow epicondylitis, one for Achilles tendon, one for rotator cuff, and one for plantar fasciitis, as well as a number of case series with no control groups. A meta-analysis of studies on the use of platelets in the treatment of Achilles tendon injuries, and another network meta-analysis on the comparative effectiveness of injection therapies were also identified by the search. The meta-analyses were not selected for critical appraisal as the one that examined the role of platelets in the treatment of Achilles tendon injuries also included models and trials on the use of the therapy for tendon rupture repairs. The network meta-analysis on injection therapies included all types of injection therapy including PRP. The individual trails on PRP in either meta-analysis was reviewed separately. The following RCTs were critically appraised: *Achilles Tendinopathy* de Vos RJ, Weir A, van Schie HTM, et al. Platelet-rich plasma injection for chronic Achilles tendinopathy. *JAMA 2010;* 303:144-149. de Vos, Weir A, Tol JL, et al. No effects of PRP on ultrasonographic tendon structure and neovascularization in chronic midportion Achilles tendinopathy. *Br J Sports Med* 2011*;* 45:387-392. See Evidence Table De Jonge S, de Vos RJ, Weir A, et al. One-year follow-up of platelet-rich plasma treatment in chronic Achilles tendinopathy: a double-blind randomized placebo-controlled trial. *Am J Sports Med* 2011; 39:16231629. *Lateral Epicondylitis* Gosens T, Peerbooms JC, van Laar W, et al. Ongoing positive effect of platelet-rich plasma versus corticosteroid injection in lateral epicondylitis: a double-blind randomized controlled trial with 2-year follow-up. *Am J Sports Med* 2011; 39:1200-1208. Peerbooms JC, Sluimer J, Bruijn DJ, and Gosens T. Positive effect of an autologous platelet concentrate in lateral epicondylitis in a double-blind randomized controlled trial. *Am J Sports Med* 2010*;* 38:255-262. See Evidence Table. Krogh TP, Fredberg U, Stengaard-Pederson K, et al. Treatment of lateral epicondylitis with platelet-rich plasma, glucocorticoid, or saline: a randomized, double-blind, placebo-controlled trial. *Am J Sports Med* 2013; 41:625-635.
Peerbooms (2010), Gosens (2011) and colleagues Krogh et al 2013, See Evidence Table

The use of Autologous Platelet Derived Wound Healing Factors in the treatment of Tendinopathy does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*

Autologous Platelet Derived Wound Healing Factors
06/04/2008: MTAC REVIEW
Evidence Conclusion: *Wound Healing (Procuren)* The reviewer's conclusion in the previous MTAC report of 1999 was, "The published evidence on the effect of Procuren™ for treating non-healing cutaneous wounds consists of two small randomized controlled trials, one of which reports improvements in wound healing for Procuren™ as compared to placebo, and the other trial reports worse outcomes with Procuren™. The available evidence does not allow any conclusion about the effects of Procuren™ on non-healing cutaneous wounds." The literature search for the current review did not reveal any additional evidence that would determine the efficacy and safety of platelet derived growth factor for the treatment of non-healing cutaneous wounds.
Bone Fracture Healing (GEM 21STM) There insufficient published evidence to determine the efficacy and safety of autologous platelet derived wound healing factors for the treatment of non-healing fractures.
Articles: *Wound Healing* The search yielded around 100 articles. Many were review articles or publications not related to the current review. No meta-analyses of empirical studies, randomized or non-randomized controlled

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studies, published after the last review, were identified. *Bone Fracture Healing* The literature search did not reveal any empirical studies on the use of PDGF for bone fractures. The published studies were all related to the use of PDGF for of dental implants, periodontal wounds, defects, or bone turnover during periodontal repair. None was selected for critical appraisal.

The use of Autologous Platelet Derived Wound Healing Factors in the treatment of Non-Healing Wounds does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

The use of Autologous Platelet Derived Wound Healing Factors in the treatment of Non-Healing Fractures does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Autologous Platelet Derived Wound Healing Factors in the treatment of Tendinopathy

02/14/2011: MTAC REVIEW

Evidence Conclusion: *Achilles tendinopathy* A recent double-blind, placebo-controlled RCT evaluated the effects of adding a platelet rich plasma (PRP) injection to an eccentric exercise program in 54 patients with chronic midportion Achilles tendinopathy. The primary outcome measures were pain and activity level, measured using the Victorian Institute of Sports Assessment-Achilles (VISA-A). In both groups, VISA-A scores improved significantly after 24 weeks; however, there was no significant difference in VISA-A score between the two groups. With regard to safety, no microbial growth was found in the collected PRP samples, and no complications (infections, hematomas, or ruptures) were reported after the treatment (de Vos 2010). *Lateral epicondylitis (tennis elbow)* A double-blind RCT that included 100 subjects compared the efficacy of a platelet rich plasma injection to a corticosteroid injection for the treatment of lateral epicondylitis in patients who had failed non-operative treatment. In addition to a platelet rich plasma injection or a corticosteroid injection subjects also participated in an eccentric exercise program. The primary outcome measures were pain, measured using the visual analog scale (VAS), and disability, measured using the disability of the arm, shoulder, hand (DASH) outcome measure. Successful treatment was defined as more than a 25% reduction in VAS or DASH without a re-intervention after 1 year. According to the VAS, treatment was successful for 73% of subjects in the platelet rich plasma group and 49% in the corticosteroid group (P<0.001). When using the DASH, treatment was successful for 73% of subjects in the platelet rich plasma group and 51% in the corticosteroid group (P=0.005). This trial did not address safety. Results from this study should be interpreted with caution as there are several methodological limitations (Peerbooms 2010). *Conclusion:* There is insufficient evidence to support the use of platelet rich plasma injection for the treatment of Achilles tendinopathy. There is evidence from one small RCT that supports the use of this technology for patients with lateral epicondylitis; however, because of methodological limitations results from this trial are insufficient to determine the safety and efficacy of this procedure. Several trials are currently underway to determine the safety and efficacy of platelet rich plasma injections for the treatment of tendinopathy.

Articles: Studies were selected for review if they included at least 25 subjects and assessed either the safety or efficacy of platelet rich plasma injections for the treatment of tendinopathy. Studies were excluded if they lacked a valid comparison group. Two RCTs were selected for review. The following studies were critically appraised: de Vos RJ, Weir A, van Schie HTM, et al. Platelet-rich plasma injection for chronic Achilles tendinopathy. JAMA 2010; 303:144-149. See Evidence Table. Peerbooms JC, Sluimer J, Bruijn DJ, and Gosens T. Positive effect of an autologous platelet concentrate in lateral epicondylitis in a double-blind randomized controlled trial. Am J Sports Med 2010; 38:255-262. See Evidence Table.

The use of Autologous Platelet Derived Wound Healing Factors in the treatment of Tendinopathy does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

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Platelet Rich Plasma for Knee Osteoarthritis

04/21/2018: MTAC Review

Evidence Conclusion:

- The published evidence on the use of PRP for knee OA is inconclusive and do not allow making a recommendation for or against using PRP for the treatment of knee osteoarthritis. The published studies have methodological limitations and their results are mixed. It is difficult to determine whether the inconsistency in the outcomes of the individual trials and their pooled results is due to the severity of the knee OA, differences in platelet separation technique, concentration or activation, timing and frequency of administration of PRP, variations in response between the individuals, quality of the studies including blinding of the patients, or the outcome measures used. None of the published studies evaluated the effect of PRP therapy on any structural changes or remodeling of the knee joint.

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- The published literature does not provide sufficient evidence to determine the long-term comparative efficacy and safety of PRP to other standard recommended pharmacological or non-pharmacological therapies for knee osteoarthritis.
- Additional studies are needed to determine the optimal protocol for delivering PRP, the criteria for selecting the patients who may benefit from the treatment, as well as the long-term efficacy and safety of PRP for the treatment of knee OA. An ideal study would be double-blinded RCTs with sufficient statistical power, adequate randomization, standardized inclusion/exclusion criteria for patient selection, standardized protocol for PRP preparation and delivery, valid comparator, with objective as well as the subjective outcome measures, and long-term follow-up.
- A search of the National Institute of Health Clinical Trials website for ongoing trial identified several active trials including:
  - Bone Marrow Aspirate Compared to Platelet Rich Plasma for Treating Knee Osteoarthritis ClinicalTriasl.gov Identifier NCT03289416
  - Efficacy of Hyaluronic Acid and Platelet-rich Plasma Combination in Knee Osteoarthritis ClinicalTrials.gov Identifier NCT03211650
  - Steroids, Hyaluronic Acid or Platelet Rich Plasma versus Placebo for Knee Osteoarthritis the (KIT). ClinicalTrials.gov Identifier NCT02776514
  - Intraarticular Platelet Rich Plasma Injections versus Intraarticular Corticosteroid Injections in Primary Knee Osteoarthritis. ClinicalTriasl.gov Identifier NCT01923909

Articles: The literature search for studies on the comparative efficacy and safety of PRP and standard therapies used for knee OA revealed eight meta-analyses (MAs) published in the last 4 years, 19 relevant randomized and nonrandomized trials published in the last 10 years, and less than 10 case series/reports. The published meta-analyses were overlapping, 4 included randomized controlled trials (RCTs) as well as quasi- randomized trials and observational studies, and 4 included only RCTs. The meta-analyses of RCTs were given preference over the individual RCTs, which were small, had insufficient statistical power, and conflicting results. A meta-analysis of RCTs provides greater statistical power to detect significant differences and allows performing subgroup analyses. Three of the 4 identified meta-analyses of RCTs were selected for critical appraisal, based on their methodological quality, inclusiveness, inclusion of the more recently published RCTs, grading the quality the studies included, quantitative synthesis of the results of RCTs as a primary analysis, and/or comparing the outcomes of PRP versus an active treatment separately either as the primary analysis or in a subgroup analysis.

A more recently published meta-analysis (See Evidence Table 1 - Zhang et al, 2018) was identified by the search but was not selected for critical appraised as it pooled the results of prospective non-randomized trials together with the RCTs, and had no subgroup analysis for the RCTs.

Two recent trials (See Evidence Table 2 - Cole et al, 2017, and See Evidence Table 3 - Joshi Jubert et al, 2017) not included in the three meta-analyses reviewed was also selected for critical appraisal.

The use of Platelet Rich Plasma (PRP) for the Treatment of Knee Osteoarthritis (OA) does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Platelet Rich Plasma (PRP) for the treatment of Plantar Fasciitis (PF) (Plantar Fasciopathy)

04/21/2018: MTAC REVIEW

Evidence Conclusion:

- There is insufficient published evidence to determine that the effectiveness and safety of the local injection of platelet rich plasma is equivalent or superior to local steroid injection or to other pharmacological or nonpharmacological therapies currently used for the treatment of patients with plantar fasciitis. The overall quality of published studies is poor, with some trials reporting improvement with PRP and others reporting no improvement. It is difficult to determine whether the differences in the reported results are due to differences in the platelet separation technique, concentration or activation; or due to differences in the timing and frequency of administration or outcome measures.
- There is insufficient published evidence to determine the long-term efficacy and safety of PRP in treating patients with chronic plantar fasciitis.
- Large-scale, high-quality randomized controlled trials with blinding of outcome assessment and longer follow-up are required to provide evidence on the long-term safety and effectiveness of PRP for treating patients with plantar fasciitis.
- Ongoing trials:

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- o RCT Comparing Steroid Injections and Platelet Rich Plasma Injections in the Treatment of Plantar Fasciitis. ClinicalTrials.gov Identifier: NCT01957631.
- o RCT Comparing ESWT with PRP for Plantar Fasciitis in High Demand Cohort. ClinicalTrials.gov Identifier: NCT02668510

Articles: The literature search for studies on the efficacy and safety of platelet rich plasma injections, published after the 2010 MTAC review identified three systematic reviews with meta-analyses, one network meta-analysis, two qualitative systematic review, and 14 small trials (10 RCTs and 4 non-randomized) that compared local injection of platelet rich plasm versus steroid injection in the majority of trials. PRP was compared to shock wave therapy in one trial, dextrose prolotherapy in another and to low-dose radiation also in one trial.
One meta-analysis (Tsikopoulos, 2016) included only 3 earlier studies and was excluded from the review. The other two meta-analyses (See Evidence Table 1 - Yang, 2017 and See Evidence Table 2, 2017 and) as well as the randomized controlled trial with the lowest risk of bias (See Evidence Table 3 - Mahindra, 2016) were selected for critical appraisal.

The use of Platelet Rich Plasma (PRP) for the treatment of Plantar Fasciitis (PF) (Plantar Fasciopathy) does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Applicable Codes

Medicare- Considered Medically Necessary when criteria in the applicable policy statements listed above are met
Non-Medicare-Considered Not Medically Necessary

CPT® or HCPC Codes	Description
0232T	Injection(s), platelet rich plasma, any site, including image guidance, harvesting and preparation when performed
G0460	Autologous platelet rich plasma for chronic wounds/ulcers, including phlebotomy, centrifugation, and all other preparatory procedures, administration and dressings, per treatment
P9020	Platelet rich plasma, each unit
S9055	Procuren or other growth factor preparation to promote wound healing

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed	Date Revised
04/1999	10/05/2010 MDCRPC, 04/05/2011 MDCRPC, 11/01/2011 MDCRPC, 09/04/2012 MDCRPC, 07/02/2013 MDCRPC, 08/06/2013 MPC, 06/03/2014 MPC, 04/07/2015 MPC, 02/02/2016 MPC, 12/06/2016 MPC, 10/03/2017 MPC, 09/04/2018 MPC, 09/03/2019 MPC, 09/01/2020 MPC, 09/07/2021 MPC, 09/06/2022 MPC, 09/05/2023 MPC	09/13/2021

MDCRPC Medical Director Clinical Review and Policy Committee
MPC Medical Policy Committee

Revision History	Description
11/22/2017	Added non-covered services LCD
05/01/2018	Added MTAC reviews for Platelet Rich Plasma (PRP) for the treatment of Plantar Fasciitis (PF) (Plantar Fasciopathy) & Knee Osteoarthrtitis
09/01/2020	Added Medicare LCA A57642
04/15/2021	Added CPT code S9055
08/02/2021	Removed LCD L35008 and LCA A57642; added LCA A58351

09/13/2021	Updated NCD version 270.3

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Date Sent: 3/29/24
These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage.
Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

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Clinical Review Criteria
Plethysmography

- Lower Limb Deep Vein Thrombosis (DVT)
- Occlusive Peripheral Arterial Disease (PAD)

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Plethysmography (20.14)
Local Coverage Determinations (LCD)	None
Local Coverage Article	None

For Non-Medicare Members

Clinical review is no longer required for this service.

PADnet System for the Detection of Peripheral Vascular Disease

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Plethysmography (PG) is a noninvasive method used to measure changes in blood flow or air volume within an organ or the whole body. The term plethysmography is a combination of the ancient Greek words plethysmos, which means increase, and grapho which means write (Alnaeb 2007).Total body plethysmography measures intrathoracic gas volume and volume change, pulmonary plethysmography measures the volume of air that can be voluntarily inhaled or exhaled, limb plethysmography measures changes in the volume of a limb in response to change in blood volume, and genital plethysmography measures blood flow in the genitals.

There are several types of plethysmographic systems that measure blood flow and velocity in the carotid artery and peripheral vascular system. These include electrical impedance plethysmography, segmental plethysmography, oculoplethysmography, strain gauge plethysmography, photoelectric plethysmography, air plethysmography, and several others. These instruments indirectly detect and quantify vascular disease based in alterations in pulse wave contour, blood pressure, or arterial or venous blood flow (Barnes 1991, Graham 1996).

Oculoplethysmography indirectly measures the hemodynamic significance of internal carotid artery stenosis or occlusion by demonstration of an ipsilateral delay in the arrival of ocular pressure transmitted from branches of the ophthalmic artery. It detects only severe narrowing or blockage and is incapable of directly measuring the flow or demonstrating anatomic information or quantifying percent of stenosis. Other tests (ultrasound or angiography) are required to confirm the diagnosis and have largely replaced this technique (Graham 1996).

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Photoplethysmography (PPG) is a technique based on the determination of optical properties of the underlying tissue. It uses an optical light-emitting diodide in a sensor that is attached to the skin and transmits light through the dermis into the subcutaneous tissue. A photoelectric cell captures the reflected light to detect changes in blood volume. Changes in the beam wavelength are measured by a microcomputer and a plethysmogram representing the blood flow of the limb is produced. PPG is not strictly a plethysmographic technique as its operation is based on the principles of light densitometry and photon diffusion theory. Both PPG and light reflection rheography (also known as quantitative PPG), have been used in the detection of varicose veins, venous insufficiency, phlebothrombosis, and other peripheral venous disease (Higgins 1986, Keechi 2008, Khandanpour 2009).

Strain-gauge plethysmography (SPG) uses the technique of filling the distal veins of the lower limbs by inflation of a tourniquet around the thigh, causing occlusion of the veins, then indirectly measuring the changes in venous outflow and capacitance in response to release of tourniquet by a strain gauge placed around the calf. The strain-gauge plethysmography may also be used to assess the effectiveness of different types of compression devices on the legs of patients with venous deficiency (Siau 2010).

Impedance plethysmography is performed by placing two sets of electrodes around the patient's calf and an oversized blood pressure cuff around the thigh. The electrodes sense a change in blood volume and record it on a strip chart. Changes in venous filling are produced by inflating the thigh cuff to obstruct venous return, then deflating the cuff to re-establish blood flow. The time required for the venous volume in the calf to return to baseline is recorded. A clot in the popliteal or proximal veins will delay venous emptying. In water plethysmography, an extremity is enclosed in a water-filled chamber where volume changes can be detected. Air plethysmography is based on the same principle but uses an air-filled long cuff. As indicated these techniques depend on detecting alterations in venous outflow and capacitance in the presence of thrombi in the deep veins. Extrinsic compression of the proximal veins by pregnancy tumor, or poor venous outflow in cases of severe edema, all may lead to false positive results. It was also reported that plethysmographic techniques are inaccurate in detecting deep vein thrombosis in vessels in which the venous outflow has not been significantly impeded by the thrombus (Graham1996, Locker 2006, Mosti 2010).

Segmental plethysmography (or pulse volume recording [PVR]) is a noninvasive hemodynamic measurement that can potentially provide an initial assessment of the location and severity of peripheral arterial disease. Segmental limb plethysmography waveform analysis is based on evaluation of waveform shape and signal amplitude. Standardized criteria relating waveform changes to anatomic site and hemodynamic severity of disease are used in the diagnostic interpretation. The test involves placing cuffs around the leg at selected locations and connecting them to a plethysmograph to detect and graphically record changes in limb volume. Normally, a single, large thigh cuff is used along with regular-sized calf and ankle cuffs, plus a brachial cuff that reflects the undampened cardiac contribution to arterial pulsatility. Once the cuff is inflated to 60–65 mmHg (a pressure sufficient to detect volume changes without resulting in arterial occlusion), pulse volume recordings are obtained. These PVRs have the potential of detecting and localizing significant occlusive lesions. The tests can also be repeated over time to follow disease progression. Segmental plethysmography is an indirect examination of the artery and may not detect multiple stenoses located at or above the level of the cuff (Gerhard-Herman 2006. Clements, TASC).

Plethysmography have the potential of providing rapid and non-invasive diagnosis of deep vein thrombosis, and peripheral arterial diseases, and was once considered to be the primary diagnostic test for noninvasive detection of deep vein thrombosis (Stevens 2007, Abbara 2010). However, it has been reported that due to its inaccuracy and with the improvements in both direct real-time ultrasonic imaging and Doppler ultrasonic flow detection and color-flow mapping, plethysmography as well s other indirect techniques are assuming a less important role in vascular diagnosis (Barnes 1991, Stevens 2007).

Several plethysmographic devices have received FDA clearance as Class II medical devices to assist in the diagnosis of vascular disease. PADnet System for the detection of peripheral vascular disease was previously reviewed by MTAC in 2005 and did not meet its evaluation criteria due to lack of evidence on the system. The current review focuses on the use of plethysmography in the diagnosis of deep vein thrombosis and occlusive peripheral arterial disease.

The PADnet lab, manufactured by BioMedix, is a noninvasive cardiovascular blood flow monitor intended for use by trained medical professionals for the early detection of peripheral vascular disease (FDA Home page). The manufacturer claims that it detects blockages in arteries and the quality of blood flow using pulse volume recording and oscillometer segmental blood pressure measurement. It is used with a pressure cuff that is applied

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and inflated to shut off the flow in the artery. When deflated the device records the oscillations and assigns a systolic pressure value and the results sent to the vascular specialists (BioMedix Web site). The device includes a laptop computer and a color printer on a medical grade car.

The FDA cleared PADnet for marketing in October 2004 based on its equivalence to legally marketed predicate devices.

Medical Technology Assessment Committee (MTAC)

PADnet system

08/01/2005: MTAC REVIEW

Evidence Conclusion: There is no published data to date on the PADnet system other than the marketing information provided by BioMedix, the manufacturer of the device, on their web site.
Articles: The search did not reveal any studies or articles on the PADnet system.

The use of PADnet system in the evaluation for early detection of peripheral vascular disease does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

PADnet system

06/20/2011: MTAC REVIEW

Evidence Conclusion: Use of plethysmography for detecting deep vein thrombosis. The published studies showed variable accuracies for the different plethysmographic techniques. The sensitivity ranged from 20-100% and specificity from the lower 60s to the upper 90s. The negative predictive value was as high as 100% for some systems such as digital photoplethysmography (D-PPG) used for screening asymptomatic patients at high risk for developing DVT. It performed better for proximal vs. distal (calf) DVTs. In a meta-analysis of 78 studies, Locker and colleagues (Evidence table 1) evaluated the performance of plethysmography and rheography in the diagnosis of DVT. Sensitivity and specificity were 75% and 90% respectively for impedance plethysmography, 83% and 81% for strain-gauge plethysmography, 85% and 91% for air plethysmography, and 91% and 71% for light-reflex rheography. The authors concluded that the accuracy of these techniques is insufficient to use them as stand-alone tests for screening for DVT. Siau and colleagues, 2010 (Evidence table 2) examined the accuracy of Well's clinical predictive tool, D-dimer analysis, and computerized strain-gauge plethysmography (CSGP) in the assessment of patients with suspected DVT, using imaging as a gold standard. The results showed that CSPG had a poor sensitivity and relatively low negative predictive value. CSPG performed better for above knee DVT vs. calf DVT, but still had an insufficient accuracy. Its use with D-Dimer did not add value to D-Dimer testing alone.
Williams and colleagues (2005) also assessed the clinical utility of D-Dimer, strain-gauge plethysmography and a combination of both in the diagnosis of DVT in 243 patients with low, moderate, and high clinical pretest probability (PTP) of DVT. A definitive diagnosis of the disease was made based on a compression ultrasound. The results of the study showed that the plethysmography had lower negative predictive values than those of D-dimer test for patients with low, moderate, or high PTP. The addition of strain-gauge plethysmography did not improve clinical decision making in any of the groups. Sharif-Kashani, et al (Evidence table 3) evaluated the role of digital photoplethysmography (D-PPG) in screening asymptomatic patients at high risk for developing DVT. They examined 337 lower limbs of 169 patients and showed that D-PPG had 100% sensitivity in detecting DVT in these patients at high risk. It also had a 100% negative predictive value, i.e. it is a good test for excluding the disease. However, it had a lower specificity indicating that patients with abnormal results will need further investigations. It is to be noted that all detected DVTs were proximal and the results cannot be generalized to distal vein thrombosis. There is insufficient published evidence evaluate the accuracy of plethysmography in the diagnosis of clinically suspected upper extremity DVT. Use of plethysmography for detecting occlusive peripheral artery disease (PAD). The majority of published studies on the use plethysmography for detecting lower limb peripheral occlusive disease examined the accuracy and predictive values of photoplethysmography (PPG) and/ or agreement with other standard measures of ankle brachial pressure index (ABPI). In a study of selected 131 patients diagnosed with PAD, Khandanpour and colleagues, 2009 (Evidence table 4) found a significant agreement between ankle brachial pressure index (ABPI) derived from photoplethysmography (PPG) or continuous wave Doppler (CW-Doppler). Allen et al, 2008 (Evidence table 5) assessed the diagnostic accuracy of novel bilateral photoplethysmography toe pulse measurement techniques for the detection of significant lower limb PAD. The study included 111 subjects of whom 48 (43%) had a significant disease. The study results show high accuracy and significant agreement between bilateral PPG and ankle-brachial pressure index in detecting higher grade peripheral artery disease in the lower limbs. With the pulse measurement techniques studied PPG was found to have high negative predictive value when used to screen population with low prevalence of the

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disease, and a high positive predictive value among high disease prevalence patients referred to a vascular laboratory.
Other published small studies evaluated different algorithms and devices based on PPG for the assessment of PAD and concluded that the technology may be used as a noninvasive screening tool for early detection of the disease. It was reported however, that the technology may not provide valid measurements for patients with very high systolic arterial pressure, obesity, edema, or those with stiff arteries e.g. in diabetes mellitus, hypercholesterolemia, end-stage renal disease, and advanced age (Alnaeb 2007). The effect of using plethysmography vs. other standard techniques on clinical decision making and outcome of patients diagnosed with early or significant peripheral artery disease was not studied.
Articles: The following studies were selected for critical appraisal based on their population sizes and methodological quality: Allen J, Overbeck K, Nath AF, et al. A prospective comparison of bilateral photoplethysmography versus the ankle-brachial pressure index for detecting and quantifying lower limb peripheral arterial disease. J Vasc Surg. 2008; 47:794-802. See Evidence Table. Khandanpour N, Armon MP, Jennings B, et al. Photoplethysmography, an easy and accurate method for measuring ankle brachial pressure index: can photoplethysmography replace Doppler? Vasc Endovascular Surg. 2009; 43:578-582. See Evidence Table. Locker T, Goodacre S, Sampson F, et al. Meta-analysis of plethysmography and rheography in the diagnosis of deep vein thrombosis. Emerg Med J 2006; 23:630-635. See Evidence Table. Sharif-Kashani B, Behzadnia N, Shahabi P, et al. Screening for deep vein thrombosis in asymptomatic high-risk patients: a comparison between digital photoplethysmography and venous ultrasonography. Angiology. 2009; 60:301-317. See Evidence Table. Siau K, Davies A, and Laversuch. Is there still a role for computerized strain gauge plethysmography in the assessment of aptients with suspected deep vein thrombosis? Q J Med 2010; 103:259-264. See Evidence Table.

The use of plethysmography in the evaluation of lower limb deep vein thrombosis (DVT) and occlusive peripheral arterial disease (PAD) does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Medicare – Considered Medically Necessary when criteria in the applicable policy statements listed above are met:
Non-Medicare – medical necessity review no longer required

CPT® or HCPC Codes	Description
93050	Arterial pressure waveform analysis for assessment of central arterial pressures, includes obtaining waveform(s), digitization and application of nonlinear mathematical transformations to determine central arterial pressures and augmentation index, with interpretation and report, upper extremity artery, non-invasive
93922	Limited bilateral noninvasive physiologic studies of upper or lower extremity arteries, (eg, for lower extremity: ankle/brachial indices at distal posterior tibial and anterior tibial/dorsalis pedis arteries plus bidirectional, Doppler waveform recording and analysis at 1-2 levels, or ankle/brachial indices at distal posterior tibial and anterior tibial/dorsalis pedis arteries plus volume plethysmography at 1-2 levels, or ankle/brachial indices at distal posterior tibial and anterior tibial/dorsalis pedis arteries with, transcutaneous oxygen tension measurement at 1-2 levels)
93923	Complete bilateral noninvasive physiologic studies of upper or lower extremity arteries, 3 or more levels (eg, for lower extremity: ankle/brachial indices at distal posterior tibial and anterior tibial/dorsalis pedis arteries plus segmental blood pressure measurements with bidirectional Doppler waveform recording and analysis, at 3 or more levels, or ankle/brachial indices at distal posterior tibial and anterior tibial/dorsalis pedis arteries plus segmental volume plethysmography at 3 or more levels, or ankle/brachial indices at distal posterior tibial and anterior tibial/dorsalis pedis arteries plus segmental transcutaneous oxygen tension measurements at 3 or more levels), or single level study with provocative functional maneuvers (eg, measurements with postural provocative tests, or measurements with reactive hyperemia)
93924	Noninvasive physiologic studies of lower extremity arteries, at rest and following treadmill stress testing, (ie, bidirectional Doppler waveform or volume plethysmography recording and analysis at rest with ankle/brachial indices immediately after and at timed intervals following performance of a standardized protocol on a motorized treadmill plus recording of time of onset of claudication or other symptoms, maximal walking time, and time to recovery) complete bilateral study

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***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed	Date Last Revised
08/01/2005	08/01/2005 MDCRPC, 07/05/2011MDCRPC, 05/01/2012MDCRPC, 03/05/2013MDCRPC, 01/07/2014MPC, 11/04/2014MPC, 09/01/2015MPC, 07/05/2016MPC, 05/02/2017MPC, 03/06/2018MPC, 03/05/2019MPC, 03/03/2020MPC, 03/02/2021MPC, 03/01/2022MPC, 03/07/2023MPC	08/02/2016

MDCRPC Medical Director Clinical Review and Policy Committee
MPC Medical Policy Committee

Revision History	Description
08/02/2016	Approved to stop clinical review for non-medicare members

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Clinical Review Criteria

Pneumatic Compression Devices

- Treatment of Lymphedema and Chronic Venous Insufficiency
- Prevention of Deep Vein Thrombosis

Intermittent Pneumatic Compression for the Treatment of Peripheral Arterial Occlusive Disease

- ArtAssist Device
- ArterialFlowTM System
- Flow MedicTM System

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Pneumatic Compression Devices (280.6)
Local Coverage Determinations (LCD)	Pneumatic Compression Devices (L33829)
Local Coverage Article	Pneumatic Compression Devices (A52488)

A PCD coded as E0676 is used only for prevention of venous thrombosis. Refer to the related Policy Article NONMEDICAL NECESSITY COVERAGE AND PAYMENT RULES section for information about lack of a Medicare benefit for devices used for prophylaxis of venous thrombosis.

Prevention of Post-Operative Deep Vein Thrombosis in the outpatient setting
There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

For Non-Medicare Members

***Definitions**

Edema: Edema is a non-specific term for the accumulation of fluid in tissue, most often in the extremities. There are numerous causes for edema, ranging from systemic disorders (e.g. congestive heart failure, etc.) to local conditions (post-surgery, congenital abnormalities, etc.). (Examples are not all-inclusive).

Lymphedema, as discussed below, is just one group of conditions that can be a cause of accumulation of fluid in the tissue. Lymphedema arises from disorders of the lymphatic system. It is essential to rule out other causes of edema in order to diagnose lymphedema. Edema from other causes is not classified as lymphedema for purposes of Medicare reimbursement for PCDs (E0650-E0652).

Primary lymphedema: Primary lymphedema is a disorder of the lymphatic system that occurs on its own. It is inherited and uncommon. Examples (not all-inclusive) are:

A. Congenital lymphedema due to lymphatic aplasia or hypoplasia
B. Milroy's disease, an autosomal dominant familial form of congenital lymphedema
C. Lymphedema praecox

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D. Lymphedema tarda

Secondary lymphedema: Secondary lymphedema is a disorder of lymphatic flow that is caused by some other disease or condition. It is more common than primary lymphedema. It is most commonly caused by surgery (especially lymph node dissection, such as for breast cancer), radiation therapy (especially axillary or inguinal), trauma, lymphatic obstruction by tumor, and, in developing countries, lymphatic filariasis. Secondary lymphedema may also result from compression of the lymphatic and venous channels resulting from leakage of fluid into interstitial tissues in patients with chronic venous insufficiency. (See below)

Chronic Venous Insufficiency (CVI): Lymphedema may also be caused by CVI when fluid leaks into the tissues from the venous system. CVI of the lower extremities is a condition caused by abnormalities of the venous wall and valves, leading to obstruction or reflux of blood flow in the veins. Signs of CVI include hyperpigmentation, stasis dermatitis, chronic edema, and venous ulcers. The incidence of lymphedema from CVI is not well established.

Peripheral Arterial Disease (PAD)

Peripheral artery disease is a circulatory problem in which narrowed arteries reduce blood flow to limbs, resulting in compromised blood flow to the distal tissue and failure to keep up with oxygen demands.

Service	Criteria
Effective until June 1, 2024 I. **Lymphedema** A PCD coded as E0650 or E0651 is covered for both primary and secondary lymphedema*, see definitions above, in beneficiaries with chronic and severe lymphedema when **ALL** of the following three requirements are met: 1. The beneficiary has a diagnosis of lymphedema as defined below, and 2. The beneficiary has persistence of chronic and severe lymphedema as identified by the documented presence of at least one of the following clinical findings: o Marked hyperkeratosis with hyperplasia and hyperpigmentation o Papillomatosis cutis lymphostatica, o Deformity of elephantiasis, o Skin breakdown with persisting lymphorrhea, o Detailed measurements over time confirming the persistence of the lymphedema with a history evidencing a likely etiology, and 3. In addition to this documented persistence, the lymphedema is then documented to be unresponsive to other clinical treatment over the course of a required four-week trial* (see below for trial guidelines): A. A four-week trial of conservative therapy demonstrating failed response to treatment is required. The four-week trial of conservative therapy must include **ALL** of the following: 1. Regular and compliant use of an appropriate compression bandage system or compression garment to provide adequate graduated compression a. Adequate compression is defined as (1) sufficient pressure at the lowest	**Effective June 1, 2024** **LCD Pneumatic Compression Devices L33829** **I. LYMPHEDEMA** A PCD coded as E0650 or E0651 is covered for both primary and secondary lymphedema in beneficiaries with chronic and severe lymphedema when all of the following three requirements are met: 1. The beneficiary has a diagnosis of lymphedema as defined above, and 2. The beneficiary has persistence of chronic and severe lymphedema as identified by the documented presence of at least one of the following clinical findings: o Marked hyperkeratosis with hyperplasia and hyperpigmentation, o Papillomatosis cutis lymphostatica, o Deformity of elephantiasis, o Skin breakdown with persisting lymphorrhea, o Detailed measurements over time confirming the persistence of the lymphedema with a history evidencing a likely etiology, and 3. In addition to this documented persistence, the lymphedema is then documented to be unresponsive to other clinical treatment over the course of a required four-week trial. (See below for trial guidelines.) A PCD coded as E0650 or E0651 used to treat lymphedema that does not meet all of the requirements above is not eligible for reimbursement. Claims will be denied as not reasonable and necessary. A PCD coded as E0650 or E0651 used to treat edema from causes other than lymphedema is not eligible for

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pressure point to cause fluid movement and (2) sufficient pressure across the gradient (from highest to lowest pressure point) to move fluid from distal to proximal. The compression used must not create a tourniquet effect at any point
   b. The garment may be prefabricated or custom-fabricated but must provide adequate graduated compression starting with a minimum of 30 mmHg distally
2. Regular exercise
3. Elevation of the limb

II. Chronic Venous Insufficiency with Venous Stasis Ulcers (CVI)

A PCD coded as E0650 or E0651 is covered for the treatment of CVI*, see definitions above, of the lower extremities only if the patient has **ALL** of the following:

A. Edema in the affected lower extremity
B. One or more venous stasis ulcer(s)
C. The ulcer(s) have failed to heal after a six-month trial of conservative therapy directed by the treating physician. (See below for trial guidelines)

Six-Month Trial for CVI

A six-month trial of conservative therapy demonstrating failed response to treatment is required. The six-month trial of conservative therapy must include **ALL** of the following:

A. Compliant use of an appropriate compression bandage system or compression garment to provide adequate graduated compression
   a. Adequate compression is defined as (1) sufficient pressure at the lowest pressure point to cause fluid movement and (2) sufficient pressure across the gradient (from highest to lowest pressure point) to move fluid from distal to proximal. The compression used must not create a tourniquet effect at any point
   b. The garment may be prefabricated or custom-fabricated but must provide adequate graduated compression starting with a minimum of 30 mmHg distally
B. Medications as appropriate (e.g. diuretics and/or other treatment of congestive failure, etc.)
C. Regular exercise
D. Elevation of the limb
E. Appropriate wound care for the ulcer (including sharp debridement where appropriate)

At the end of the six-month trial, if there has been improvement, then reimbursement for a PCD is not reasonable and necessary. Where improvement has occurred, the trial of conservative therapy must be continued with subsequent reassessments. When no further improvement has occurred for a continuous reimbursement. Claims will be denied as not reasonable and necessary.

A PCD coded as E0652 is not covered for the treatment of lymphedema of the extremities alone even if the criteria in this section are met. Claims will be denied as not reasonable and necessary. Refer below to the sections III - LYMPHEDEMA EXTENDING ONTO THE CHEST, TRUNK AND/OR ABDOMEN and PCD Code Selection for additional information about the limited coverage for PCD coded as E0652.

Four-Week Trial for Lymphedema

A four-week trial of conservative therapy demonstrating failed response to treatment is required. The four-week trial of conservative therapy must include all of the following:

- Regular and compliant use of an appropriate compression bandage system or compression garment to provide adequate graduated compression
  - Adequate compression is defined as (1) sufficient pressure at the lowest pressure point to cause fluid movement, and (2) sufficient pressure across the gradient (from highest to lowest pressure point) to move fluid from distal to proximal. The compression used must not create a tourniquet effect at any point.
  - The garment may be prefabricated or custom-fabricated but must provide adequate graduated compression starting with a minimum of 30 mmHg distally.
- Regular exercise
- Elevation of the limb

When available, manual lymphatic drainage is a key component of conservative treatment as is appropriate medication treatment when there is concurrent congestive heart failure.

The medical necessity determination for a PCD by the treating practitioner must include symptoms and objective findings, including measurements, to establish the severity of the condition.

The documentation by the treating practitioner of the medical necessity of a PCD must include:

- The patient's diagnosis and prognosis;
- Symptoms and objective findings, including measurements which establish the severity of the condition;
- The reason the device is required, including the treatments which have been tried and failed; and
- The clinical response to an initial treatment with the device

The trial of conservative therapy must be documented in the beneficiary's medical record before prescribing any type of PCD (E0650, E0651, E0652). This

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period of six months and the coverage criteria above are still met, then the use of a PCD to treat CVI is eligible for reimbursement.

III. Continuation of Use
Kaiser Permanente covers continuation of use of a pneumatic compression device as medically necessary when **BOTH** of the following criteria are met:
A. there is adherence with the use of equipment as ordered by the healthcare professional
B. clinical documentation from the health care professional confirms clinical improvement (e.g., improvement in venous stasis ulcers, decrease in edema or lymphedema)

IV. Not covered

Kaiser Permanente does not cover an advanced pneumatic compression pump or a pump with additional features (HCPCS code E0652*) (e.g., specific programming to treat problem areas, a pre-therapy phase) because it has not been demonstrated to be superior to a standard segmented, calibrated gradient system, and is not considered the lowest-cost alternative and thus is not medically necessary. These devices include but are not limited to:
A. Flexitouch® System
B. Lympha Press Optimal™
*HCPCS code E0652 is covered when used to report a standard segmented, calibrated gradient system. Not covered when used to report an advanced pneumatic compression pump or a pump with additional features.

Kaiser Permanente does not cover **ANY** of the following because each is considered experimental, investigational or unproven:
A. A chest (HCPCS code E0657) and/or trunk (HCPCS code E0656, E0670) pneumatic appliance for use with a pneumatic compression pump
B. A compression garment for trunk or chest
C. A pneumatic compression device, with or without a cooling component, utilized in the home setting for ANY other indication including but not limited to the prevention of deep vein thrombosis

assessment may be performed by the treating practitioner or any other licensed/certified medical professional (LCMP) directly involved in the beneficiary's lymphedema treatment. The LCMP may not have any financial relationship with the DMEPOS supplier providing the device. If the assessment is performed by an LCMP, the treating practitioner must receive and review the report of the evaluation. In addition, the treating practitioner must sign and date the report, and state concurrence or disagreement with the assessment. The signature date must be on or before the prescription date.

II. CHRONIC VENOUS INSUFFICIENCY (CVI) WITH VENOUS STASIS ULCERS
A PCD coded as E0650 or E0651 is covered for the treatment of CVI of the lower extremities only if the patient has all of the following:
- Edema in the affected lower extremity
- One or more venous stasis ulcer(s)
- The ulcer(s) have failed to heal after a six-month trial of conservative therapy directed by the treating practitioner. (See below for trial guidelines.)

A PCD coded as E0650 or E0651 used to treat CVI that does not meet all of the requirements above is not eligible for reimbursement. Claims will be denied as not reasonable and necessary.

A PCD coded as E0650 or E0651 used to treat ulcers in locations other than the lower extremity or ulcers and wounds from other causes is not eligible for reimbursement. Claims will be denied as not reasonable and necessary.

A PCD coded as E0652 is not covered for the treatment of CVI even if the criteria in this section are met. Claims will be denied as not reasonable and necessary. Refer below to the sections

III. **LYMPHEDEMA EXTENDING ONTO THE CHEST, TRUNK AND/OR ABDOMEN** and PCD Code Selection for additional information about the limited coverage for PCD coded as E0652.

Six-Month Trial for CVI
A six-month trial of conservative therapy demonstrating failed response to treatment is required. The six-month trial of conservative therapy must include all of the following:
- Compliant use of an appropriate compression bandage system or compression garment to provide adequate graduated compression
    - Adequate compression is defined as (1) sufficient pressure at the lowest pressure point to cause fluid movement and (2) sufficient pressure across the gradient (from highest to lowest pressure point) to

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move fluid from distal to proximal. The compression used must not create a tourniquet effect at any point.
    - The garment may be prefabricated or custom-fabricated but must provide adequate graduated compression starting with a minimum of 30 mmHg distally.
- Medications as appropriate (e.g. diuretics and/or other treatment of congestive heart failure)
- Regular exercise
- Elevation of the limb
- Appropriate wound care for the ulcer (including sharp debridement where appropriate)

At the end of the six-month trial, if there has been improvement, then reimbursement for a PCD is not reasonable and necessary. Where improvement has occurred, the trial of conservative therapy must be continued with subsequent reassessments. When no significant improvement has occurred for a continuous period of six months and the coverage criteria above are still met, then the use of a PCD to treat CVI is eligible for reimbursement.

The trial of conservative therapy must be documented in the beneficiary's medical record before prescribing any type of PCD (E0650, E0651, E0652). This assessment may be performed by the treating practitioner or any other licensed/certified medical professional (LCMP) directly involved in the beneficiary's CVI treatment. The LCMP may not have any financial relationship with the DMEPOS supplier providing the device. If the assessment is performed by an LCMP, the treating practitioner must receive and review the report of the evaluation. In addition, the treating practitioner must sign and date the report, and state concurrence or disagreement with the assessment. The signature date must be on or before the prescription date.

IV. LYMPHEDEMA EXTENDING ONTO THE CHEST, TRUNK AND/OR ABDOMEN

A segmented, calibrated gradient PCD (E0652) is only covered when the individual has unique characteristics which prevent them from receiving adequate satisfactory pneumatic compression treatment using a nonsegmented device along with a segmented appliance or compression device without manual control of the pressure in each chamber.
A PCD coded as E0652, is covered for the treatment of lymphedema extending onto the chest, trunk and/or abdomen when all of the following are met:

- The beneficiary has lymphedema of an extremity as defined above
- The coverage criteria for an E0650 or E0651 are met
- The beneficiary has lymphedema extending onto the chest, trunk and/or abdomen that extends past the limits of a standard

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	compression sleeve, and the chest, trunk and/or abdominal lymphedema has failed to improve with a four-week trial. (See below for trial guidelines.) A PCD coded as E0652 used to treat lymphedema extending onto the chest, trunk and/or abdomen that does not meet all of the requirements above is not eligible for reimbursement. Claims will be denied as not reasonable and necessary. A PCD coded as E0652 used to treat lymphedema not extending onto the chest, trunk and/or abdomen or CVI is not eligible for reimbursement. Claims will be denied as not reasonable and necessary. Four-Week Trial for Lymphedema Extending Onto the Chest, Trunk and/or Abdomen A four-week trial of conservative therapy demonstrating failed response to treatment with and E0650 or E0651 is required. The four-week trial of conservative therapy must include all of the following: • At least four weeks of regular, daily, multiple-hour home usage of the E0650 or E0651 after careful, in-person fitting, training and supervision by a technician who is skilled in and who regularly and successfully uses the appliance provided • Compliant use of an appropriate compression bandage system or compression garment to provide adequate graduated compression o Adequate compression is defined as (1) sufficient pressure at the lowest pressure point to cause fluid movement and (2) sufficient pressure across the gradient (from highest to lowest pressure point) to move fluid from distal to proximal. The compression used must not create a tourniquet effect at any point. o The garment may be prefabricated or custom-fabricated but must provide adequate graduated compression starting with a minimum of 30 mmHg distally • Regular exercise • Elevation where appropriate • Manual lymphatic drainage (where available) and self-manual lymphatic drainage (MLD) for at least 30 minutes per day • Evaluation of diet and implementation of any necessary change • Medications as appropriate (e.g. diuretics and/or other treatment of congestive heart failure) • Correction (where possible) of anemia and/or hypoproteinemia The trial of conservative therapy must be documented in the beneficiary's medical record before prescribing any type of PCD (E0650, E0651, E0652). This assessment may be performed by the treating practitioner or any other licensed/certified medical professional (LCMP) directly involved in the

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beneficiary's lymphedema treatment. The LCMP may not have any financial relationship with the DMEPOS supplier providing the device. If the assessment is performed by an LCMP, the treating practitioner must receive and review the report of the evaluation. In addition, the treating practitioner must sign and date the report, and state concurrence or disagreement with the assessment. The signature date must be on or before the prescription date.

V. PERIPHERAL ARTERY DISEASE (PAD)

A PCD coded as E0675 to treat PAD is not eligible for reimbursement. There is insufficient evidence to demonstrate that reimbursement is justified. Claims for E0675 will be denied as not reasonable and necessary.

VI. DEEP VENOUS THROMBOSIS (DVT) PREVENTION

A PCD coded as E0676 is used only for prevention of venous thrombosis. Refer to the related Policy Article NON-MEDICAL NECESSITY COVERAGE AND PAYMENT RULES section for information about lack of a Medicare benefit for devices used for prophylaxis of venous thrombosis.

ACCESSORIES

PCD related accessories (E0655, E0656, E0657, E0660, E0665, E0666, E0667, E0668, E0669, E0670, E0671, E0672, E0673) are eligible for reimbursement only when the appropriate, related base PCDs (E0650, E0651, E0652, E0675) meets the applicable coverage criteria for that type of PCD. If the base PCD is not covered, related accessories are not eligible for reimbursement. Claims for related items will be denied as not reasonable and necessary.

PCD CODE SELECTION (E0650, E0651, E0652, E0675, E0676)

A PCD coded as E0650 or E0651 is used for lymphedema or CVI. An E0650 compressor with a segmented appliance/sleeve (E0671, E0672, E0673) is considered functionally equivalent to an E0651 compressor with a segmented appliance/sleeve (E0667, E0668, E0669).

A segmented, calibrated gradient PCD (E0652) is only covered when the individual has unique characteristics which prevent them from receiving adequate satisfactory pneumatic compression treatment using a nonsegmented device along with a segmented appliance or compression device without manual control of the pressure in each chamber.

The only "unique characteristics" identified in the clinical literature that requires the use of an E0652 device is lymphedema extending onto the chest, trunk and/or abdomen which has remained unresponsive to all other therapies.

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	A PCD coded as E0675 is used only for peripheral artery disease. Other PCD codes are not used for this condition. A PCD coded as E0676 is used only for prevention of venous thrombosis. Refer to the related Policy Article NONMEDICAL NECESSITY COVERAGE AND PAYMENT RULES section for information about lack of a Medicare benefit for devices used for prophylaxis of venous thrombosis.
Intermittent Pneumatic Compression for the Treatment of Peripheral Arterial Occlusive Disease • ArtAssist Device • ArterialFlowTM System • Flow MedicTM System	**Effective until June 1, 2024** There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies. **Effective June 1, 2024** **LCD Pneumatic Compression Devices L33829**

If requesting these services, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist
- Last 6 months of radiology notes if applicable

Prevention of Post-Operative Deep Vein Thrombosis in the outpatient setting
There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Pneumatic Compression Device

Thromboembolic disease is a common complication following surgery particularly total joint replacement arthroplasty. It has been reported that without prophylaxis the rate of deep vein thrombosis (DVT) is as high as 88% after total knee arthroplasty and as high as 50% after total hip arthroplasty. It is also reported that lower extremity DVT is the origin of 90% of symptomatic pulmonary embolism (PE). Prophylaxis for DVT has become the standard of care for total joint arthroplasty. Chemical prophylaxis with warfarin or low-molecular weight heparin effectively reduces the incidence of DVT but carries a risk of bleeding. Orthopedic surgeons thus often use mechanical methods of prophylaxis as an alternative to chemoprophylaxis in patients with higher bleeding risk. Other surgeons also use it in standard risk patients in conjunction with the anticoagulant-based prophylaxis (Edwards 2008, Zywiel 2010).

Graduated compression stockings (GCSs) and intermittent pneumatic compression (IPC) are the two predominant mechanical methods used for DVT prevention. These have quite different methods of action; graduated compression stockings apply a constant pressure to the limb with the aim of maintaining a reduced venous caliber and preventing the static accumulation of blood. Intermittent pneumatic compression actively empties the deep veins of the limb in a predetermined cycle of pressure, producing a pulse of blood that travels proximally preventing stasis. On deflation of the cuff, the veins will refill, the intermittent nature of the system will insure periodic blood flow through the deep veins, as long as there is a supply. The IPC cuffs are normally

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wrapped around a limb, secured by velcro, and attached with tubes to an electric pump to regulate the pressure applied (Morris 2004, Morris 2010, Sobieraj-Teague 2011).

GCSs do not require attachment to any device and allow the patient to move freely. They come in a range of sizes and the limb has to be measured accurately to prevent incorrect pressure gradients, which may increase the risk of DVT. Intermittent compression devices are available in different forms; the cuff can cover the whole leg, the calf, or just the feet, it may inflate uniformly or sequentially with graded pressure; and can have rapid or moderate inflation rates. These characteristics my influence patient compliance which is critical as the longer the device is used, the better is the protection. The major disadvantages for standard IPC devices used in hospitals are their size, weight, and reliance on external power source, all of which result in poor patient compliance and in turn limit the efficacy of the device (Morris 2004, Froimson 2009).

In an attempt to overcome the problem of poor patient compliance with traditional mechanical compression systems, several lightweight, portable, battery-powered devices were developed to allow their use by the patient while ambulating in the hospital or at home after discharge. Many of these devices have received FDA clearance.

Background

Intermittent Pneumatic Compression for the Treatment of Peripheral Arterial Occlusive Disease

Peripheral arterial disease (PAD) is a common condition that affects approximately 8-12 million people in the US. The prevalence of the disease increases rapidly with age and is associated with significant morbidity and mortality. PAD commonly affects the arteries supplying the leg and is mostly caused by atherosclerosis. Restriction of blood flow due to arterial stenosis or occlusion is commonly clinically presented as intermittent claudication which is pain in the calf muscles that occurs on walking or exercising and is rapidly relieved by resting.

The clinical course of patients with intermittent claudication is variable. Most patients either improve or have a stable condition, but over one fourth will experience deterioration in symptoms. These patients may eventually develop critical leg ischemia or gangrene which can lead to amputation. Fontaine classified chronic leg ischemia into four stages: Stage I: asymptomatic, stage II: intermittent claudication, stage III: ischemic rest pain, and stage IV: ulceration, gangrene, or both (Hirsch 2001, Leng 1993, Delis 2000, 2005, Beard 2000).

The treatment of PAD aims at increasing blood flow to alleviate symptoms and prevent arterial leg ulcers, critical leg ischemia, and major complications. Management options for claudication include a structured program of regular exercise, smoking cessation, control of risk factors or associated medical diseases, percutaneous transluminal angioplasty, and surgical revascularization. Drug therapy, even with the most effective agents, was found to result in only a modest improvement. Surgical bypass reconstruction is indicated for severe cases and after failure of other forms of conservative therapy. Patients with non-healing ulcers may not be suitable for revascularization for technical reasons, frail condition, or rejection of surgical intervention. Due to the limited non-operative treatment options, long-term graft failure, perioperative deaths, and imitations or contraindications to intervention, researchers have focused their attention on mechanical methods as potential means for augmenting arterial volume flow in lower limbs (Delis 2000, Montori 2002, 2005).

The concept of using mechanical means to increase blood flow to an ischemic limb dates back to 1930s when a group of investigators applied alternating external pressure to ischemic legs with advanced atherosclerotic peripheral vascular disease. They were however unable to measure blood flow or optimize pneumatic compression. The interest in using intermittent pneumatic compression was renewed in the late 1970s when researchers observed that intermittent pneumatic compression can temporarily increase the arterial blood flow to the limbs. The devices developed apply high pressures by compression cuffs placed on the thigh, calf, and/or foot, intermittently inflate and deflate with cycle times and pressures that vary between devices.

The ArtAssist© Device (ACI Medical Inc., San Marcos, California), is a mechanical pneumatic pump consisting of an impulse generator and two plastic inflatable cuffs. It applies high pressure in a synchronized manner to the foot and calf. This outpatient treatment usually performed for three 1-hour sessions per day while the patient is sitting upright. According to the manufacturer, when the device compresses tissue below the knee, venous blood is emptied, and the venous pressure drops to near zero. The resultant increase in the arteriovenous pressure gradient increases arterial blood inflow. Another potential mechanism also described by the manufacturer involves the release of vasodilating substances as endothelial nitric oxide due to the decreased local vascular resistance. Stimulation of collateral blood vessel formation may also occur (ACI medical Inc. web site).

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The ArtAssist device as well as the Flow MedicTM system, and ArterialFlowTM system are all FDA approved for use to improve blood circulation in the lower extremities to help prevent and reduce complications of poor circulation.

Medical Technology Assessment Committee (MTAC)

Portable Compression Devices for Prevention of Post op DVT

4/16/2012: MTAC REVIEW

Evidence Conclusion: The published trials on the use of portable compression devices for the prophylaxis against DVT mainly compared the devices to chemoprophylaxis. Generally, patients randomized to the portable compression devices also received chemoprophylaxis, and in one study they also used graduated compression stockings (GCS). There were no head-to-head trials that compared the portable devices to the GCS. The trials reviewed were randomized and controlled, but were not blinded, used different definitions of major bleeds, and were financially supported by the manufacturers of the devices. Colwell and colleagues, 2010 (Evidence table 1) compared a new portable intermittent calf compression device (Continuous Enhanced Circulation Therapy Plus Synchronized Flow Technology [CECT+SFT]) versus a low molecular weight heparin (LMWH), for the prevention of thromboembolic disease after total hip replacement in 410 patients. The compression device was applied preoperatively and the LMWH was started the morning after the surgery. Patients in the compression group were allowed to receive 81mg of aspirin daily after surgery according to the surgeon's discretion. Both treatments were continued for 10 days, and the patients were followed-up clinically for 10 weeks. Bleeding was the primary outcome of the trial and rate of thromboembolic events was a secondary outcome. Overall, the results of the trials showed that the rate of major bleeds was significantly lower among the patients randomized to the portable compression group. There was no difference in the rate of thromboembolic events, but this was a secondary outcome and the study was not designed to determine equivalence. Edwards and colleagues, 2008 (Evidence table 2) compared an earlier version of the portable intermittent calf compression device (CECT) given together with LMWH versus LMWH alone in the prevention of VTE in patients undergoing either total hip or total knee arthroplasty. Patients randomized to the CECT group had the device applied in the operating room and continued during hospitalization, and the two groups received a LMWH for 7-8 days after surgery. The results of the study showed a significantly lower rate of DVT in patients in the portable compression device plus LMWH after a total knee arthroplasty compared to those using chemoprophylaxis alone, with a NNT of 8. No such significant difference was observed among those who underwent total hip replacement. In a similar trial Gelfer and colleagues (2006) compared prophylaxis with the CECT and aspirin versus LMWH and showed significant reduction in the incidence of DVT in the compression group vs. the LMWH group. In a more recent RCT, Sobieraj-Teague and colleagues, 2012 (Evidence table 3) examined the efficacy and tolerability of a new portable intermittent calf compression device (Venowave) in high risk neurosurgical patients. Patients were randomized to usual care alone or in addition to the portable compression device, and all participants in the two groups were prescribed below the knee graduated compression stockings. They could also receive pharmacological prophylaxis (aspirin, LMWH, or unfractionated heparin) according to the discretion of the neurosurgeon. The overall results indicate the rate of DVT was significantly lower in the study group that used a portable compression device in addition to the graduated compression stocking and chemoprophylaxis as needed in this high risk neurosurgical patients. The portable devices used in the trials had an average compliance rate around 80%, and the associated side effects were mainly discomfort especially at night, pruritis, and sweating.

Articles: The literature search revealed a number of earlier RCTs that compared the graduated compression stockings to intermittent compression therapy. However, IPC systems used in these studies were the standard devices used in the hospitals and not the portable IPCs which are the focus of this review. There were three RCTs that compared the use chemoprophylaxis given alone or with IPC using portable devices after total joint arthroplasty, and one trial that evaluated the efficacy of using a portable compression device in addition to graduated compression stockings and chemoprophylaxis in high risk neurosurgical patients. The following studies were selected for critical appraisal;

Colwell CW Jr, Froimson MI, Mont MA, et al. Thrombosis prevention after total hip arthroplasty: a prospective, randomized trial comparing a mobile compression device with low-molecular-weight heparin. J Bone Joint Surg Am. 2010; 92:527-535. See Evidence Table

Edwards JZ, Pulido PA, Ezzet K A, et al. Portable compression device and low-molecular-weight heparin compared with low-molecular-weight heparin for thromboprophylaxis after total joint arthroplasty. J Arthroplasty. 2008; 23:1122-1127. See Evidence Table

Sobieraj-Teague M, Hirsh J, Yip G, Gastaldo F, et al. Randomized controlled trial of a new portable calf compression device (Venowave) for prevention of venous thrombosis in high-risk neurosurgical patients. J Thromb Haemost. 2012; 10:229-235. See Evidence Table

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The use of portable compression devices does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Portable Compression Devices

BACKGROUND

Thromboembolic disease is a common complication following surgery particularly total joint replacement arthroplasty. It has been reported that without prophylaxis the rate of deep vein thrombosis (DVT) is as high as 88% after total knee arthroplasty and as high as 50% after total hip arthroplasty. It is also reported that lower extremity DVT is the origin of 90% of symptomatic pulmonary embolism (PE). Prophylaxis for DVT has become the standard of care for total joint arthroplasty. Chemical prophylaxis with warfarin or low-molecular weight heparin effectively reduces the incidence of DVT but carries a risk of bleeding. Orthopedic surgeons thus often use mechanical methods of prophylaxis as an alternative to chemoprophylaxis in patients with higher bleeding risk. Other surgeons also use it in standard risk patients in conjunction with the anticoagulant-based prophylaxis (Edwards 2008, Zywiel 2010). Graduated compression stockings (GCSs) and intermittent pneumatic compression (IPC) are the two predominant mechanical methods used for DVT prevention. These have quite different methods of action; graduated compression stockings apply a constant pressure to the limb with the aim of maintaining a reduced venous caliber and preventing the static accumulation of blood. Intermittent pneumatic compression actively empties the deep veins of the limb in a predetermined cycle of pressure, producing a pulse of blood that travels proximally preventing stasis. On deflation of the cuff, the veins will refill, the intermittent nature of the system will ensure periodic blood flow through the deep veins, as long as there is a supply. The IPC cuffs are normally wrapped around a limb, secured by velcro, and attached with tubes to an electric pump to regulate the pressure applied (Morris 2004, Morris 2010, Sobieraj-Teague 2011). GCSs do not require attachment to any device and allow the patient to move freely. They come in a range of sizes and the limb has to be measured accurately to prevent incorrect pressure gradients, which may increase the risk of DVT. Intermittent compression devices are available in different forms; the cuff can cover the whole leg, the calf, or just the feet, it may inflate uniformly or sequentially with graded pressure; and can have rapid or moderate inflation rates. These characteristics my influence patient compliance which is critical as the longer the device is used, the better is the protection. The major disadvantages for standard IPC devices used in hospitals are their size, weight, and reliance on external power source, all of which result in poor patient compliance and in turn limit the efficacy of the device (Morris 2004, Froimson 2009). In an attempt to overcome the problem of poor patient compliance with traditional mechanical compression systems, several lightweight, portable, battery-powered devices were developed to allow their use by the patient while ambulating in the hospital or at home after discharge. Many of these devices have received FDA clearance.

04/16/2012: MTAC REVIEW

Portable Compression Devices

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reduction in the incidence of DVT in the compression group vs. the LMWH group. In a more recent RCT, Sobieraj-Teague and colleagues, 2012 (Evidence table 3) examined the efficacy and tolerability of a new portable intermittent calf compression device (Venowave) in high risk neurosurgical patients. Patients were randomized to usual care alone or in addition to the portable compression device, and all participants in the two groups were prescribed below the knee graduated compression stockings. They could also receive pharmacological prophylaxis (aspirin, LMWH, or unfractionated heparin) according to the discretion of the neurosurgeon. The overall results indicate the rate of DVT was significantly lower in the study group that used a portable compression device in addition to the graduated compression stocking and chemoprophylaxis as needed in this high-risk neurosurgical patients. The portable devices used in the trials had an average compliance rate around 80%, and the associated side effects were mainly discomfort especially at night, pruritis, and sweating.

Articles: The literature search revealed a number of earlier RCTs that compared the graduated compression stockings to intermittent compression therapy. However, IPC systems used in these studies were the standard devices used in the hospitals and not the portable IPCs which are the focus of this review. There were three RCTs that compared the use chemoprophylaxis given alone or with IPC using portable devices after total joint arthroplasty, and one trial that evaluated the efficacy of using a portable compression device in addition to graduated compression stockings and chemoprophylaxis in high risk neurosurgical patients.

The following studies were selected for critical appraisal; Colwell CW Jr, Froimson MI, Mont MA, et al. Thrombosis prevention after total hip arthroplasty: a prospective, randomized trial comparing a mobile compression device with low-molecular-weight heparin. J Bone Joint Surg Am. 2010; 92:527-535. See Evidence Table. Edwards JZ, Pulido PA, Ezzet K A, et al. Portable compression device and low-molecular-weight heparin compared with low-molecular-weight heparin for thromboprophylaxis after total joint arthroplasty. J Arthroplasty. 2008; 23:1122-1127. See Evidence Table. Sobieraj-Teague M, Hirsh J, Yip G, Gastaldo F, et al. Randomized controlled trial of a new portable calf compression device (Venowave) for prevention of venous thrombosis in high-risk neurosurgical patients. J Thromb Haemost. 2012; 10:229-235. See Evidence Table.

The use of portable compression devices does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Intermittent Pneumatic Compression

02/04/2008: MTAC Review

Evidence Conclusion: The trials on intermittent pneumatic compression (IPC) studied the efficacy of the therapy, mainly using the ArtAssist device, for patients with stable intermittent claudication. There were no RCTs with clinical outcomes that evaluated the IPC for use among patients with more severe condition or those who failed revascularization. All published trials were small, single centered, conducted among highly selected groups of patients, were not blinded, short-term, and none compared IPC to a sham therapy. Kakkos and colleagues (2005), randomized 34 highly selected patients with stable intermittent claudication to receive IPC (n=13), supervised exercise (n=12), or unsupervised exercise (n=9). The study was too small, was unblinded, and had a high dropout rate. Its results show that compared to the unsupervised exercise, both IPC and supervised exercise increased the initial claudication distance (ICD) and the absolute claudication distance (ACD). The difference in improvement observed was statistically significant at the end of the six-month treatment and after six additional months of follow-up. There was no significant difference however between the IPC and supervised exercise groups.

In their pilot study, Ramaswami and colleagues (2005) evaluated the efficacy of IPC among 34 patients with stable intermittent claudication who were randomized to receive IPC with daily unsupervised exercise or to just perform daily unsupervised exercise. IPC was not compared to sham treatment or to a supervised exercise program. The results showed an increase in the initial and absolute claudication distances with IPC at 4 and 6 months of treatment and the improvement was sustained at 1 year. Delis and Nicolaides (2005) also evaluated the effectiveness of IPC in 41 highly selected patients with stable intermittent claudications. These were randomly assigned to receive IPC and salicylic acid (75 mg/dL), or salicylic acid (75 mg/dL) alone. All participants in the two groups were encouraged to exercise daily and were followed up for 12 months after the treatment period. The results of the trial show that the ICD, ACD, increased significantly in the IPC group starting at the first month of treatment and was sustained for one year after completing the therapy. Only a small insignificant change was observed in the control group, and the difference between the two study groups was significant. The quality of life also improved significantly in the IPC group, but not in the control group. *Conclusion*: The available evidence from these trials as well as other earlier studies and case series suggest that intermittent pneumatic compression therapy of the foot and calf with ArtAssist device might be associated with improvement in the arterial blood flow and in the walking distance over a short term among patients with stable intermittent claudication. However, the studies included highly selected groups patients with stable claudications who had superficial femoral artery occlusion, and patent iliac arteries (also patent popliteal artery as indicated by some studies). Those with a history of a lower extremity revascularization history were excluded, as well as those with several other comorbidities.

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Moreover, the studies had control groups not placebo groups undergoing a sham IPC treatment. There were no long-term outcomes beyond one year of follow-up, and the studies did not determine the effectiveness of treatment in improving rest pain, ulcer healing, or reducing amputation rate, all of which may limit generalization of the results. In conclusion there is insufficient evidence to determine the efficacy of pneumatic compression devices for the treatment intermittent claudication, or more severe symptoms among patients with peripheral artery occlusive disease.

Articles: There were five small RCTs, one nonrandomized controlled study, and several prospective and retrospective small case series with no control or comparison groups. The majority of trials were conducted among patients with stable claudication. There was a small trial, with intermediate outcomes that compared three modes of IPC in healthy limbs as well as those with successful grafts. The literature search did not reveal RCT that evaluated the IPC use for patients with more severe condition or those who failed revascularization. *Studies with an appropriate comparison group and/or longer follow-up duration were selected for critical appraisal:* Kakkos SK, Geroulakos G, Nicolaides AN. Improvement of the walking ability in intermittent claudication due to superficial femoral artery occlusion with supervised exercise and pneumatic foot and calf compression: A randomized controlled trial. Eur J Vasc Endovasc Surg. 2005; 30:164-175. **See** Evidence Table
Ramaswami G, D'ayala M, Hollier LH, et al., rapid foot and calf compression increases walking distance in patients with intermittent claudication: Results of a randomized study. J Vasc Surg. 2005; 41:794-801. **See** Evidence Table Delis KT, Nicolaides AN. Effect of intermittent pneumatic compression on foot and calf on walking distance, hemodynamics, and quality of life in patients with arterial claudication. A prospective randomized controlled study with 1-year follow-up. Ann Surg 2005;241:431-441 **See** Evidence Table

The use of Intermittent pneumatic compression in the treatment of peripheral arterial occlusive disease does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Effective until June 1st, 2024
Medicare: Considered Medically Necessary when criteria in the applicable policy statements listed above are met

HCPC Codes	Description
E0650	Pneumatic compressor, nonsegmental home mode
E0651	Pneumatic compressor, segmental home model without calibrated gradient pressure
E0652	Pneumatic compressor, segmental home model with calibrated gradient pressure
E0655	Nonsegmental pneumatic appliance for use with pneumatic compressor, half arm
E0656	Segmental pneumatic appliance for use with pneumatic compressor, trunk
E0657	Segmental pneumatic appliance for use with pneumatic compressor, chest
E0660	Nonsegmental pneumatic appliance for use with pneumatic compressor, full leg
E0665	Nonsegmental pneumatic appliance for use with pneumatic compressor, full arm
E0666	Nonsegmental pneumatic appliance for use with pneumatic compressor, half leg
E0667	Segmental pneumatic appliance for use with pneumatic compressor, full leg
E0668	Segmental pneumatic appliance for use with pneumatic compressor, full arm
E0669	Segmental pneumatic appliance for use with pneumatic compressor, half leg
E0670	Segmental pneumatic appliance for use with pneumatic compressor, integrated, two full legs and trunk
E0671	Segmental gradient pressure pneumatic appliance, full leg
E0672	Segmental gradient pressure pneumatic appliance, full arm
E0673	Segmental gradient pressure pneumatic appliance, half leg

Effective until June 1st, 2024
Non-Medicare: Considered Medically Necessary when criteria in the applicable policy statements listed above are met

HCPC Codes	Description
E0650	Pneumatic compressor, nonsegmental home mode
E0651	Pneumatic compressor, segmental home model without calibrated gradient pressure
E0655	Nonsegmental pneumatic appliance for use with pneumatic compressor, half arm
E0660	Nonsegmental pneumatic appliance for use with pneumatic compressor, full leg

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E0665	Nonsegmental pneumatic appliance for use with pneumatic compressor, full arm
E0666	Nonsegmental pneumatic appliance for use with pneumatic compressor, half leg
E0667	Segmental pneumatic appliance for use with pneumatic compressor, full leg
E0668	Segmental pneumatic appliance for use with pneumatic compressor, full arm
E0669	Segmental pneumatic appliance for use with pneumatic compressor, half leg
E0671	Segmental gradient pressure pneumatic appliance, full leg
E0672	Segmental gradient pressure pneumatic appliance, full arm
E0673	Segmental gradient pressure pneumatic appliance, half leg

Effective until June 1st, 2024

Medicare: Considered not medically necessary

HCPC Codes	Description
E0675	Pneumatic compression device, high pressure, rapid inflation/deflation cycle, for arterial insufficiency (unilateral or bilateral system)
E0676	Intermittent limb compression device (includes all accessories), not otherwise specified
A4600	Sleeve for intermittent limb compression device, replacement only, each *(used for devices described by E0676)*

Effective until June 1st, 2024

Non- Medicare: Considered not medically necessary

HCPC Codes	Description
E0652	Pneumatic compressor, segmental home model with calibrated gradient pressure
E0656	Segmental pneumatic appliance for use with pneumatic compressor, trunk
E0657	Segmental pneumatic appliance for use with pneumatic compressor, chest
E0670	Segmental pneumatic appliance for use with pneumatic compressor, integrated, two full legs and trunk
E0675	Pneumatic compression device, high pressure, rapid inflation/deflation cycle, for arterial insufficiency (unilateral or bilateral system)
E0676	Intermittent limb compression device (includes all accessories), not otherwise specified
A4600	Sleeve for intermittent limb compression device, replacement only, each *(used for devices described by E0676)*

Effective June 1st, 2024

Medicare & Non-Medicare: Considered Medically Necessary when criteria in the applicable policy statements listed above are met

HCPC Codes	Description
E0650	Pneumatic compressor, nonsegmental home mode
E0651	Pneumatic compressor, segmental home model without calibrated gradient pressure
E0655	Nonsegmental pneumatic appliance for use with pneumatic compressor, half arm
E0660	Nonsegmental pneumatic appliance for use with pneumatic compressor, full leg
E0665	Nonsegmental pneumatic appliance for use with pneumatic compressor, full arm
E0666	Nonsegmental pneumatic appliance for use with pneumatic compressor, half leg
E0667	Segmental pneumatic appliance for use with pneumatic compressor, full leg
E0668	Segmental pneumatic appliance for use with pneumatic compressor, full arm
E0669	Segmental pneumatic appliance for use with pneumatic compressor, half leg
E0671	Segmental gradient pressure pneumatic appliance, full leg
E0672	Segmental gradient pressure pneumatic appliance, full arm
E0673	Segmental gradient pressure pneumatic appliance, half leg

Effective June 1st, 2024

Medciare & Non-Medicare: Considered not medically necessary

HCPC	Description

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Codes	
E0675	Pneumatic compression device, high pressure, rapid inflation/deflation cycle, for arterial insufficiency (unilateral or bilateral system)
E0676	Intermittent limb compression device (includes all accessories), not otherwise specified
A4600	Sleeve for intermittent limb compression device, replacement only, each *(used for devices described by E0676)*

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed	Date Last Revised
05/01/2012	05/01/2012[MDCRPC], 06/05/2012[MDCRPC], 04/02/2013[MDCRPC], 02/04/2014 [MPC], 12/02/2014[MPC], 10/06/2015[MPC], 08/02/2016[MPC], 06/06/2017[MPC], 04/03/2018[MPC], 04/02/2019[MPC], 04/07/2020[MPC], 04/06/2021[MPC], 04/05/2022[MPC], 04/04/2023[MPC]	01/09/2024

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
07/21/2015	Title Change
03/08/2016	Updated Medicare links
05/08/2018	Added Policy article language for non-coverage of E0676
7/10/2018	Added new review criteria for pneumatic devices for Non-Medicare members with effective date 10/15/2018
04/05/2022	Updated applicable codes
04/18/2023	Updated Medicare Pneumatic Compression Devices – Policy Article A52488
01/09/2024	MPC approved to adopt the Medicare LCD Pneumatic compression devices L33829 for commercial members. Requires 60-day notice, effective June 1st, 2024. Merged Intermittent Pneumatic Compression Device with this criteria set.

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KAISER PERMANENTE®

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Clinical Review Criteria
Peroral Endoscopic Myotomy (POEM) for Esophageal Achalasia

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article	None
Kaiser Permanente Medical Policy	Due to the absence of a NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Clinical Review Criteria, "***Peroral Endoscopic Myotomy (POEM) for Esophageal Achalasia***" for medical necessity determinations. Use the Non-Medicare criteria below.

For Non-Medicare Members

Peroral endoscopic myotomy (POEM) is considered medically necessary when **ALL of the following** criteria are met:

- Individual is age 18 years or older
- Achalasia type III is diagnosed using esophageal manometry
- Achalasia type I and II covered only if patient is deemed not a surgical candidate
- Patient must be counseled about 20-25% risk of GERD after POEM

Peroral endoscopic myotomy (POEM) for **ANY other indication** is considered experimental, investigational, and unproven.

Contraindications for Peroral endoscopic myotomy (POEM); if **ONE of the following** conditions is present, the patient should not undergo POEM:

- Severe erosive esophagitis
- Significant coagulation disorders
- Liver cirrhosis with portal hypertension
- Severe pulmonary disease
- Esophageal malignancy
- ASA IV or greater
-
- Prior therapy that may compromise the integrity of the esophageal mucosa or lead to submucosal fibrosis, including recent esophageal surgery, radiation, endoscopic mucosal resection, or radiofrequency ablation

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Definitions: The three types of achalasia based on the Chicago Classification of patterns of esophageal pressurization on high-resolution manometry (HRM) (CC v3.0) include the following:

- Type I (classic achalasia) – Incomplete LES relaxation, aperistalsis and absence of esophageal pressurization. Swallowing results in no significant change in esophageal pressurization and has 100% failed peristalsis with a distal contractile integral (DCI, an index of the strength of distal esophageal contraction) < 100 mmHg.
- Type II – Incomplete LES relaxation, aperistalsis and panesophageal pressurization in at least 20% of swallows. Swallowing results in simultaneous pressurization that spans the entire length of the esophagus. Type II achalasia has 100% failed peristalsis and pan-esophageal pressurization with ≥ 20 percent of swallows.
- Type III (spastic achalasia) – Incomplete LES relaxation and premature contractions (distal latency [DL] < 4.5 seconds) in at least 20% of swallows. Swallowing results in abnormal, lumen-obliterating contractions or spasms. Type III achalasia has no normal peristalsis and premature (spastic) contractions with DCI >450 mmHg-sec-cm with ≥ 20 percent of swallows (Spechler, 2021a; Schlottmann, et al., 2017).

If requesting this service, please send the following documentation to support medical necessity:

- Last 3 months of clinical notes from requesting provider &/or consulting specialist.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Esophageal achalasia (EA) is a rare esophageal motility disorder characterized by loss of peristalsis of the esophageal body and failure of the lower esophageal sphincter (LES) to relax in response to swallowing. The most common form of EA is idiopathic and the exact etiology for the disappearance of myenteric neurons that coordinate esophageal peristalsis and relaxation of LES is unknown. Esophageal achalasia results in retention of food and saliva in the esophagus leading to difficulty in swallowing, regurgitation, aspiration, chest pain, weight loss, and eventually irreversible dilatation of the esophageal body (Kumagai 2015, Patel 2016, Zhang 2016).

Esophageal achalasia is irreversible, and all current therapeutic interventions are palliative with the aim of reducing the pressure at the esophagastric junction (EGJ), to facilitate the transit of food boluses into the stomach and reduce the related symptoms. Treatment options vary from pharmacotherapy (e.g., calcium channel antagonists and nitrates), botulinum toxin injection (BTI), endoscopic pneumatic dilatation (PD), surgical myotomy of the lower esophageal sphincter, to esophagostomy for end-stage achalasia. Each of the therapeutic modalities has its indications, advantages, and limitations. e.g., pharmacological therapy does not have a durable effect and may be only suitable for patients with mild disease, elderly patients or those who cannot undergo more invasive treatment; BTI has a short-lived action; pneumatic dilatation is associated with symptom recurrence and post-procedure gastroesophageal reflux (GERD); and surgical myotomy usually requires and additional fundoplication procedure to prevent GERD (Talukdar 2015, Marano 2016, Zhang 2016).

Currently laparoscopic Heller myotomy (LHM) is the treatment of choice for patients with esophageal achalasia who are fit for surgery. It provides superior and long-lasting symptom relief compared to other treatment modalities including pneumatic dilatation of the esophagus. LHM involves full thickness myotomy along the distal 4-6 cm of the esophagus and extending to 2-3 cm on to the gastric wall allowing the LES to remain open. LMH is usually followed by partial anterior fundoplication (Dor fundoplication). The procedure is minimally invasive, yet, the surgical access to the abdomen remains a potential source of wound infection, port-site hernia formation, and immediate postoperative pain (Kumagai 2015, Wei 2015, Morano 2016, Zhang 2016, Sanaka 2017, Docimo 2017, Kahrilis 2017).

Per-Oral Endoscopic Myotomy (POEM), was developed in Japan in 2008, and introduced into practice as a minimally invasive technique for the management of patients with achalasia. The procedure involves the creation of a submucosal tunnel followed by myotomy of the circular muscle layer to reduce pressure at the LES. It is performed under general anesthesia and consists of five major steps: 1. Patient position and planning endoscopy, 2. Entry into the submucosal space, 3. Creation of a submucosal tunnel, 4. Endoscopic myotomy of the circular muscles, and 5. Closure of the mucosal entrance. Unlike LHM which involves complete division of both circular

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and longitudinal LES muscle layers, POEM only cuts the inner, circular LES muscles maintaining the integrity of the longitudinal muscles. Thus, POEM has the potential advantages of both endoscopic dilatation and durable surgical myotomy in a single procedure (Talukdar 2015, Zhang 2016, Leeds 2017).

A major concern with POEM is the high rate of gastroesophageal reflux, which was observed in more than 50% of the patients undergoing the procedure despite the theoretical advantage of avoiding the esophagastric junction dissection required for the LHM. Other reported serious adverse events associated with POEM include mucosal injury, esophageal perforation, major bleeding, pneumothorax, subcutaneous emphysema, pleural effusion, and pneumoperitoneum (Akintoye 2016, Kahrilas 2017). Esophageal achalasia (EA) is a rare esophageal motility disorder characterized by loss of peristalsis of the esophageal body and failure of the lower esophageal sphincter (LES) to relax in response to swallowing. The most common form of EA is idiopathic and the exact etiology for the disappearance of myenteric neurons that coordinate esophageal peristalsis and relaxation of LES is unknown. Esophageal achalasia results in retention of food and saliva in the esophagus leading to difficulty in swallowing, regurgitation, aspiration, chest pain, weight loss, and eventually irreversible dilatation of the esophageal body (Kumagai 2015, Patel 2016, Zhang 2016).

EA is irreversible and all current therapeutic interventions are palliative with the aim of reducing the pressure at the esophagastric junction (EGJ), to facilitate the transit of food boluses into the stomach and reduce the related symptoms. Treatment options vary from pharmacotherapy (e.g., calcium channel antagonists and nitrates), botulinum toxin injection (BTI), endoscopic pneumatic dilatation (PD), surgical myotomy of the lower esophageal sphincter, to esophagostomy for end-stage achalasia. Each of the therapeutic modalities has its indications, advantages, and limitations. e.g., pharmacological therapy does not have a durable effect and may be only suitable for patients with mild disease, elderly patients or those who cannot undergo more invasive treatment; BTI has a short-lived action; PD is associated with symptom recurrence and post-procedure gastroesophageal reflux (GERD); and surgical myotomy usually requires and additional fundoplication procedure to prevent GERD (Talukdar 2015, Marano 2016, Zhang 2016).

Currently laparoscopic Heller myotomy (LHM) is the gold standard surgical treatment for patients with esophageal achalasia who are fit for surgery. It provides superior and long-lasting symptom relief compared to other treatment modalities including pneumatic dilatation of the esophagus. LHM involves full thickness myotomy along the distal 4-6 cm of the esophagus and extending to 2-3 cm on to the gastric wall allowing the LES to remain open. LMH is usually followed by partial anterior fundoplication (Dor fundoplication). The procedure is minimally invasive, yet the surgical access to the abdomen remains a potential source of wound infection, port-site hernia formation, and immediate postoperative pain (Wei 2015, Morano 2016, Zhang 2016, Sanaka 2017, Docimo 2017, Kahrilis 2017, Liu-Burdowski 2021).

Per-Oral Endoscopic Myotomy (POEM), was developed in Japan in 2008, and introduced into practice as a minimally invasive technique for the management of patients with achalasia. It is a complex procedure that requires training both in surgery and gastroenterology, good understanding of the pathophysiology of achalasia, esophageal manometry, very good knowledge of the anatomy of the mediastinum and upper abdomen, as well as endoscopic skills, judgment, and ability to manage the potential adverse events associated with the procedure. POEM involves the creation of a submucosal tunnel followed by myotomy of the circular muscle layer to reduce pressure at the LES. It is performed under general anesthesia and consists of five major steps: 1. Patient position and planning endoscopy, 2. Entry into the submucosal space, 3. Creation of a submucosal tunnel, 4. Endoscopic myotomy of the circular muscles, and 5. Closure of the mucosal entrance. Unlike LHM which involves complete division of both circular and longitudinal LES muscle layers, POEM only cuts the inner, circular LES muscles maintaining the integrity of the longitudinal muscles. Thus, POEM may have a potential advantage of performing both endoscopic dilatation and durable surgical myotomy in a single procedure (Talukdar 2015, Zhang 2016, Leeds 2017).

A major concern with POEM is the high rate of gastroesophageal reflux, which was observed in more than 50% of the patients undergoing the procedure despite the theoretical advantage of avoiding the esophagastric junction dissection required for the LHM. Other reported serious adverse events associated with POEM include mucosal injury, esophageal perforation, major bleeding, pneumothorax, subcutaneous emphysema, pleural effusion, and pneumoperitoneum (Akintoye 2016, Kahrilas 2017).

Medical Technology Assessment Committee (MTAC)

Peroral Endoscopic Myotomy

12/15/2014:

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Evidence Conclusion: Bhayani and colleagues compared the experience of 101 patients from a single institution undergoing either LHM or POEM. Swallowing outcomes at one and six months were assessed via objective measures (manometry and pH levels). In addition, the investigators collected information regarding operative time, complications and postoperative gastro-esophageal reflux disease (GERD). Manometry indicated that there were decreases in pressure across both groups, however, the postmyotomy resting pressures were higher for the POEM group than for LHMs (16 vs. 7 mm Hg, P=0.006). The same effect was not seen between groups for relaxation pressure (9 vs. 4). Both groups experienced relief of symptoms with the POEM group showing significantly lower Eckhardt scores when compared with the LHM group at one month (0.8 vs. 1.8, P<0.0001). At six months, however, the difference was no longer significant (1.7 vs. 1.2, P=0.1). Ultimately, the investigators conclude that POEM is comparable with LHM for safe and effective treatment of EA (Bhayani, Kurian et al. 2014). While POEM appears to be comparable to LHM, the technique is still evolving. At this particular point in time, the body of evidence only reports on the success of POEM in highly select populations with short-term follow-up. To add to this, the study is not randomized and relies on a small sample or subjects. Ultimately, the literature does not support the safety and effectiveness of POEM for the treatment of achalasia when compared to LHM. Conclusions: There is insufficient evidence to support the effectiveness of POEM compared to LHM for the treatment of EA. There is insufficient evidence to support the safety of POEM compared with LHM for the treatment of EA.

Articles: The literature search revealed over 200 studies relating to the use of POEM for the treatment of achalasia. The literature was dominated by publications that introduce and describe the technique as well as studies from individual centers describing their experience with POEM with short-term follow-up. A search of the clinicaltrials.gov website revealed several ongoing studies with the aim to evaluate of the clinical utility and safety of POEM (NCT01832779). For the purposes of this review, one of the larger and more recent nonrandomized comparison studies was identified for critical appraisal. The following articles were selected for critical appraisal: Bhayani NH, Kurian AA, Dunst CM, et al. A comparative study on comprehensive, objective outcomes of laparoscopic Heller myotomy with per-oral endoscopic myotomy (POEM) for achalasia. Annals of Surgery. 2014; 259(6): 1098-1103. See Evidence Table 1.

The use of Peroral Endoscopic Myotomy does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Peroral Endoscopic Myotomy

12/18/2017

Evidence Conclusion: The literature search did not reveal any randomized controlled trials that compared POEM with laparoscopic Heller myotomy, the current standard of care; only noncompetitive case series and a small number of observational nonrandomized comparative studies and meta-analyses that pooled their results were identified. **Meta-analyses of comparative studies:** The published comparative studies identified by the search were relatively small observational studies that compared the outcomes of patients with esophageal achalasia treated POEM versus matched controls who had undergone treatment with LHM. The population sizes of the studies ranged from 8 patients to ~200 participants and there may be potential overlap between the studies published by the same groups of investigators. A number of systematic reviews with meta-analysis pooled the results of the majority of these studies three of which (Bhayani 2014, Ujiki 2013, and Hugeness 2013) were included in almost all meta-analyses. Based in the inclusion /exclusion criteria of the systematic reviews, smaller and/or studies with potentially overlapping population were added or excluded from the analyses. The overall pooled results of these comparative studies, none of which was randomized) as shown in Evidence Table 1, show no significant differences between the two procedures as regards their effect on reducing the achalasia symptoms as measured by the Eckardt score, perioperative pain score, complication rate, and length of hospital stay. POEM however, was associated with a significantly higher rate of symptomatic gastroesophageal reflux and esophagitis that required treatment. Based on these results some investigators concluded that the efficacy and safety of POEM appear to be comparable to those of LMH, and others (Wei and colleagues 2015) concluded that POEM achieves equivalent short-term outcomes compared to LHM. However, observational studies do not allow making any conclusion on the efficacy of POEM relative to LHM or other established treatments. The studies were only observational studies with potential bias and confounding. Patients were not randomly assigned the procedures, instead, POEM was compared to historical controls, the numbers of participants were small, with baseline differences in their characteristics, there were significant heterogeneity between the studies, and the follow-up duration was short, all of which limit generalization of the results. Large prospective randomized controlled trials with long-term outcomes are needed to determine the relative safety and efficacy of POEM and LHM. Schlottmann and colleagues', 2017 systematic review and meta-analysis (Evidence Table 2) compared outcomes of POEM performed among different patient cohorts along the years (total N=1,958) versus LHM performed among a total of 5,834 participants. The studies included were not comparative; instead, the authors pooled the results of case series for each procedure and compared the overall summary results. This indirect

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comparison suggests that POEM may be more effective than LHM in reducing dysphagia symptoms in the short-term but is associated with a significantly higher incidence of pathologic reflux. These, similar to the results of other case series and nonrandomized studies, have to be interpreted with caution. **Non-comparative studies:** A large number of prospective and retrospective case series reported on the outcomes of the POEM procedure used for the management of patients with esophageal achalasia. The majority of the studies were conducted in Asia and included a small number of participants (<10-100 participants in each study). Only two case series included a little over 200 patients, and the largest reported on 500 consecutive patients treated in one center in Japan (Inoue 2015). In addition to these differences, other variations between the studies included differences in the patient characteristics, date and period the procedures were performed, technique used, length of myotomy, treatment success and other outcome measures, duration of follow-up, as well as other differences. A number of systematic review performing quantitative and qualitative analysis of the published case series were identified by the literature search (Barbieri 2015; Akintoye, 2016; and Crespin 2016). Akintoye and colleagues' 2016 meta-analysis that was more comprehensive and more inclusive was selected for critical appraisal. Akintoye et al, 2016 meta-analysis (Evidence Table 3) had generally valid methodology; however, a meta-analysis is as good as the studies it includes. All were case series subject to selection and observation bias. There was significant heterogeneity between the studies that were published over a span of 4 years and reported on outcomes of POEMs performed in different countries between 2008 and 2014. The studies varied in population sizes, many were retrospective, and had short and variable follow-up durations. According to the pooled results, a higher success rate was observed in Asian countries where the procedure had been introduced into practice earlier allowing for more development in its technique and acquisition of more skills by the interventionists. In addition, the outcomes of the studies were reported after variable follow-up durations and some e.g. symptoms relief, symptomatic gastroesophageal reflux, and esophagitis may be time dependent. Overall, the pooled results of the Akintoye's meta-analysis as well as the non-comparative case series and their pooled results suggest that POEM may be effective in reducing dysphagia symptoms in the short-term among patients with esophageal achalasia. The POEM procedure, however, is associated with a high rate of symptomatic gastroesophageal reflux, esophagitis, and abnormal acid exposure. Reported perioperative adverse events of the procedure include mucosal injury, subcutaneous emphysema, pneumoperitoneum, and other serious events that occurred at a lower rate.

Conclusions

- The published literature is insufficient to determine the effects of POEM on the net health outcomes of patients with esophageal achalasia. The studies published to date, provide weak evidence on the short-term efficacy of POEM in reducing dysphagia symptoms in patients with esophageal achalasia, but on the expense of an increased rate of symptomatic gastroesophageal reflux and esophagitis.
- There is insufficient evidence to determine the long-term efficacy and safety of POEM for the management of patient with esophageal achalasia.
- The lack of randomized controlled trials, the small number of nonrandomized observational studies, design and quality of studies, short duration of follow-up, and significant variations between the studies in the surgical techniques and learning curve, operative time, definitions and reporting of the procedural success and adverse events, do not allow supporting the use of POEM as an alternative to LHM for the management of patients with esophageal achalasia.
- Long-term large randomized controlled trials are needed to determine the safety and efficacy of POEM in the management of patients with esophageal achalasia compared to other established procedures.
- Several RCTs comparing POEM to other established procedures is ongoing and may provide more evidence on its long-term safety and efficacy. Among these are the following:
    - Endoscopic Versus Laparoscopic Myotomy for Treatment of Idiopathic Achalasia: A Randomized, Controlled Trial: ClinicalTrials.gov Identifier: NCT01601678
    - Multi-center Study Comparing Endoscopic Pneumodilation and Peroral Endoscopic Myotomy (POEM). ClinicalTrials.gov Identifier: NCT01793922
    - Laparoscopy Heller Myotomy with Fundoplication Associated Versus Peroral Endoscopic Myotomy (POEM). ClinicalTrials.gov Identifier: NCT02138643

Articles: The literature search for recently published studies after the last MTAC review did not identify any randomized controlled trials that compared POEM with laparoscopic Heller myotomy or other standard treatments options. The published literature consisted of case series, non-randomized comparative studies, and a number of systematic reviews with quantitative meta-analyses (MAs) that pooled the results the published case series and/or nonrandomized comparative observational studies. Among these systematic reviews and meta-analyses were Barbieri, 2015, Talukdar 2015, Wei 2015, Akintoye 2016, Marano 2016, Patel 2016, Zhang 2016, Crespin 2017, Repici 2017, Schlottmann 2017, and Khan 2017. The latter examined the safety and efficacy of POEM for spastic esophageal disorders in general and was excluded from current review.

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The use of Peroral Endoscopic Myotomy does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Peroral Endoscopic Myotomy

12/18/2017

Evidence Conclusion:

- There is insufficient published evidence to determine that POEM is superior to LHM in alleviating the symptoms associated with achalasia.
- Moderate quality evidence from a single published open-label non-inferiority trial RCT with potential observation bias, shows that POEM was noninferior to LHM in alleviating the symptoms of achalasia in the short-term (2 years follow-up).
- There is evidence from the published RCT as well as several other non-randomized observational studies and meta-analyses indicating that POEM is associated with a significantly higher rate of developing acid reflux and /or erosive esophagitis.
- There is insufficient evidence to determine the long-term effectiveness and safety of POEM for the management of patient with esophageal achalasia.
- Long-term large randomized controlled trials are needed to determine the safety and efficacy of POEM in the management of patients with esophageal achalasia

Articles: The literature search for studies published after the 2017 review conducted for MTAC identified only one RCT that compared POEM versus laparoscopic surgical myotomy (Werner et al, 2019) and another that compared it with pneumatic dilatation (Ponds et al, 2019).The search also identified several prospective or retrospective observational studies and more than 10 systematic reviews (SRs) with or without aggregate data meta-analyses or network meta-analysis that pooled the results the published observational studies comparing POEM to other therapies used for the management of achalasia. There was a major overlap in the studies included in the systematic reviews. The RCT comparing POEM to surgical myotomy (Werner et al, 2019) was selected for critical appraisal, as well as a recent relevant, peer reviewed, and inclusive SR (Park et al, 2019) with valid methodology and analysis. The only other published RCT (Ponds et al, 2019) evaluating POEM compared to PD was briefly summarized.

Hayes Technology Assessment

POEM is a natural orifice transluminal endoscopic surgery technique. The technique involves guiding an endoscope through the esophagus, making an incision in the mucosa, creating a submucosal tunnel for access to the lower esophagus and gastroesophageal junction, and cutting the muscle fibers in the lower esophagus and proximal stomach. Internal incisions are closed with clips after myotomy is complete. Rationale for developing the POEM procedure includes the ability to combine the minimal invasiveness of endoscopic procedures, such as PD, with the therapeutic goal of a surgical myotomy, such as LHM. Natural orifice surgery, such as POEM, aims to reduce procedure-related pain and return patients to regular activities sooner than surgeries requiring external incisions.

Conclusion

The available evidence, mainly from poor-quality studies, suggests that the POEM procedure is generally safe and may achieve at least similar results to both LHM and PD for most efficacy and harms outcomes. The clinical significance of any differences detected from baseline or between groups was not discussed in the evaluated studies. The body of evidence regarding comparisons between POEM and LHM is of moderate size (16 studies), whereas evidence on POEM versus PD was presented in only 4 studies. Additional studies of fair to good quality are needed to elucidate optimal treatment protocols, patient selection criteria, and provide information for longer-term outcomes.

Hayes Rating: C—For use of peroral endoscopic myotomy (POEM) as an alternative to laparoscopic Heller myotomy (LHM) for the treatment of adult patients with esophageal achalasia (EA). **C**—For use of POEM as an alternative to pneumatic dilation (PD) for the treatment of adult patients with EA.

Hayes. Hayes Technology Assessment. *Peroral Endoscopic Myotomy for Treatment of Esophageal Achalasia.* Dallas, TX: Hayes; December 03, 2019. Retrieved February 21, 2023, from https://evidence.hayesinc.com/report/dir.peroral3346

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X. Tang, W. Gong, Z. Deng, J. Zhou, Y. Ren, Q. Zhang, Z. Chen, B. Jiang, Feasibility and safety of peroral endoscopic myotomy for achalasia after failed endoscopic interventions, *Diseases of the Esophagus*, Volume 30, Issue 3, March 2017, Pages 1–6, https://doi.org/10.1111/dote.12457

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met

CPT® or HCPC Codes	Description
43497	Lower esophageal myotomy, transoral (ie, peroral endoscopic myotomy [POEM])

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed	Date Last Revised
12/29/2014	01/06/2015[MPC], 12/01/2015[MPC], 10/04/2016[MPC], 08/01/2017[MPC], 07/10/2018[MPC], 07/09/2019[MPC], 07/07/2020[MPC], 07/06/2021[MPC], 07/05/2022[MPC], 07/11/2023[MPC]	02/07/2023

[MPC] Medical Policy Committee

Revision History	Description
02/06/2018	Added MTAC review for Per-Oral Endoscopic Myotomy (POEM) for Esophageal Achalasia
07/19/2018	Added coverage language – In the absence of direction for CMS Kaiser Permanente criteria will be used
12/08/2022	Added new applicable CPT code to criteria
02/07/2023	MPC adopted new clinical criteria for Per-Oral Endoscopic Myotomy (POEM) for Esophageal Achalasia. Requires 60-Day notice. Effective 07/01/2023. Added October 2022 MTAC review.

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KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Fecal DNA Testing

- Cologuard™
- Colorectal Neoplasm Detection
- PreGen-Plus Test

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Colorectal Cancer Screening Tests (210.3)
Local Coverage Determinations (LCD)	None
Local Coverage Article	None

For Non-Medicare Members

Medical necessity review no longer required.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Colorectal cancer is the second leading cause of death from cancer in the United States. Most colorectal cancers begin with the development of benign adenomatous polyps. It is believed that cells acquire genetic changes as adenomatous polyps develop into an adenocarcinoma, a process that can take 10-20 years.

EXACT Sciences Corporation (Marlborough, MA) has developed tests that analyze patient stool samples to see whether they contain genetic markers associated with colorectal cancer. The PreGen-Plus, the topic of the current review, is a test for the early detection of colorectal cancer in an average-risk population. It uses a multitarget assay panel that incorporates 21-point mutations in K-*ras*, adenomatous polyposis coli (APC) and *p53* genes, a microsatellite instability marker (BAT-26) and a proprietary marker, the DNA Integrity Assay (Tagore, 2003). A similar test, PreGen-26, is intended to detect colorectal cancer in high-risk patients. The BAT-26 is the basis of the PreGen-26 test (manufacturer's website).

According to a review article on emerging technologies for colorectal cancer screening (Levin, 2003), it may be possible to identify cancer at an earlier stage with DNA tests such as the PreGen-Plus than with fecal occult blood test (FOBT), the standard non-invasive test. Other potential advantages of the PreGen-Plus test may be a reduced false-positive rate because the test targets mutations specific to colorectal cancer, and the need for only a single stool sample since DNA is shed continuously from
colorectal cancer and precursor polyps. A potential disadvantage is that the most appropriate makers for DNA detection of colorectal cancer are not known and clinical evaluation of the tests is limited.

The FDA has determined that approval of the PreGen-Plus test is not required.

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Medical Technology Assessment Committee (MTAC)

Fecal DNA Testing

02/11/2004: MTAC REVIEW

Evidence Conclusion: The Tagore study provides preliminary data on the sensitivity of the PreGen-Plus test in a population with known colorectal neoplasia (47-85% depending on the stage of disease) and specificity in normal individuals (96%). This is not an accurate assessment of how the screening test would perform in a general population sample. Studies that include a blinded comparison of PreGen-Plus to a gold standard in a screening population are needed. In addition, head-to-head comparisons with the standard noninvasive test for colorectal cancer, fecal occult blood testing, would strengthen the evidence.

Articles: The manufacturer's website had an announcement dated October 2003 stating that a study comparing the sensitivity of the PreGen-Plus test and FOBT had been conducted and would be submitted to a peer-reviewed journal when data analysis was finished.

One was on the sensitivity and specificity of a multitarget assay panel labeled as PreGen Plus using colonoscopy as the gold standard (Tagore, 2003). The second article was on a plasma DNA test, not a stool test. The broader search on DNA testing for colorectal cancer yielded 49 articles. There was an empirical study demonstrating the successful extraction of DNA from the stool of colorectal cancer patients (Dong, 2001). Another empirical study extracted DNA from stool and evaluated the sensitivity and specificity of the DNA analysis compared to colonoscopy (Ahlquist, 2000). The PreGen-Plus test was not mentioned, although analysis for the Ahlquist study was done by Exact Laboratories. The Tagore study was critically appraised because it clearly used the PreGen-Plus test and had a larger sample size than the Ahlquist study (n=292 vs. n=61). The citation is as follows: Tagore KS, Lawson MJ, Yucaitis JA. et al. Sensitivity and specificity of a stool DNA multitarget assay panel for the detection of advanced colorectal neoplasia. *Clin Colorectal Cancer 2003*; 1: 47-53. See Evidence Table

The use of PreGen-Plus in screening of colorectal cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*

Fecal DNA Testing

10/20/2014: MTAC REVIEW

Evidence Conclusion: In an effort to establish the accuracy of the Cologuard™ test, Imperiale et al. compared the tests performance to the gold standard, colonoscopy. As a secondary endpoint, the investigators also compared the tests performance to the FIT. The cross-sectional study evaluated 9,989 asymptomatic averaged-risk adults between the ages of 50 and 84 years who were scheduled to undergo screening colonoscopy. All participants provided a stool specimen before routine bowel preparation for colonoscopy. Stool specimens were analyzed in three laboratories and colonoscopy results were evaluated by independent local pathologists and further confirmed and categorized by a central independent pathologist. The gold standard identified CRC in 65 participants and advanced adenomas (AA) in 757 participants. The Cologuard™ was able to accurately detect 60 cancers and 321 AA (sensitivities 92.3% and 42.4%, respectively) while the FIT identified 48 cancers and 180 AA (sensitivities 73.8% and 23.8%, respectively). The Cologuard™ had a lower specificity for detecting all nonadvanced adenomas or negative results when compared with FIT (86.6% vs. 94.9%, respectively) (Imperiale, Ransohoff et al. 2014). Risks of Diagnostic Test In terms of risk, the Cologuard™ test itself presents low risk to the patient as it is noninvasive, requires no bowel preparation or dietary restrictions and allows for collection during normal bowel movements in the toilet. The study reported four mild adverse events and one death. The death occurred prior to colonoscopy and was deemed to be unrelated to the study. Of particular concern, however, is the indirect risk as it relates to false positives and negatives. Although the Cologuard™ test yields a high sensitivity, that came at the cost of a lower specificity which could lead to additional colonoscopies as well as unnecessary stress and anxiety.

Table 1. Number Needed to Screen (NNS) to detect one CRC

	Colonoscopy	Cologuard	FIT
Any CRC	154 (120-200)	166 (130-217)	208 (156-286)
Stage I to III CRC	166 (130-217)	178 (140-238)	227 (169-313)
Advanced precancerous lesion	13 (12-24)	31 (28-35)	55 (48-65)

Conclusions from the last review of multitarget stool DNA testing in MTAC did not live up to genetic test evaluation criteria citing the need for additional research that includes blinded comparison with the gold standard in a screening population as well as, head-to-head comparison with the current standard noninvasive test. Since then, the Cologuard™ has undergone several evolutions reflected throughout the literature with the most current

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version validated by a large cross-sectional study including comparisons with the gold standard, colonoscopy, as well as the FIT. Generally speaking, the study, which was financially supported by the manufacturer Exact Sciences Inc., appears to be well-designed and well-conducted including almost 10,000 participants in 90 centers across the United States and parts of Canada. The investigators, who are also the developers of the device, fail to describe the baseline characteristics of the study population but do identify the significant differences between the participants whose results could be fully evaluated and those whose results could not. Further to this, recruitment was weighted towards the older age of the eligible age spectrum which might limit the generalizability of the results. The design of the study was the primary limiting factor. While it is typical to use a cross-sectional study design to compare diagnostic tests, the results provide only a snapshot of the situation at one given time, failing to provide adequate follow-up to demonstrate how the Cologuard™ might function in clinical practice. Further to this, the sensitivity and specificity is based on stool samples collected at one point in time limits the ability to provide an interval at which the Cologuard™ would be applied. Exact Sciences has provided the protocol for a longitudinal post-market approval study that will likely address these limitations. Conclusions: There is evidence to establish the analytic validity of the Cologuard™ test, that is, the test accurately identifies the particular gene variant.
There is evidence to establish the clinical validity of the Cologuard™ test, that is, how well the test is related to the presence, absence or risk of a disease. There is insufficient evidence to conclude that the test is not harmful to patients. There is insufficient evidence to establish the clinical utility of the Cologuard™ test, that is, the test is reasonably expected to lead to more appropriate patient management than if the test were not available.
Articles: The literature search for multitarget stool DNA testing for CRC screening yielded numerous publications. Among them were various editorials addressing the recent FDA approval, as well as commentary recognizing the Cologuard™ as the first product to be reviewed through the joint FDA-CMS parallel review pilot program. In addition, several publications that mirror the evolution of the device over the years were identified. The FDA's current approval relied on one clinical trial to establish the safety and effectiveness of the Cologuard™ test. This article was selected for review. See Evidence Table

The use of Stool DNA Testing for Colorectal Cancer Screening does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Medical necessity review no longer required:

CPT® or HCPC Codes	Description
81528	Oncology (colorectal) screening, quantitative real-time target and signal amplification of 10 DNA markers (KRAS mutations, promoter methylation of NDRG4 and BMP3) and fecal hemoglobin, utilizing stool, algorithm reported as a positive or negative result

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed	Date Last Revised
02/11/2004	02/11/2004, Instituted annual review because of Medicare criteria 04/05/2011 MDCRPC, 02/07/2012 MDCRPC,12/04/2012 MDCRPC, 04/02/2013 MDCRPC ,10/01/2013 MPC,08/05/2014 MPC, 05/15/2015 MPC, 03/01/2016MPC, 01/03/2017MPC, 11/07/2017MPC , 10/02/2018MPC , 10/01/2019MPC, 10/06/2020MPC , 10/05/2021MPC , 10/04/2022MPC, 10/03/2023MPC	05/11/2017

MDCRPC Medical Director Clinical Review and Policy Committee
MPC Medical Policy Committee

Revision History	Description
05/11/2017	Cologuard was added to the covered services

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Date Sent: 3/29/24
These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage.
Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

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Clinical Review Criteria
Preimplantation Genetic Diagnosis (PGD)

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Preferred Lab for Genetic Testing for Kaiser Permanente non-Medicare enrollees (for in-network coverage)

Prevention and Invitae Corporation is the preferred lab for genetic testing when the test(s) is/are available at Prevention or Invitae and medical necessity criteria are met.*

Invitae's test catalog can be found here: Invitae Test Catalog
Prevention test catalog can be found here: Prevention Test Catalog

**Note: This does not affect processing of tumor or other pathology specimens as they are not performed by Invitae/prevention.*

PPO/POS members may use non-preferred labs at the out of network cost share.

Criteria

For Non-Medicare Members

Preimplantation genetic diagnosis (PGD) is performed on single cells removed from an embryo. Standard prenatal diagnosis is customarily performed on multiple cells obtained by chorionic villous sampling (CVS) or amniocentesis. PGD on single, embryonic cells is considered medically necessary only when there is a need to diagnose a specific, detectable single gene mutation in an embryo at risk due to an identified deleterious genetic mutation in one or both genetic parents, as defined below:

I. In order to meet medically necessary criteria for PGD, **both A and B must be met:**
   A. There must be documentation confirming that PGD is medically necessary to detect a single gene disorder or chromosomal abnormality whose expression in the fetus or child would be expected to have a significant adverse medical impact and that detection in the pre-implantation period would directly affect reproductive decisions.
   B. **One of the following** clinical circumstances must be documented:
      1. One genetic parent has a balanced, reciprocal translocation or Robertsonian translocation
      2. One genetic parent has a single gene autosomal dominant disorder
      3. Both genetic parents are known carriers of the same single gene autosomal recessive disorder
      4. The female genetic parent is a known carrier of a single gene X-linked recessive disorder

The procedure to obtain a cell sample from an embryo for PGD is covered when the above criteria for PGD are met. However, the procedures and services (such as IVF) required to create the embryos to be tested and the transfer of embryos to the uterus after testing, are covered only for members with advanced reproductive technology (ART) benefits and who meet medical necessity criteria for IVF (in vitro fertilization).

II. The following are *not* covered for preimplantation screening:
   A. Aneuploidy screening, including in the setting of recurrent miscarriage or repeated failure of IVF (e.g. screening for Down Syndrome, in women over the age of 35)

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B. Screening for chromosomal abnormalities in the absence of a known, clinically significant genetic or chromosomal defect in a genetic parent
C. Selecting against conditions or disorders in the absence of a known and identifiable genetic or chromosomal defect in a genetic parent
D. Gender selection of selection of nonmedical trait to determine an embryo's carrier status
E. Screening for autosomal recessive disorders when the embryos are created using donor egg or sperm
F. Detecting genetic or chromosomal abnormalities contributed by donor egg or sperm
G. Screening for adult-onset disorders or for genetic predisposition to adult-onset disease
H. HLA typing of an embryo to identify a future suitable stem cell, tissue or organ transplantation donor.

If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist

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Background

Historically, couples at high risk of transmission of a genetic disorder have had limited reproductive options, forced after prenatal diagnosis to choose between either termination of affected pregnancies or acceptance of the emotional and financial burden of having a child with severe disability and early mortality. Preimplantation genetic diagnosis (PGD) was introduced to enhance efficiency in assisted conception. It is a technique for reducing the burden of genetic disease performed on couples who are at risk of a specific inherited disorder and used to identify genetic defects present in embryos created through in vitro fertilization (IVF) before transferring them to the uterus.

PGD is performed in conjunction with IVF and is offered to both fertile and infertile couples. Introduced in 1990 as an experimental procedure, PGD has now become an established clinical option in reproductive medicine (Handyside, Kontogianni et al. 1990; Verlinsky, Ginsberg et al. 1990). Because only unaffected embryos are transferred to the uterus for implantation, PGD can provide an alternative to current post conception diagnostic procedures such as amniocentesis or chorionic villus sampling which are sometimes followed by pregnancy termination when results are unfavorable (Verlinsky, Cohen et al. 2004). PGD techniques are now also being utilized for preimplantation genetic screening (PGS) with the intent to identify potential genetic abnormalities in conjunction with IVF for couples without specific known inherited disorders.

With single gene disorders and inherited chromosomal abnormalities being the main indicators for PGD, the technique is available for most known genetic mutations. With that said, PGD can be considered a rapidly evolving technique. Put simply, PGD requires egg extraction, IVF, cell biopsy, genetic analysis and embryo transfer (Handyside, Kontogianni et al. 1990). At present, there are three different procedures utilized for cell biopsy, each with its own advantages and disadvantages, including polar body biopsy, cleavage-stage embryo biopsy and blastocyst biopsy. Depending on the whether the characteristic being tested for is associated with chromosomes or DNA, the sample can be analyzed in one of three ways including polymerase chain reaction (PCR), fluorescence in situ hybridization (FISH) and comparative genomic hybridization with new technologies emerging rapidly. Regardless of the methods, the results are used by parents and providers to select which embryos are transferred back to the uterus with the ultimate goal of establishing an unaffected pregnancy.

The accuracy and reliability of PGD are key issues and exploring these matters requires consideration of the technical challenges and risks inherent in the genetic test itself and in the IVF procedure that it entails. Any PGD strategy has to deal with the detection and avoidance of misdiagnosis from the onset with the risk and outcome relating directly to the type of genetic disorder for which testing is performed. Although PGD has been suggested as an alternative for current post conception diagnostic procedures, the amount of DNA available for testing is limited. Due to this risk, prenatal diagnosis by amniocentesis or chronic villus sampling testing is strongly recommended upon established pregnancy to confirm genetic health.

Applicable Codes

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Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® Codes	Description
89290	Biopsy, oocyte polar body or embryo blastomere, microtechnique (for pre-implantation genetic diagnosis); less than or equal to 5 embryos
89291	Biopsy, oocyte polar body or embryo blastomere, microtechnique (for pre-implantation genetic diagnosis); greater than 5 embryos

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
12/03/2013	12/03/2013 MPC, 10/07/2014MPC, 08/04/2015MPC, 06/07/2016MPC, 04/04/2017MPC, 02/06/2018MPC, 01/08/2019MPC, 01/07/2020MPC, 01/05/2021MPC, 03/01/2022MPC, 01/10/2023MPC	10/10/2022

MPC Medical Policy Committee

Revision History	Description
06/02/2020	Added section: “Preferred Lab for Genetic Testing for Kaiser Permanente non-Medicare enrollees.” Requires 60-day notice, effective date 10/01/2020.
10/10/2022	Noted Prevention lab as a preferred vendor for genetic testing.

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Clinical Review Criteria
Prolotherapy/Sclerotherapy

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Prolotherapy, Joint Sclerotherapy, and Ligamentous Injections with Sclerosing Agents (150.7) *This service is not covered per Medicare criteria.*
Local Coverage Determinations (LCD)	None
Local Coverage Article	None

For Non-Medicare Members

Service	Policy
Prolotherapy/Sclerotherapy for **ANY** indication	There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

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Background

Back pain is the most prevalent musculoskeletal condition encountered in primary care and is estimated to affect 65-80% of people during their life. The majority of back pain is benign, self-limiting and requires symptomatic therapy only. Back pain is often related to muscular, tendon or ligament strain or injury. Common treatments include physical therapy, steroidal and nonsteroidal anti-inflammatory drugs and chiropractic manipulation. One proposed treatment for chronic low back pain, which is resistant to other treatments, is the injection of sclerosing compounds into back tissue to produce scarring and potentially stabilize soft tissue in the area of the injury.

Prolotherapy, also called sclerotherapy and proliferative injection therapy, has been used as a treatment for chronic low-back pain since the 1950s (Dechow). Sclerosing agents are injected into the fibro-osseous junctions of the lower back. The rationale for using prolotherapy is that the injection of irritant solutions into a pain site will initiate local inflammation. The inflammation then begins a cascade of wound healing which results in the deposition of new collagen and stronger ligaments (Banks).

Medical Technology Assessment Committee (MTAC)

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Prolotherapy/Sclerotherapy for Low Back Pain

06/09/1999: MTAC REVIEW

Evidence Conclusion: The published evidence consists of two randomized trials, one showing a 1.5-point improvement (7.5-point visual analogue scale) in pain and a 4.9 point improvement (33 item scale) in disability between the proliferant and placebo groups at 6 months. The experimental regimen also included injectable steroids, forceful spinal manipulation and different anesthetic volumes, therefore differences between experimental and placebo groups cannot be attributed only to proliferant. The second trial reports a less than 1-point difference in pain and disability scores between proliferant and placebo at 6 months. Overall, there is weak evidence that an intensive intervention (including proliferant) produces a statistically and clinically significant improvement in pain and disability. When proliferant and placebo are directly compared, there is weak evidence that proliferant provides no additional benefit compared to placebo.

Articles: Ongley, MJ, et al, A New Approach to the Treatment of Chronic Low Back Pain, 1987, *Lancet*, ii: 143-148. See Evidence Table. Klein, RG, et al, A Randomized Double-Blind Trial of Dextrose-Glycerine-Phenol Injections for Chronic Low Back Pain, *Journal of Spinal Disorders*, 1993, 6:23-33 See Evidence Table.

The use of prolo/sclerotherapy in the treatment of low back pain does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

04/10/2002: MTAC REVIEW

Prolotherapy/Sclerotherapy for Low Back Pain

Evidence Conclusion: One new RCT was identified on prolotherapy/sclerotherapy for low back pain (Dechow). This was a valid RCT that compared three, once-weekly injections with sclerosing agents to placebo injections. The authors did not find statistically significant differences in pain, disability or spinal flexion between groups. There was clearly no effect of the intervention on disability, but it is possible that there could be smaller, yet clinically significant differences in pain or spinal flexion that this study was unable to detect. Prolotherapy/sclerotherapy was previously reviewed by MTAC in April 1999. In the first MTAC review, two RCTs were critically appraised. Both were limited in that the treatment group received multiple interventions so the effectiveness of prolotherapy itself could not be determined. In summary, there is insufficient evidence that prolotherapy/sclerotherapy as a stand-alone intervention is effective for reducing low back pain. The results of one RCT powered to detect a 50% reduction in pain levels between groups suggest that it may be an ineffective intervention.

Articles: The search yielded six articles. There were two empirical studies, one of which was included in the initial MTAC review in 1999. The other study, an RCT, was evaluated. No additional empirical studies were identified from the appeal materials. The following article was critically appraised: Dechow E, Davies RK, Carr AJ, Thompson PW. A randomized, double-blind, placebo-controlled trial of sclerosing injections in patients with chronic low back pain. Rheumatology 1999; 38:1255-59. See Evidence Table.

The use of prolo/sclerotherapy in the treatment of low back pain does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Considered Not Medically Necessary:

CPT® or HCPC Codes	Description
M0076	Prolotherapy

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
04/1999	04/05/2011 MDCRPC, 02/07/2012 MDCRPC, 12/04/2012 MDCRPC, 12/01/2013MPC, 08/05/2014MPC, 06/02/2015MPC, 04/05/2016MPC, 02/07/2017MPC, 12/05/2017MPC, 11/06/2018MPC, 11/05/2019MPC, 11/03/2020MPC, 11/02/2021MPC, 11/01/2022MPC, 11/07/2023MPC	04/05/2011

MDCRPC Medical Director Clinical Review and Policy Committee

MPC Medical Policy Committee

Revision History	Description

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KAISER PERMANENTE®

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Clinical Review Criteria
Proton Radiation Therapy

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article	None
Kaiser Permanente Medical Policy	Due to the absence of an active NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Clinical Review Criteria, ***Proton Beam Therapy***, for medical necessity determinations. Refer to the Non-Medicare criteria below.

For Non-Medicare Members

Kaiser Permanente has elected to use the Proton Beam Therapy (KP-0389) MCG* for medical necessity determinations. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.

***MCG Manuals are proprietary and cannot be published and/or distributed**. However, on an individual member basis, Kaiser Permanente can share a copy of the specific criteria document used to make a utilization management decision. If one of your patients is being reviewed using these criteria, you may request a copy of the criteria by calling the Kaiser Permanente Clinical Review staff at 1-800-289-1363.

If requesting this service, please send the following documentation to support medical necessity:

- Most recent medical oncology notes
- Most recent radiation oncology notes
- Most recent imaging (i.e., CT/MRI)

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Background

Proton beam therapy (PBT) is a form of stereotactic radiosurgery that delivers a focused dose of radiation energy to the targeted area while surrounding normal tissue receives minimal radiation. PBT releases its highest percentage of energy at the end of its path (i.e., Bragg peak), depositing 100% of the dosage at the targeted tissue.

Prostate cancer is one of the most common cancers, and the second leading cause of cancer death in men in the US. The standard management options for a localized disease include surgery, radiotherapy, and watchful

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waiting. The optimal treatment, however, is not well defined; both surgery and radiation therapy are reported to have equivalent outcomes, and each approach has its advantages and side effects. Researchers have reported that for intermediate and high-risk disease, radical external beam treatment is the standard treatment, and that there is a dose response for biochemical relapse-free survival. The success of radiation therapy depends on the dose delivered to the tumor and the accuracy of delivery. However, dose escalation to >70 Gy is associated with an increase in genitourinary and gastrointestinal side effects. Several techniques have been developed to deliver high doses of radiation to the prostate while sparing surrounding normal tissue. Among these are the three-dimensional conformal radiotherapy external beam radiotherapy (EBRT), intensity modulated radiation therapy (IMRT), brachytherapy, and proton therapy (Vordermark 2006, Hoskin 2007, Rades 2007).

Proton therapy, like other forms of radiotherapy, works by aiming ionizing particles onto the target tumor. Theoretically proton radiation therapy has the benefit of more localized delivery of radiotherapy than that achieved with photons produced by a linear accelerator. Unlike X-ray beams, a single proton beam can be shaped to deliver a homogeneous radiation dose to irregular three-dimensional volumes. Due to their relatively large size, protons scatter less easily in the tissue with very little lateral dispersion. They follow a predetermined track and stop abruptly at any prescribed depth. The proton beam energy is at its minimum at entry to the body, and maximum, known as 'Bragg-peak', near the end of the range of the proton beam. Beyond the Bragg-peak, the dose falls practically to zero. By choosing appropriate proton beam energies, the depth of the Bragg-peak can be adjusted according to the depth and extent of the target volume. The improved dose distribution can potentially allow higher doses of radiotherapy to the tumor without increasing the normal tissue toxicity (Slater 1999, Brada 2007, Olsen 2007). There is a concern however, that proton beam radiotherapy exposes healthy tissue to stray radiation emitted from the treatment unit and secondary radiation produced within the patient. These exposures may potentially increase a patient's risk of developing a radiogenic second cancer (Taddei 2008).

Proton therapy was initially used for the treatment of choroidal malignant melanomas, and tumors of the skull base. Currently there is a growing interest in the use of proton therapy for the treatment of tumors where conventional radiation therapy would damage surrounding radiosensitive tissues to an unacceptable level as brain tumors, lung cancers, and other tumors in the neck, vicinity of the spinal cord, liver, upper abdomen and pelvis. Proton therapy is also favored for pediatric patients where long-term side effects, as occurrence of secondary tumors resulting from overall radiation dose to the body, are of concern.

Some investigators have questioned the ability of proton therapy to limit morbidity, and others have questioned its value relative to the cost. In addition, concerns have been raised about a potential risk for secondary malignancies.

National Cancer Institute Clinical Trials
Two Phase III trials are comparing photon versus carbon ion radiation therapy in patients with low and intermediate grade chondrosarcoma of the skull base (NCT01182753) and chordoma of the skull base (NCT01182779).

A Phase III trial is comparing hypo fractionated proton radiation versus standard dose for prostate cancer (NCT01230866).

National Comprehensive Cancer Network (NCCN) Guidelines
Prostate Cancer: NCCN guidelines for prostate cancer (v 3.2012) state that "proton beam therapy can be added as an alternative radiation sources. However, proton therapy is not recommended for routine use at this time since clinical trials have not yet yielded data that demonstrates superiority to, or equivalence of, proton beam and conventional external beam for the treatment of prostate cancer". (1)

Bone Cancer: NCCN guideline for bone cancer (v 2.2012) states that "proton and/or photon beam RT may be useful for patients with chondrosarcomas of the skull base and axial skeleton with tumors in unfavorable location not amenable to resection." (3)

The FDA cleared several medical devices designed to produce and deliver a proton beam for the treatment of patients with localized tumors and other conditions susceptible to treatment by radiation.

Medical Technology Assessment Committee (MTAC)

Proton Radiation Therapy
12/01/2008: MTAC REVIEW

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Evidence Conclusion: No randomized clinical trials, to date, have directly compared the efficacy of protons and conventional radiation therapy using photons in the treatment of clinically localized prostate cancer. The only two published RCTs involving proton therapy were evaluating the effect of dose escalation on cancer control. Both studies used protons as a boost to photon irradiation and neither was intended to compare the efficacy of protons versus the conventional photon radiation therapy. Zietman et al's (2005) trial randomized 393 patients with early stage (T1B-T2B) prostate cancer to a proton dose of 19.8 GyE or 28.8 GyE followed by photon irradiation to 50.4 Gy. All patients in the two arms of the study received both photons and protons. The results showed no significant difference in 5-year survival (96% vs. 97%) between the two proton doses, but there was an improvement in 5-year biochemical total control rate from 61.4% for the low-dose group to 80.4% to the high dose group (p<.001). The higher radiation dose was however associated with an increase in acute and late grade 2 rectal toxicity. The largest published case series on proton therapy (Slater 2004) was retrospective, had selection bias, and no comparison or control group. Patients with localized prostate cancer who received proton therapy in the early 1990s were treated with a combination therapy of both protons and photons. Later, after the proton treatment capacity increased, the patients were selected to receive either proton therapy alone or in combination with photon therapy. Therapy was selected based on the patient's risk of lymph node micrometastases as calculated by Partin normogram. The study does not allow making any conclusion on the comparative efficacy of protons versus photon therapy. There is insufficient evidence to determine whether the use of protons for the treatment of patients with localized prostate cancer would improve survival and reduce biochemical failure rate compared with the highly conformal photon therapy currently used. There is insufficient evidence to determine whether the use of protons for treating patients with localized prostate would reduce acute or late rectal and urinary toxicity compared with the highly conformal photon therapy currently used.
Articles: The literature search revealed over 170 published articles on proton therapy for prostate cancer. The majority were review articles on the technical aspects of the therapy. No randomized controlled trials that directly compared proton therapy to any other conventional radiation therapy were identified. There were two published RCTs on dose escalation (Shipley 1995, and Zietman 2005) using a combination of photon and proton therapy for localized prostate cancer, and several case series with historical, or no controls. Shipley's trial (1995) used inadequate photon doses and techniques compared to the current standards. Zietman and colleagues' trial as well as the largest published case series on proton therapy were selected for critical appraisal. Zietman AL, Desilvio ML, Slater JD, et al. Comparison of conventional-dose vs. high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate. A randomized controlled trial. JAMA 2005; 294:1233-1239. See Evidence Table. Slater JD, Rossi CJ, Yonemoto LT, et al. Proton therapy for prostate cancer.: The initial Loma Linda University experience Int J Radiat Oncol Biol Phys 2003;59:348-352. See Evidence Table.

The use of Proton radiation therapy for the treatment of prostate cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
77520	Proton treatment delivery; simple, without compensation
77522	Proton treatment delivery; simple, with compensation
77523	Proton treatment delivery; intermediate
77525	Proton treatment delivery; complex
S8030	Scleral application of tantalum ring(s) for localization of lesions for proton beam therapy

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
06/04/2009	05/03/2011 MDCRPC, 08/02/2011 MDCRPC, 06/05/2012 MDCRPC, 03/05/2013MDCRPC,	09/01/2015

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	01/07/2014[MPC], 11/04/2014[MPC], 09/01/2015[MPC], 07/05/2016[MPC], 05/02/2017[MPC], 03/06/2018[MPC], 02/05/2019[MPC], 02/04/2020[MPC], 02/02/2021[MPC], 02/01/2022[MPC], 02/07/2023[MPC]	

[MDCRPC] Medical Director Clinical Review and Policy Committee

[MPC] Medical Policy Committee

Revision History	Description
09/01/2015	Added indication for pediatric central nervous
09/02/2015	Added new link for LCD
02/01/2022	Removed link to retired SRS/SBRT LCD L34151. Adopted KPWA policy for Medicare Advantage members.

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KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
LASIK (Laser Assisted In-situ Keratomileusis)
PTK (Phototherapeutic Keratectomy)

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Refractive Keratoplasty (80.7)
Local Coverage Determinations (LCD)	None
Local Coverage Article	None

For Non-Medicare Members

Lasik is covered when **All of the following** conditions are met:

1. Astigmatism and/or anisometropia have been surgically induced.
2. Patient is unable to wear glasses or contact lenses after surgery due to anisometropia (eyes having unequal refractive power) and/or high astigmatism.
3. Documented attempts to correct the surgical error with historical means of refraction and/or contact lens fitting.
4. There must be 2.5 diopter or more increase in astigmatism and/or anisometropia from the pre to the postoperative state.
5. Patient must express some functional disability due to the increased astigmatism and the surgeon must have a reasonable expectation that the laser will improve the patient's function.
6. The patient's primary problem is not corneal graft rejection or multiple failures when comfort may be the goal, not vision improvement.
7. The equipment used is FDA approved and the procedure is performed by an ophthalmologist trained to use the equipment.
   Relative contraindications include:
   a. Poorly controlled autoimmune disease
   b. Immunosuppressive medications
   c. Keratoconus and other corneal ectasias
   d. History of keloid formation
   e. Coexisting ocular disease
   f. Unstable refractive error
   g. Underlying systemic disease affecting wound healing

Phototherapeutic keratectomy (PTK) is covered when the **ALL of the following** criteria are met:

1. It is being used to remove damaged and/or diseased tissue from the anterior surface of the cornea.
2. **ONE of the following** is true:
   a) The proposed treatment area is up to 300 microns thick or the cornea is at least 250 microns thick after ablation and other less invasive treatments are not possible or have failed (such as stromal puncture)
   b) The treatment of anterior corneal dystrophies, removal of scars and other opacities in the anterior third of the cornea and smoothing of irregular corneal surfaces to improve visual acuity and reduce pain

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associated with the corneal condition or improve the patient's ability to wear or tolerate spectacles or contact lenses.

3. And **None of the following** conditions exist:
   a) Active infections of the cornea
   b) Bullous keratopathy
   c) Deep pathology extending beyond the anterior third of the cornea
   d) Depressed scars
   e) Unstable keratometry
   f) Existing hyperopia

Photorefractive keratectomy (PRK) is considered cosmetic and is not covered.

Note: Phototherapeutic keratectomy (PTK) should not be confused with photorefractive keratectomy (PRK). Although technically the same procedure, PTK is used for the correction of particular corneal diseases; PRK involves use of the excimer laser for correction of refractive errors (e.g., myopia, hyperopia, astigmatism, and presbyopia) in persons with otherwise non-diseased corneas.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

In 1995 the FDA approved the use of Excimer 193nm laser as an effective tool for performing phototherapeutic (PTK=correcting corneal pathology) and photorefractive (PRK=correcting visual abnormalities) keratectomy of PRK and PTK. In early 1996 Kaiser Permanente evaluated the use of this technology and its efficacy. Following that evaluation, it was recommended that Kaiser Permanente would provide PRK/LASIK as a non-covered service. However, in a few cases where traditional treatment options, including surgery, have failed and the only option available is PRK/LASIK.

Evidence and Source Documents

On March 13, 1996, The GHC Committee on Medically Emerging Technology (COMET) reviewed key articles and concluded that the recent FDA approved Excimer 193nm laser is an effective tool for performing phototherapeutic (PTK=correcting corneal pathology) and photorefractive (PRK=correcting visual abnormalities) keratectomy. In the case of photorefractive keratectomy, its use should be restricted to patients with low to moderate myopia (1 to 8 diopters of visual correction) until efficacy data becomes available for PRK in high myopes. For GHC patients, it was recommended that PTK for corneal pathology should be a covered service and that PRK for refractive errors should be a non-covered service.

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
65765	Keratophakia
65767	Epikeratoplasty
65771	Radial keratotomy
65772	Corneal relaxing incision for correction of surgically induced astigmatism
65775	Corneal wedge resection for correction of surgically induced astigmatism
65760	Keratomileusis
S0800	Laser in situ keratomileusis (LASIK) ***S codes not covered by Medicare***
S0812	Phototherapeutic keratectomy (PTK) ***S codes not covered by Medicare***

Considered Cosmetic & Not Medically Necessary:

CPT® or HCPC Codes	Description

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S0810	Photorefractive keratectomy (PRK) ***S codes not covered by Medicare***

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Creation Date	Revision Dates	Date Last Revised
02/26/1998	08/03/2010[MDCRPC],06/7/2011[MDCRPC],04/03/2012[MDCRPC],05/01/2012[MDCRPC], 03/05/2013[MDCRPC],01/07/2014[MDCRPC], 11/04/2014[MPC], 09/01/2015[MPC], 07/05/2016[MPC], 05/02/2017[MPC], 03/06/2018[MPC], 02/05/2019[MPC], 02/04/2020[MPC], 02/02/2021[MPC], 02/07/2023[MPC]	02/16/2022

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
02/16/2016	Added additional keratoplasty codes
02/16/2022	Updated applicable codes

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KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Pulmonary Rehabilitation

- COPD
- Chronic Pulmonary Lung Disease
- Emphysema

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Pulmonary Rehabilitation Services 240.8
Local Coverage Determinations (LCD)	None
Local Coverage Article	Billing and Coding: Pulmonary Rehabilitation Services (A52770)

For Non-Medicare Members

Clinical review is no longer required

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

The American Thoracic Society and the European Respiratory Society define pulmonary rehabilitation as “an evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities. Integrated into the individualized treatment of the patient, pulmonary rehabilitation is designed to reduce symptoms, optimize functional status, increase participation, and reduce health care costs through stabilizing or reversing systemic manifestations of the disease. Comprehensive pulmonary rehabilitation programs include patient assessment, exercise training, and psychosocial support”.

Individuals with chronic obstructive pulmonary disease (COPD) constitute the largest population of those referred for pulmonary rehabilitation. COPD is defined as a slowly progressive disease of the airways characterized by airflow limitation and loss of lung function that is not fully reversible. Pulmonary rehabilitation may also be of value for other patients who have respiratory symptoms associated with reduced functional capacity or health-related quality of life (Celli 2008; Nici 2006).

The American Academy of Chest Physicians and the American Association of Cardiovascular and Pulmonary Rehabilitation updated their guideline on pulmonary rehabilitation in 2007. The new guideline accepts the above definition of pulmonary rehabilitation. This guideline considers the three most important features of a successful pulmonary rehabilitation program to be: a multidisciplinary approach, individual assessment and goal-setting, and paying attention to physical functioning and social functioning. The guideline recommends at least 6 weeks of pulmonary rehabilitation; however, no specific combination of program components is recommended (Ries 2007).

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Medical Technology Assessment Committee (MTAC)

Pulmonary Rehabilitation

05/01/2000: MTAC REVIEW

Evidence Conclusion: Although there is some evidence that specific pulmonary rehabilitation programs have lasting benefits for selected patients (Guell et al., Griffiths et al.), conclusions cannot be drawn about the effectiveness of pulmonary rehabilitation in general for the following reasons: Each pulmonary rehabilitation program has different components (see attached table): study methodologies do not permit conclusions about which component or components affect outcomes. Each pulmonary rehabilitation program is a different length and has a different intensity (see attached table): it is not possible to draw conclusions about what length or intensity is necessary to improve outcomes. Study methodologies do not permit conclusions about whether the pulmonary rehabilitation program itself or other factors such as the social support provided by program participation affects outcomes. Most programs have small sample sizes and results may be unreliable. Replications of individual programs are not available. The results of programs are not necessarily generalizable to other populations. For example, the Guell et al. study was conducted only with men and results may not be generalizable to women. Most of the early studies examining the effectiveness of PR were of poor quality (as reported in the meta-analysis by Cambach et al.) The ideal evidence, which does not currently exist, would be well conducted RCTs that examine different combinations of PR program components (e.g. education alone, education+exercise, exercise alone, etc.). In addition, there needs to be sufficient numbers of participants and data for the entire population of interest (i.e. both men and women).

Articles: The literature search yielded 73 articles. There were 8 randomized controlled trials (RCTs) and 2 meta-analyses. Five RCTs were excluded because of one of the following reasons: The groups compared were not directly relevant to this review (in-patient vs. out-patient PR, PR vs. lung surgery); had a small sample size (total n □50); or were included in the meta-analysis that was selected for review.

Articles selected for critical appraisal include: The more recent meta-analysis: Cambach, W, Wagenaar, RC, Koelman, TW, van Keimpema, T, Kemper, HCG. The long-term effects of pulmonary rehabilitation in patients with asthma and chronic obstructive pulmonary disease: A research synthesis. Arch Phys Med Rehabil 1999; 80: 103-111. See Evidence Table. Griffiths, TL, Burr, ML, Campbell, IA et al. results at one year of outpatient multidisciplinary pulmonary rehabilitation: a randomized controlled trial. Lancet 2000; 355: 362-8. See Evidence Table. Guell, R, Casan, P, Belda, J et al. Long-term effects of outpatient rehabilitation of COPD: a randomized trial. Chest 2000; 117: 976-83. See Evidence Table. Wedzicha, JA, Bestall, JC, Garrod, R et al. Randomized controlled trial of pulmonary rehabilitation in severe chronic obstructive pulmonary disease patients, stratified with the MRC dyspnoea scale. Eur Respir J 1999; 12: 363-9. See Evidence Table.

The evidence failed MTAC evaluation criteria due to the lack of a standard definition of pulmonary rehabilitation and the paucity of rigorous studies.

Pulmonary Rehabilitation

12/01/2008: MTAC REVIEW

Evidence Conclusion: The best evidence on the efficacy of pulmonary rehabilitation for COPD is a Cochrane review of randomized controlled trials (Lacasse et al., 2006). PR was defined as a program of at least 4 weeks' duration that included exercise therapy, with the optional addition or education or psychosocial support. The meta-analysis did not specify whether programs included individualized assessment or a multidisciplinary team, so it is not clear how many programs met the criteria defined for this review. Pooled analyses in the Cochrane report found significantly better functional exercise capacity, maximal exercise capacity and quality of life in patients randomized to PR compared to usual care. Limitations of the evidence included in the Cochrane review include:

Most of the published RCTs were small, and of low-quality. None were rated by the Cochrane reviewers as high-quality. No data were reported on long-term effectiveness of PR. Most studies reported findings at the end of the active intervention. The outcomes reported were exercise capacity and quality of life. There are insufficient data on the impact of PR on the rate of exacerbations and hospitalizations. The comparison intervention in the Cochrane review was usual care, the content of which varied from study to study. Thus, we cannot draw conclusion on which components of PR might be effective. Another limitation of the body of evidence is that RCTs comparing PR to sham PR programs are not available. Therefore, we cannot determine whether PR programs per se are effective or whether there is a 'placebo effect' of participating in a program believed by patients to be beneficial. One RCT (Sewell et al., 2005) suggests that an individually tailored exercise program, a key feature of pulmonary rehabilitation, may not be any more effective than a general exercise program in which all participants perform the same exercise. The Sewell study did not find statistically significant differences in functional ability or exercise performance in patients with COPD randomly assigned to receive a 7-week PR program of education

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plus a general or individualized exercise program. The Sewell study is not conclusive—sample size calculations were not reported, and it may have been underpowered. In conclusion: The evidence on pulmonary rehabilitation for COPD has important limitations. RCTs were small and of low quality, outcome data are short-term and are only available for exercise capacity and quality of life, and a placebo effect of participating in a PR program cannot be ruled out. There are no RCTs comparing some PR program meeting criteria established for this review and a less-intensive intervention. It is important to know whether a comprehensive PR program that includes individualized assessment and involves a multi-disciplinary team is more effective than a less resource-intensive intervention such as an exercise program. There is insufficient evidence on the effectiveness of pulmonary rehabilitation for conditions other than COPD.

Articles: The ideal study is a double-blind randomized controlled trial comparing pulmonary rehabilitation to a sham rehabilitation program (i.e. a program of similar intensity without the therapeutic content under evaluation). No studies meeting these criteria were identified. However, there was one relatively large RCT (Sewell et al., 2005) that compared an individualized exercise program to a general exercise program for COPD. The general exercise program could be considered a type of sham and could allow for blinding of participants. Other than a sham-controlled trial, the next best design is a study comparing two PR programs with a different combination of components, especially if one of the PR programs met the definition for this review. One small RCT was identified that compared exercise only, exercise plus activity training and exercise plus didactic education (Norweg et al., 2005). This study, however, was excluded due to the small number of participants. A third type of comparison intervention is “usual care”. Since the previous MTAC review, a Cochrane review of randomized controlled trials comparing pulmonary rehabilitation to usual care for patients with COPD has been published (Lacasse et al., 2006). No large, well-conducted RCT on PR versus any comparison intervention published after the Cochrane review was identified. The search did not yield any randomized controlled trials or meta-analyses that evaluated pulmonary rehabilitation for any lung condition other than COPD.The Cochrane review and one RCT were critically appraised: Lacasse Y, Goldstein R, Lasserson TJ, Martin S. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2006. Issue 4. See Evidence Table. Sewell L, Singh SJ, Williams JEA et al. Can individualized rehabilitation improve functional independence in elderly patients with COPD? Chest 2005; 128: 1194-1200. See Evidence Table.

The use of pulmonary rehabilitation in the treatment of COPD, chronic pulmonary lung disease and emphysema does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Pulmonary Rehabilitation

12/20/2010: MTAC REVIEW

Evidence Conclusion: A recent meta-analysis that evaluated the effectiveness of pulmonary rehabilitation after an acute exacerbation of COPD found that compared to usual care, subjects in the pulmonary rehabilitation intervention had fewer hospital admissions. However, only 3 studies with a total of 93 subjects were included in the meta-analysis (Puhan 2009).

Pulmonary Rehabilitation vs. Usual Care

Outcome	# of studies	# of subjects	Odds Ratio (95% CI)	NNT (95% CI)
Hospital admission	3	93	0.13 (0.04 to 0.35)	3* (2 to 4)

*NNT over 34 weeks

Conclusion: Evidence from a meta-analysis that included small studies of moderate quality suggests that pulmonary rehabilitation is effective at reducing hospital admissions in patients with an acute exacerbation of COPD.

Articles: Only randomized controlled trials, meta-analyses, and clinical trials were included in the review. Studies were excluded if they were: community based; if they did not have sufficient statistical power to detect a difference in one of the main outcomes; or if they did address one of the main outcome measures (hospitalizations or emergency department visits). The following study was critically appraised: Puhan M, Scharplatz M, Troosters T, Walters ED and Steurer J. Pulmonary rehabilitation following exacerbation of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2009, Issue 1. Art No.: CD005305. DOI: 10.1002/14651858. CD005305.pub2. See Evidence Table.

The use of pulmonary rehabilitation in the treatment of COPD, chronic pulmonary lung disease and emphysema does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

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Applicable Codes

Medically necessary review is no longer required:

CPT® or HCPC Codes	Description
94625	Physician or other qualified health care professional services for outpatient pulmonary rehabilitation; without continuous oximetry monitoring (per session)
94626	Physician or other qualified health care professional services for outpatient pulmonary rehabilitation; with continuous oximetry monitoring (per session)
G0237	Therapeutic procedures to increase strength or endurance of respiratory muscles, face-to-face, one-on-one, each 15 minutes (includes monitoring)
G0238	Therapeutic procedures to improve respiratory function, other than described by G0237, one-on-one, face-to-face, per 15 minutes (includes monitoring)
G0239	Therapeutic procedures to improve respiratory function or increase strength or endurance of respiratory muscles, two or more individuals (includes monitoring)
S9473	Pulmonary rehabilitation program, nonphysician provider, per diem ***S codes not covered by Medicare***

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Date Created	Review Date	Date Last Revised
01/16/2009	02/10/2011[MDCRPC], 12/06/2011[MDCRPC], 10/02/2012[MDCRPC] ,08/06/2013[MPC], 01/07/2014[MPC], 11/04/2014[MPC], 09/01/2015[MPC], 07/05/2016[MPC], 05/02/2017[MPC], 03/06/2018[MPC], 03/05/2019[MPC], 03/03/2020[MPC], 03/02/2021[MPC], 03/01/2022[MPC] , 03/07/2023[MPC]	12/21/2023

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
07/05/2016	Added NCD
09/03/2015	Changed Medicare link
11/17/2016	Added LCA A52770
09/07/2017	Clinical Review no longer required
03/01/2022	Updated applicable codes.
12/21/2023	Added NCD Pulmonary Rehabilitation Services 240.8

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KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Facet Neurotomy/SI Joint Neurotomy

- Radiofrequency Neurotomy
- Neurolytic Agent

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Induced Lesions of Nerve Tracts (160.1)
Local Coverage Determinations (LCD)	Facet Joint Interventions for Pain Management (L38803) Sacroiliac Joint Injections and procedures (L39464) *__Please Note:__ Noridian currently does not cover RFA ablation of the SIJ joint
Local Coverage Article (LCA)	Facet Joint Interventions for Pain Management (A58405) Billing and Coding: Sacroiliac Joint Injections and Procedures (A59246)

For Non-Medicare Members

Kaiser Permanente has elected to use the Facet Neurotomy, SI Joint Neurotomy (KP-0218 08012023v2) MCG* for medical necessity determinations. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.

***MCG manuals are proprietary and cannot be published and/or distributed.** However, on an individual member basis, Kaiser Permanente can share a copy of the specific criteria document used to make a utilization management decision. If one of your patients is being reviewed using these criteria, you may request a copy of the criteria by calling the Kaiser Permanente Clinical Review staff at 1-800-289-1363 or access the MCG Guideline Index using the link provided above.

If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist (Neurology, physiatrist, anesthesia, orthopedics)

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Radiofrequency (RF) neurotomy is a treatment for various conditions, including certain types of back and neck pain. It is based on the premise that severing the nerve supply to a painful structure may reduce pain and allow a restoration of function. It was first described by Shealy in 1975 and the technique has been modified since that time (Niemisto, 2003). Generally, in order to use RF neurotomy, two criteria must be fulfilled: 1) the structure responsible for the pain must be at or near the spinal facet joints and 2) the painful structure must be identified with a diagnostic block of local anesthesia causing temporary relief of pain. Due to the high false-positive rate of single local anesthetic blocks, placebo-controlled blocks are recommended, particularly for the lumbar spine (Lord and Bogduk, 2002).

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The RF neurotomy procedure consists of inserting a radiofrequency electrode percutaneously under fluoroscopy guidance to the targeted area. A small amount of electrical stimulation is initially used to identify the nerve position. A regional anesthetic is then injected. After that, RF current is applied to the tissue. RF current is low energy, high frequency alternating current. When applied to biological tissue, the current causes charged molecules to oscillate and the resulting friction produces heat. A RF lesion is made by raising the temperature of the electrode to 70-90°C for 60-90 seconds. The size of the lesion varies with the size of the electrode; the maximum width of the lesion is 3-4 times the width of the electrode tip. Since the lesions are small, accurate placement of the electrode requires knowledge of the topography of the target nerve tissues and surgical precision (Lord and Bogduk, 2002)

Documentation should include:

- Pre-procedural documentation must include a complete initial evaluation including history and an appropriately focused musculoskeletal and neurological physical examination. There should be a summary of pertinent diagnostic tests or procedures justifying the possible presence of facet joint pain.
- A procedure note must be legible and include sufficient detail to allow reconstruction of the procedure. Required elements of the note include a description of the techniques employed, nerves injected and sites(s) of injections, drugs and doses with volumes and concentrations as well as pre and post-procedural pain assessments. With RF neurotomy, electrode position, cannula size, lesion parameters, and electrical stimulation parameters and findings must be specified and documented.
- Facet joint interventions (diagnostic and/or therapeutic) must be performed under fluoroscopic or computed tomographic (CT) guidance. Facet joint interventions performed under ultrasound guidance will not be reimbursed.
- A hard (plain radiograph with conventional film or specialized paper) or digital copy image or images which adequately document the needle position and contrast medium flow (excluding RF ablations and those cases in which using contrast is contra-indicated, such as patients with documented contrast allergies), must be retained and submitted if requested.
- In order to maintain target specificity, total IA injection volume must not exceed 1.0 mL per cervical joint or 2 mL per lumbar joint, including contrast. Larger volumes may be used only when performing a purposeful facet cyst rupture in the lumbar spine.
- Total MBB anesthetic volume shall be limited to a maximum of 0.5 mL per MB nerve for diagnostic purposes and 2ml for therapeutic. For a third occipital nerve block, up to 1.0 mL is allowed for diagnostic and 2ml for therapeutic purposes.
- In total, no more than 100 mg of triamcinolone or methylprednisolone or 15 mg of betamethasone or dexamethasone or equivalents shall be injected during any single injection session.
- Both diagnostic and therapeutic facet joint injections may be acceptably performed without steroids.

Medical Technology Assessment Committee (MTAC)

Back/Neck Pain

07/14/2004: MTAC REVIEW

Evidence Conclusion: Back Pain There is insufficient evidence to conclude that RF neurotomy improves health outcomes among patients with back pain. Two of the three RCTs on back pain that were reviewed (LeClaire; Barendse) did not find a significant benefit of RF neurotomy compared to a sham intervention in the primary analysis. Barendse may have been underpowered to detect a clinically significant difference between groups. The third study (van Kleef, 1999), which included patients with low back pain originating from the lumber zygapophysial joint, found significantly more clinical successes in the RF neurotomy group. The latter study (n=32), which included a multivariate analysis to adjust for baseline differences, had imprecise estimates with large confidence intervals and only an 8-week follow-up period. All of the studies were limited by small sample sizes. In addition, all of the studies used non-blinded diagnostic blocks and there may have been false positive findings of the location of pain. Long-term safety and efficacy of RF neurotomy for treating back pain was not evaluated.

Evidence Conclusion: Neck pain There is insufficient evidence to conclude that RF neurotomy improves health outcomes among patients with neck pain. One of the two RCTs reviewed (Lord) was well designed but had a biased presentation of study results. The authors did not report their primary outcomes, pain and impact of pain on activities of daily living, at the end of the double-blind follow-up period at 3 months. The results they did report were confounded by rescue treatment. The other RCT (van Kleef, 1996) found a significant benefit of RF neurotomy compared to sham intervention for patients with cervicobrachial pain. The study is limited by its short (8-week) follow-up period and small sample size (n=20), which can result in baseline differences between groups. Also, the van Kleef, 1996 study used non-blinded diagnostic blocks and some patients may have been falsely

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identified with cervicobrachial pain. Long-term safety and efficacy of RF neurotomy for treating neck pain was not evaluated.
Articles: The search yielded 23 articles. There was a Cochrane library review from 2003 that reviewed the randomized controlled trials on the topic but did not conduct a quantitative meta-analysis to evaluate the overall effectiveness of the treatment. Seven double-blind sham-controlled RCTs met the inclusion criteria for the Cochrane review. One additional small RCT published after the Cochrane review was identified in the Medline search, but this study was excluded because the patient population had already failed intradiscal electrothermal annuloplasty (IDET). The Cochrane investigators assigned a methodological quality score to each RCT they included. Studies that received a quality score of at least 7 out of 10 were selected for this review. The Leclaire and Barendse articles were by the same research groups but included different study populations. Back pain: There were four RCTs on the treatment of back pain. One RCT that had a low methodology score in the Cochrane review was not reviewed. The remaining three RCTs were critically appraised: Leclaire R, Fortin L, Lambert R et al. Radiofrequency facet joint denervation in the treatment of low back pain. *Spine* 2001; 26: 1411-1418. See Evidence Table van Kleef M, Barendse GAM, Kessels A et al. Randomized trial of radiofrequency lumbar facet denervation for chronic low back pain. *Spine* 1999; 24: 1937-1942. See Evidence Table Barendse GAM, van den Berg SGM, Kessels AHF et al. Randomized controlled trial of percutaneous intradiscal radiofrequency thermocoagulation for chronic discogenic back pain. *Spine* 2001; 26: 287-292. See Evidence Table Lord SM, Barnsley L, Wallis BJ et al. Percutaneous radio-frequency neurotomy for chronic cervical zygapophyseal-joint pain. *N Engl J Med* 1996; 335: 1721-1726. See Evidence Table

The use of radiofrequency neurotomy in the treatment of chronic neck and back pain does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

07/29/2005: MTAC REVIEW
Back Pain/Neck Pain
Evidence Conclusion: A PubMed search (2004 to present) yielded 6 articles. Four were review articles and one was a study of electrode placement, not effectiveness. There was one new RCT (Stovner et al. Cephalalgia 2004; 24: 821). The study was not worth critically appraising because it only included 12 patients. It did not find a significant benefit of radiofrequency neurotomy vs. sham treatment for next pain, but they almost certainly did not have sufficient statistical power.

This review was not taken to the Medical Technology Assessment Committee. The information was not sufficient to warrant a review by the committee.

Hayes Technology Assessment

Conventional Radiofrequency Ablation for Sacroiliac Joint Denervation for Chronic Low Back Pain
Technology Description
RFA is a percutaneous outpatient procedure involving the use of radiofrequency (RF) energy to heat tissue to the point of destruction. It is intended to prevent transmission of pain signals from the sensory nerves to the central nervous system.

Conclusion
An overall low-quality body of evidence suggests that conventional (i.e., continuous, thermal) RFA for SIJ denervation is safe and may be effective for reducing the intensity of CLBP arising from the SIJ. However, substantial uncertainty exists regarding its effect on function and QOL as well as its effectiveness compared with most treatment alternatives.

Hayes Rating: C—For the use of conventional (thermal) radiofrequency ablation (RFA) for sacroiliac join (SIJ) denervation in adults with chronic low back pain (CLBP) originating from this joint who have not responded to conventional treatment.

Hayes. Hayes Technology Assessment. Conventional Radiofrequency Ablation for Sacroiliac Joint Denervation for Chronic Low Back Pain. Dallas, TX: Hayes; December 06, 2022. Retrieved October 16, 2023 from: https://evidence.hayesinc.com/report/dir.radiofrequency2116

Applicable Codes

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Medicare and Non-Medicare: Considered Medically Necessary when criteria in the applicable policy statements listed above are met

†*Non Medicare: Thoracic Spine Neurotomy is not covered*

CPT® or HCPC Codes	Description
64633†	Destruction by neurolytic agent, paravertebral facet joint nerve(s), with imaging guidance (fluoroscopy or CT); cervical or thoracic, single facet joint
64634†	Destruction by neurolytic agent, paravertebral facet joint nerve(s), with imaging guidance (fluoroscopy or CT); cervical or thoracic, each additional facet joint (List separately in addition to code for primary procedure)
64635	Destruction by neurolytic agent, paravertebral facet joint nerve(s), with imaging guidance (fluoroscopy or CT); lumbar or sacral, single facet joint
64636	Destruction by neurolytic agent, paravertebral facet joint nerve(s), with imaging guidance (fluoroscopy or CT); lumbar or sacral, each additional facet joint (List separately in addition to code for primary procedure)

Medicare: Considered Not Medically Necessary
Non-Medicare: Considered Medically Necessary when the criteria in the applicable policy statements listed above are met

CPT® or HCPC Codes	Description
64625	Radiofrequency ablation, nerves innervating the sacroiliac joint, with image guidance (ie, fluoroscopy or computed tomography)

Medicare: Considered Not Medically Necessary
Non-Medicare: Considered Not Medically Necessary - experimental, investigational, or unproven

CPT® or HCPCS Codes	Description
0213T	Injection(s), diagnostic or therapeutic agent, paravertebral facet (zygapophyseal) joint (or nerves innervating that joint) with ultrasound guidance, cervical or thoracic; single level
0214T	Injection(s), diagnostic or therapeutic agent, paravertebral facet (zygapophyseal) joint (or nerves innervating that joint) with ultrasound guidance, cervical or thoracic; second level (List separately in addition to code for primary procedure)
0215T	Injection(s), diagnostic or therapeutic agent, paravertebral facet (zygapophyseal) joint (or nerves innervating that joint) with ultrasound guidance, cervical or thoracic; third and any additional level(s) (List separately in addition to code for primary procedure)
0216T	Injection(s), diagnostic or therapeutic agent, paravertebral facet (zygapophyseal) joint (or nerves innervating that joint) with ultrasound guidance, lumbar or sacral; single level
0217T	Injection(s), diagnostic or therapeutic agent, paravertebral facet (zygapophyseal) joint (or nerves innervating that joint) with ultrasound guidance, lumbar or sacral; second level (List separately in addition to code for primary procedure)
0218T	Injection(s), diagnostic or therapeutic agent, paravertebral facet (zygapophyseal) joint (or nerves innervating that joint) with ultrasound guidance, lumbar or sacral; third and any additional level(s) (List separately in addition to code for primary procedure)

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check.**

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07/14/2004	01/05/2010[MDCRPC], 05/04/2010[MDCRPC], 03/01/2011[MDCRPC], 01/03/2012[MDCRPC], 11/06/2012[MDCRPC] ,09/03/2013[MPC], 07/01/2014[MPC], 05/05/2015[MPC], 03/01/2016[MPC], 01/03/2017[MPC], 11/07/2017[MPC] , 10/02/2018[MPC] , 10/01/2019[MPC], 10/06/2020[MPC], 10/05/2021[MPC],10/06/2022[MPC] , 10/03/2023[MPC]	04/27/2023

[MDCRPC] Medical Director Clinical Review and Policy Committee

[MPC] Medical Policy Committee

Revision History	Description
09/08/2015	Revised LCD for Facet Joint Injections, Medial Branch Blocks, and Facet Joint Radiofrequency Neurotomy to L35178 and L34995
12/08/2016	Deleted LCD 35178 as it was retired, and LCD 34995 replaces it
07/11/2017	MPC approved criteria for repeat facet neurotomy
04/06/2021	MPC approved to adopt changes to facet neurotomy hybrid criteria. Requires 60-day notice, effective date September 1, 2021.
04/27/2021	Removed retired LCD L34995 and LCA A57728; Added replacement LCD L33803 and LCA A58405
10/04/2022	Revised criteria to clarify Facet Neurotomy for thoracic spine is not covered.
10/12/2022	Updated LCA A58405 link. Updated applicable codes.
03/06/2023	Update applicable codes.
03/07/2023	MPC approved to adopt changes to facet neurotomy hybrid criteria. Requires 60-day notice, effective date 08/01/2023.
04/27/2023	Added SI Ablation criteria from previously approved SIJ fusion from March 2023 MPC. Added Medicare non-coverage LCD for RFA ablation of SIJ.
10/16/2023	Added Billing and Coding article A59246 link

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Clinical Review Criteria
Radiopharmaceuticals

- Dotatate (Lutathera) – used for neuroendocrine tumors
- Vipivotide Tetraxetan (Pluvicto™, formerly 177Lu-PSMA) – used for metastatic prostate cancer

NOTICE: Kaiser Foundation Health Plan of Washington and Kaiser Foundation Health Plan of Washington Options, Inc. (Kaiser Permanente) provide these Clinical Review Criteria for internal use by their members and health care providers. The Clinical Review Criteria only apply to Kaiser Foundation Health Plan of Washington and Kaiser Foundation Health Plan of Washington Options, Inc. Use of the Clinical Review Criteria or any Kaiser Permanente entity name, logo, trade name, trademark, or service mark for marketing or publicity purposes, including on any website, or in any press release or promotional material, is strictly prohibited.

Kaiser Permanente Clinical Review Criteria are developed to assist in administering plan benefits. These criteria neither offer medical advice nor guarantee coverage. Kaiser Permanente reserves the exclusive right to modify, revoke, suspend or change any or all of these Clinical Review Criteria, at Kaiser Permanente's sole discretion, at any time, with or without notice. **Member contracts differ in health plan benefits. Always consult the patient's Evidence of Coverage or call Kaiser Permanente Member Services at 1-888-901-4636 (TTY 711), Monday through Friday, 8 a.m. to 5 p.m. to determine coverage for a specific medical service.**

Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article	None
Kaiser Permanente Medical Policy	Due to the absence of an active NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Clinical Review Criteria, "***Vipivotide Tetraxetan (Pluvicto™, formerly 177Lu-PSMA)" and "Dotatate (Lutathera") ,*** for medical necessity determinations. Use the Non-Medicare criteria below.

For Non-Medicare Members

Service	Criteria
Dotatate (Lutathera)	**Candidates must meet ALL of the following:** 1. Presence of metastasized or locally advanced, unresectable (with curative intent) gastroenteropancreatic neuroendocrine tumors (GEP-NET) **and** 2. Ki-67 protein ≤ 20% (patients with higher-grade disease need to be evaluated on case-by-case basis) **and** 3. Progressive disease under somatostatin analog therapy (SSA) **and** 4. At least 18 years of age **and** 5. Target lesions overexpressing somatostatin receptors as demonstrated on ^{68}Ga-DOTATATE PET/CT scan within last 3 months **and** 6. Monitoring labs must be conducted within the first 4 weeks of injection (baseline); 4-6 weeks after each Lutathera injection and 2 days prior to subsequent Lutathera injections **Contraindications:** 1. Women who are or may be pregnant, as this agent can cause fetal harm when administered to a pregnant woman (pregnancy category X) **or** 2. Women who are breast feeding **or** 3. Pediatric patients (<18 years of age)

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	4. Lutathera Therapy is not covered when: 5. Recent surgery, radioembolization, chemoembolization, radiofrequency ablation or chemotherapy within 4 weeks prior to initiation of Lutathera treatment. 6. Known brain metastases unless these metastases have been treated and stabilized. 7. Uncontrolled congestive heart failure (NYHA II, III, IV) 8. Treatment with *short-acting* somatostatin analog therapy (SSA) that cannot be interrupted for 24 hours before Lutathera administration, or treatment with *long-acting* (LAR) somatostatin analog therapy SSA that cannot be interrupted for at least 4 weeks before initiation of Lutathera a. Patient may go on short acting somatostatin analog therapy (SSA) as a bridge between LAR injection and Lutathera treatment, but this must be stopped 24 hrs. before Lutathera treatment. 9. Prior external beam radiation therapy to >25% of the bone marrow. 10. Current spontaneous urinary incontinence making it unsafe to administer Lutathera Please click here to view clinical criteria for PET Scan: Gastroenteropancreatic Neuroendocrine Tumors (GEP-NET)
Vipivotide Tetraxetan (Pluvicto™, *formerly* 177Lu-PSMA)	**Effective until June 1, 2023** Send all cases to MD for review **Effective June 1, 2023** Lutetium Lu 177 Vipivotide Tetraxetan (Pluvicto™, formerly 177Lu-PSMA) given every 6 weeks for 4-6 cycles is considered medically necessary for individuals with progressive metastatic castration-resistant prostate cancer who meet **ALL of the following** conditions: 1. Patient must be age 18 or older 2. Must be prescribed by Medical Oncology 3. Must have baseline CT/bone scan within the prior 2 months of chest/abdomen/pelvis with at least one visible lesion 4. Have been treated with 1 or more androgen-receptor pathway inhibitors (ie, enzalutamide and/or abiraterone) 5. Previously received at least 1 taxane-based chemotherapy regimens (docetaxel, cabazitaxel) for metastatic castration-resistant prostate cancer, for at least 2 cycles 6. Must have PSMA-positive mCRPC defined as having at least one tumor lesion with uptake greater than normal liver within the past 3 months 7. Does NOT have any PSMA-negative (defined as FDA approved PSMA tracer uptake less than or equal to uptake in normal liver) prostate cancer lesions exceeding the below size criteria: a. Visceral metastases ≥1cm b. Lymph node metastases ≥2.5cm c. Bone metastases ≥1cm 8. At least 30 days out from starting bisphosphonate or denosumab (if applicable) 9. No radium-223 within last 6 months 10. No chemotherapy, immunotherapy, or biologics within 28

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	days of treatment 11. No impending cord compression 12. Prior CNS metastases okay if stable; must not be on steroids for treatment of CNS metastases, OK if has received prior treatment for metastases (e.g., radiation, surgery), and must be neurologically intact 13. No NYHA 3-4 heart failure, active hep B/C, uncontrolled infection 14. Birth control if partner has child-bearing potential 15. Meets **ALL** of the following Diagnosis/Drug specific criteria below: a. WBC at least 2.5K/uL and/or ANC at least 1.5 K/uL b. Hgb > 9mg/dL (no transfusion within 30 days) c. Platelets > 100 K/uL d. T.bili < 1.5x ULN (3x for Gilbert's) e. AST/ALT < 3x ULN (5x if liver metastases) f. Serum creatinine < 1.5x ULN and creatinine clearance > 50 mL/min (using Cockcroft-Gault equation with actual body weight) g. Albumin > 3.0g/L h. ECOG* PS 0-2 (consider patients with PS2 very carefully; only 7% of patients on VISION had a PS of 2 so these patients were not well represented in the trial) If initial criteria are met, approve x4 doses. If initial criteria are not met, do not approve. **RENEWAL CRITERIA**: Must meet **ALL of the following**: *(Describe specific criteria that would warrant continuation of the drug)* 1. Patient has tolerated medication 2. Patient has shown evidence of response, defined as one of the following: a. PSA response b. Radiologic response c. Clinical benefit per treating physician If renewal criteria are met, approve x2 doses. If renewal criteria are not met, do not approve. **Pluvicto™ treatment greater than a total of 6 doses as per the Food and Drug Administration-approved regimen is considered investigational.**

Please click here to view clinical criteria for PET Scan: Gastroenteropancreatic Neuroendocrine Tumors (GEP-NET)

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Background

Neuroendocrine Tumors

Gastroenteropancreatic neuroendocrine tumors are rare. It is estimated that approximately one out of 27,000 people are diagnosed with gastroenteropancreatic neuroendocrine tumors (GEP-NETs) per year (Voelker, 2018). However, their incidence has increased in the last thirty years (Cives & Strosberg, 2018). Neuroendocrine tumors of the midgut represent the most common malignant gastrointestinal neuroendocrine tumors. Overall survival rate

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is less than 50% especially in patients with metastatic disease (Modlin, Lye, & Kidd, 2003; Yao et al., 2008). Initial therapy includes somatostatin analogue (Caplin, Pavel, & Ruszniewski, 2014). However, there exists a lack of second-line treatment for neuroendocrine tumors (except for everolimus for nonfunctional neuroendocrine tumors (Yao et al., 2016)) if first-line treatment fails. Radiolabeled somatostatin analogue, Lutetium-177, has been the center of attention and it may be promising for the management of advanced neuroendocrine tumors (NETs).

Lutathera or Lutetium Lu 177 dotatate is a radioactive targeted therapy. The medication binds to somatostatin receptors which are present on certain tumors. Once Lutathera binds to the receptor, it enters the cell and uses radiation to cause damage. However, it does not impact normal cells. Lutathera delivers beta- and gamma radionuclides to cancerous cells with a maximum particle range of 2 mm and a half-life of 160 hours (van der Zwan et al., 2015). It is administered as four infusions separated by eight weeks interval.

On January 29, 2018, the Food and Drug Administration approved lutetium Lu 177 dotatate (LUTATHERA, Advanced Accelerator Applications USA, Inc.) a radiolabeled somatostatin analog, for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults.

Prostate Cancer
Source: Verbatim from Juzeniene A, Stenberg VY, Bruland ØS, Larsen RH. Preclinical and Clinical Status of PSMA-Targeted Alpha Therapy for Metastatic Castration-Resistant Prostate Cancer. Cancers (Basel). 2021 Feb 13;13(4):779. doi: 10.3390/cancers13040779. PMID: 33668474; PMCID: PMC7918517.)
“Prostate cancer is the second most common cancer in men worldwide, with an estimated 1.3 million new cases and 359,000 deaths in 2018 [1]. The tumors of 10–20% of prostate cancer patients become refractory to androgen deprivation therapy and progress as metastatic castration-resistant prostate cancer (mCRPC) [2,3]. Bone metastases dominate, but lymph node and visceral metastases are also frequent in mCRPC patients [4–6].”

Medical Technology Assessment Committee (MTAC)

Lutetium Lu 177 Dotatate (Lutathera) for Somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs)
01/14/2019: MTAC Review
Evidence Conclusion:

- There is limited evidence comparing Lu-Dotatate and octreotide
  - Based on one RCT with moderate risk of bias, Lu-Dotatate may be more effective than octreotide LAR in adult population with predominantly low grade, higher level of expression of somatostatin receptors gastroenteropancreatic NETs who failed initial therapy.
  - However, Octreotide results in lower adverse events than Lu-Dotatate.
- In non-comparative studies, low evidence suggests that Lu-Dotatate may be effective and safe in patients with advanced gastroenteropancreatic neuroendocrine tumors.

Articles: PubMed was searched through October 19, 2018. Search terms include ((Lutathera OR lutetium Lu 177 dotatate OR lutetium 177 dotatate OR Lu-177 OR 177Lu-DOTATATE)) AND (Neuroendocrine tumors OR pancreatic neuroendocrine tumors OR gastrointestinal neuroendocrine tumors). The search was limited to English language publications and human populations. The reference lists of relevant studies were reviewed to identify additional publications. Several articles were identified but only one RCT (NETTER-1 trial) met the inclusion criteria. Clinicaltrial.gov was also searched on October 11, 2018 and identified several ongoing studies with no available results. See Evidence Table**.**

The use of Lutetium Lu 177 Dotatate (Lutathera) for Somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) does meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Prostate-Specific Membrane Antigen Radioligand Therapy for the Treatment of Metastatic Castration-Resistant Prostate Cancer
07/14/2022: Medical Technology Assessment Team (MTAT)
Evidence Conclusion:
177-Lu PRLT
Overall Conclusion(s)
Efficacy

- Overall, moderate-certainty evidence from 3 RCTs with a total of 821 mCRPC patients, with

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disease progression after various therapies including androgen-receptor pathway inhibitors, taxane chemotherapy, and palliative radiotherapy, demonstrates that 177-Lu PRLT had a statistically significant decrease in PSA levels, increase in response rates (i.e., objective or overall response, disease control rate), prolonged OS and/or PFS, and/or improvement in quality of life outcomes compared to cabazitaxel, standard care, or docetaxel. An additional 2 RCTs (71 patients) investigated 177-Lu PRLT dosing and reported inconsistent data for PSA decline and disease control rates. The overall certainty in the RCT evidence was downgraded to reflect inconsistency, indirectness, imprecision, as well as risk of bias. With respect to the quality of individual studies, risk of bias is moderate due to heterogeneity in patient populations and/or treatment protocols, lack of masking, as well as loss to follow-up in control groups. Industry sponsorship of studies was also common, although this funding source is common in cancerrelated drug trials. There is moderate confidence that the reported effect estimate is likely to be close to the true effect, but there is a possibility that it is substantially different. Additional RCTs with large sample sizes, consistent patient selection and treatment regimen, would contribute to the overall certainty in evidence.

- In addition to the RCTs, there were 95 observational studies (3 retrospective comparative, 22 prospective non-comparative, 70 retrospective non-comparative) with 5,291 mCRPC patients demonstrating that, after treatment with 177-Lu PRLT, 55.5% to 84.7% patients experienced PSA decline, 0% to 73% had partial response, 8.4% to 46% had stable disease, 4% to 46% had progressive disease, with OS ranging from median 6 to 18 months and PFS ranging from median 3.8 to 11 months. The evidence from the observational studies is rated with lowcertainty given the retrospective and/or non-comparative study design in the majority of the included studies and the inherent biases associated with this design, as well as small sample sizes.

Safety

- Overall, low-certainty evidence from 5 RCTs with 1,142 mCRPC patients reported mortality rates ranging from 0% to 87% (5 RCTs; 1,142 patients) and serious (grade ≥3) anemia, bone marrow suppression, pain, and thrombocytopenia AEs occurring in greater than 10% of patients (4 RCTs; 985 patients). One RCT with 40 patients reported no statistically significant difference in treatment-emergent grade 3-to-5 AEs (30% vs 50%) among 177-Lu PRLT and docetaxel treated patients. The evidence certainty was downgraded for heterogeneity in patient populations and treatment protocols, lack of masking, and loss to follow-up in control groups. Furthermore, the lack of analyses in 4 out of the 5 RCTs, to determine the statistical significance of the between-group difference in mortality and/or AEs, warranted further downgrading of the evidence to low-certainty.
- In addition to the RCTs, there were 44 observational studies (2 retrospective comparative, 16 prospective non-comparative, 26 retrospective non-comparative) with 2,244 mCRPC patients reporting additional AEs including: increases in aspartate aminotransferase and alanine transaminase; chronic kidney disease (grade 1 to 2); hemoglobin toxicity; and renal toxicity (grade 1). The evidence from the observational studies was rated with low certainty given the majority of included studies had small sample sizes and used a retrospective and/or noncomparative study design.

225-Actinium (Ac) PRLT

Evidence Summary and Overall Conclusion(s)

- There is very-low-certainty evidence from 1 retrospective, non-comparative study with 40 mCRPC patients demonstrating 225-Ac PRLT decreased PSA levels, had an OS greater than 12 months, radiologic PFS of 6 months, and resulted in xerostomia and/or loss of taste events. There is very-low confidence that the reported effect estimate reflects the true effect due to the small, retrospective, non-comparative design from the single study that also lacked well-defined inclusion/exclusion criteria, long-term follow-up, and comparative evidence.

131-Iodine (I)-MIP-1095 PRLT

Evidence Summary and Overall Conclusion(s)

- There is very-low-certainty evidence from 1 retrospective non-comparative study with 34 mCRPC patients demonstrating 131-I-MIP-1095 PRLT decreased PSA levels, had a median time to PSA progression of 75 days, median OS of 17 months, with patients experiencing fatigue, leukopenia, thrombopenia, and xerostomia events. There is very-low confidence that the reported effect estimate reflects the true effect due to the small, retrospective, non-comparative design from the single study that also lacked well-defined inclusion/exclusion criteria, long-term follow-up, and comparative evidence.

References

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Date Sent: 3/29/24
These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage.
Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

Abramaowitz, M., Li, T., Buyyounouski, M., Ross, E, Uzzo, R., Pollack, A. & Horwitz, E. (2007). The Phoenix definition of biochemical failure predicts for overall survival in patients with prostate cancer. *American Cancer Society, 112*(1), 55-60. Retrieved from Pubmed Database.

National Comprehensive Cancer Network (NCCN). 2022. *Prostate Cancer (Version 1.2023)*. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
A9513	Lutetium Lu 177, dotatate, therapeutic, 1 mCi
A9607	Lutetium Lu 177 vipivotide tetraxetan, therapeutic, 1 mCi

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
01/06/2023	01/10/2023[MPC]	1/23/2023

[MPC] Medical Policy Committee

Revision History	Description
1/10/2023	MPC approved coverage criteria for Pluvicto (Luteteium Lu 177 vipivotide tetraxetan) for Prostate Cancer. Requires 60-day notice; Effective June 01, 2023.
1/23/2023	Merged Lutetium Lu 177, dotatate (Lutathera) criteria to this Radiopharmaceuticals page with Lutetium Lu 177 vipivotide tetraxetan (Pluvicto). Archiving Lutathera criteria page.

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KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Breast Reduction (Mammaplasty) Surgery

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	Medicare Benefit Policy Manual Chapter 16 120 Cosmetic Surgery.
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	Plastic Surgery (L37020)
Local Coverage Article	Billing and Coding: Plastic Surgery (A57222)

For Non-Medicare Members

Kaiser Permanente has elected to use the Reduction Mammaplasty (Mammoplasty) (KP-0274 v2) MCG* for medical necessity determinations. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.

***The MCG are proprietary and cannot be published and/or distributed.** However, on an individual member basis, Kaiser Permanente can share a copy of the specific criteria document used to make a utilization management decision. If one of your patients is being reviewed using these criteria, you may request a copy of the criteria by calling the Kaiser Permanente Clinical Review staff at 1-800-289-1363 or access the MCG Guideline Index using the link provided above.

If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist (primary care physician)
- Physical Therapy notes if applicable
- Plastic surgery consultation
- Most recent height & weight

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Background

Reduction mammoplasty surgery is a covered benefit under Kaiser Permanente benefit packages when it is determined to be for medical rather than cosmetic reasons. This benefit was added by Kaiser Permanente on 11/1/83. Over the years several modifications have been made to the criteria. The main purpose of the criteria is to differentiate cosmetic from medical indications for the procedure.

Evidence and Source Documents

10/2012

Baasch M, Nielsen SF, Engholm G, Lund K Breast cancer incidence subsequent to surgical reduction of female breast. Br J Cancer April 1990; 73 (7): 961-961 1240 patients w surgical intervention for breast hypertrophy.

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Followed between 1943 and 1971. 32 cases of cancer identified by 1990. Expected number was 52.55 yielding a relative risk factor (RR) of 0.61. The greatest reduction was seen in women who had 600 or more grams or more of breast tissue. In the group who had the operation before the age of 20, 4 cases of breast cancer developed, compared to the expected 2.23, to give an RR of 1.79.
Dabbah A, Lehman J, Parker M, Tantri D, Wagner D Reduction Mammoplasty: An outcome analysis. Ann of P Surg October 1995; 35(4): 337-341
Survey of 285 consecutive female patients who had reduction mammoplasty between 1988 - 1993. Also, Chart reviews were conducted. Mean age was 40 and average follow-up was 37 months. 185 returned completed surveys and were included in the analysis. The most common complaints were: shoulder grooving (90%), back pain (82%), shoulder pain (78%), and neck pain (65%). The average amount of breast tissue removed was 855 gm from each breast (range 148 - 3,717 gm total). Most patients (97%) had improvement of symptoms. No statistically significant difference between obese and non-obese patients in outcomes or symptom relief and put into question the use of weight guidelines or bra-cup size reduction validation. The amount of breast tissue removed did not alter the outcome of surgery or relief of symptoms. The amount of breast tissue removed to relieve symptoms will vary with height, weight and bra-cup size for each patient. This puts into question the requirement of a maximum amount of breast tissue to be removed. Increase in complications when greater than 1,000 gm was removed from each breast. Overall patient satisfaction was high (95%, happy or very happy).
McMahan JD, Wolfe JA, Cromer BA, Ruberg RL. Lasting success in teenage reduction mammoplasty. Ann of P Surg September 1995; 35(3): 227-231 86 female patients less than 20 years of age. 48 contacted and returned questionnaire. Primary questions were: does the breast tissue grow back, what are the effects of future pregnancies and weight gain and do the potential consequences of surgery overshadow the early pain relief. Patient age range:15 - 19.9. Average range of follow-up was 5.9 yr (range 1.4-20.4). 72% reported regrowth of tissue. 11 patients had been pregnant since their surgery: 5 did not breast feed, 3 were unable to and 2 were still pregnant. The greatest improvements were seen in their presurgical symptoms, ability to increase their physical activity, and improvement in their self -esteem. None seemed to have problems with sexual pleasure from their breasts. Davis GM, Ringler SL, Short K, Sherrick d, Bengtson BP. Reduction Mammoplasty: Long-term efficacy, morbidity and patient satisfaction Plast Recon Surg 96: 1106-1110 780 female patients who had reduction mammoplasties between 1981 and 1992. 406 responded to a retrospective questionnaire. The mean age was 38yr. Follow-up average 4.7 yr. 60% of the study population was 5-10 kg over their ideal body weight as determined by the Metropolitan Life Insurance Company Statistical Bulletin (1985). Average reduction was 676 gram per breast (range 120-4200 gm). Conclusion was that women found that their preoperative symptoms were corrected by the surgery. Major complications are uncommon. Minor complications (50% of the women) are tolerated by the women. Thirty-seven women became pregnant following their operation. Of this population 68 % (25) successfully breast-fed their infants. Patients who lost nipple sensitivity were most likely to be dissatisfied with the procedure. Seitchik MW. Reduction Mammoplasty: Criteria for insurance coverage. Plast Recon Surg May 1995: 1029-1032The guidelines by which insurer determine eligibility for coverage of reduction mammoplasty must rely largely on subjective materials: reported patient symptoms, interpretation of photographs, determination of the amount of breast mass to be removed surgically. The author has attempted to find relationships between body weight and resected specimen weight that may be more objective.
100 consecutive reduction mammoplasties beginning 1991 recorded pre-op weight and height. The weight of resected breast tissue was obtained in the OR. Reduction planned for 46 to 70 kg body weight bra size of mid-B to small C. Above 70kg sizes ranged to a small D. Follow-up questionnaire 6 months postoperative. Based on his analysis he was unable to develop a model which would accurately predict preoperatively the amount of breast mass required to be removed to achieve the target bra size. He also felt that insurance company excise breast weight to determine eligibility for coverage was arbitrary.

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® Codes	Description
19318	Breast reduction

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
09/26/1996	04/06/2010[MDCRPC], 02/10/2011[MDCRPC], 12/06/2011[MDCRPC], 02/7/2012[MDCRPC], 12/04/2012[MDCRPC], 10/01/2013[MPC], 07/01/2014[MPC], 05/05/2015[MPC], 03/01/2016[MPC], 11/07/2017[MPC], 09/04/2018[MPC], 09/03/2019[MPC], 09/01/2020[MPC], 09/07/2021[MPC], 09/06/2022[MPC], 09/05/2023[MPC]	07/07//2020

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
09/08/2015	Revised LCD Local Coverage Determination (LCD): Non-Covered Services L34886 and L35008
12/19/2017	Added LCD L37020
04/07/2020	MPC approved to adopt updates to the clinical indications for Non-Medicare (KP-0274 MCG*): •**Added under 'Age 18* or greater'**: Younger patients can be approved on a case by case basis, with documentation from the surgeon as to the patient's appropriateness, including confirmation of full physical maturity and full understanding by the patient and her guardians as to the full nature of the surgery
07/07/2020	MPC approved to adopt updates to the clinical indications for Non-Medicare (KP-0274 MCG*-see KP-0274 v2 eff 12/01/2020), including specificity for BMI parameters and the minimum amount of breast tissue to be removed. Added requirements for preoperative mammogram and smoking cessation for at least 30 days pre-op. Requires 60-day notice, effective date 12/01/2020.

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Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Renal Sympathetic Nerve Ablation

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article (LCA)	None
Kaiser Permanente Medical Policy	Due to the absence of an active NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Clinical Review Criteria, "***Renal Sympathetic Nerve Ablation***" for medical necessity determinations. Use the Non-Medicare criteria below.

For Non-Medicare Members

Effective until August 1st, 2024

Kaiser Permanente has elected to use the Renal Sympathetic Nerve Ablation, Radiofrequency (A-1034) MCG* guideline for medical necessity determinations. This service is not covered per MCG* guidelines. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.

Effective August 1st, 2024

Renal Sympathetic Nerve Ablation will be reviewed using the Medically Necessary Services medical policy

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If requesting review for this service, please send the following documentation:

- Last 6 months of clinical notes from requesting provider &/or specialist

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Background

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Renal sympathetic nerve ablation involves introduction of a catheter into the renal artery, with subsequent ablation of the sympathetic nerves of the artery and its branch vessels via use of a radiofrequency generator. Angiography is used to direct the procedure. Ablation of the sympathetic nerves is intended to reduce overall sympathetic drive and therefore improve blood pressure, especially in patients with resistant hypertension.

Applicable Codes

Considered Not Medically Necessary:

CPT® or HCPC Codes	Description
0338T	Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery(ies), fluoroscopy, contrast injection(s), intraprocedural roadmapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; unilateral
0339T	Transcatheter renal sympathetic denervation, percutaneous approach including arterial puncture, selective catheter placement(s) renal artery(ies), fluoroscopy, contrast injection(s), intraprocedural roadmapping and radiological supervision and interpretation, including pressure gradient measurements, flush aortogram and diagnostic renal angiography when performed; bilateral

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
05/01/2021	05/04/2021[MPC], 05/03/2022[MPC], 05/02/2023[MPC], 03/12/2024[MPC]	03/12/2024

[MPC] Medical Policy Committee

Revision History	Description
05/04/2021	MPC approved to adopt MCG A-1034 for Renal Sympathetic Nerve ablation. Requires 60-day notice, effective October 1, 2021.
03/12/2024	MPC approved to archive criteria & move to Medically Necessary Services effective August 1st, 2024. Requires 60-day notice.

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Clinical Review Criteria

Transcranial Magnetic Stimulation (TMS) for Treatment-Resistant Depression

- Medical Diagnoses
- Migraine Headaches
- Treatment Resistant Depression

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	Transcranial Magnetic Stimulation (TMS) (L37088)
Local Coverage Article (LCA)	Billing and Coding: Transcranial Magnetic Stimulation (TMS) (A57693)

For Non-Medicare Members

Service	Criteria Used
TMS	
Behavioral Health (treatment resistant depression)	**Effective until August 1, 2024** MCG* B-KP-801-T For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access. **Effective August 1, 2024** MCG* B-KP-801-T 08012024 For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.
Other diagnoses	Requires Medical Director Review

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Background

Repetitive Transcranial Magnetic Stimulation (rTMS)

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Major depressive disorder is a common health condition, and is associated with substantial morbidity, mortality and health care costs. No single approach is uniformly effective at treating depression. Antidepressant treatment with SSRIs is currently a common first step. Approximately, two-thirds of patients respond to an initial course of antidepressants (O'Reardon et al., 2000). One alternative for non-responders is to switch to a different antidepressant, in the same or another class of medications. Findings from a recent RCT indicate that approximately 1 in 4 individuals who failed an initial course of SSRIs respond to a second one (Rush et al., 2006). Adding psychotherapy is another option for non-responders.

Interest in alternative treatment options, such as transcranial magnetic stimulation (TMS), has grown in recent years. TMS is a non-invasive method of modulating the brain's electrical environment by using magnetic fields. The technique involves applying alternating electrical currents through an insulated coil on the scalp which, ultimately, produces an electrical field in the brain, which in turn induces depolarization of nerve cells and results in the stimulation or disruption of brain activity. Changes in brain activity with TMS can be detected through various imaging techniques (PET, SPECT, or MRI). TMS can be delivered in either individual or repetitive pulses (the latter known as rTMS). Most studies of TMS for depression use repetitive pulses and target the left dorsal lateral prefrontal cortex (DLPFC). Reported side-effects of TMS are generally mild including headache, local discomfort, and transient change in auditory threshold, which can be prevented by the use of earplugs. Instances of mania and epileptic seizure, however, have been known to occur (Fitzgerald and Daskalakis 2008; George 2010; Shelton, Osuntokun et al. 2010; Slotema, Blom et al. 2010).

Several TMS devices, including the NeuroStar TMS system (Neuronetics, Atlanta, GA) and the Brainsway Deep TMS system (Brainsway Ltd., Jerusalem, Israel), have received 510(k) clearances by the United States Food and Drug Administration (FDA). The devices are indicated for the treatment of major depressive disorder (MDD) in adult patients who have failed one prior antidepressant medication at or above the minimal effective dose and duration. The medical technology and assessment committee (MTAC) previously reviewed TMS technology in 2009, and subsequently in 2011. In each case, the evidence failed to satisfy MTAC criteria due to inappropriate comparators and lack of established long-term efficacy.

Deep Transcranial Magnetic Stimulation (dTMS).

dTMS is a further development of the conventional rTMS. It uses a novel electromagnetic coil "the Hesel-coil or H-coil" which has a unique configuration designed to activate the brain tissue at a greater depth. the H-coil, comes in different variations and features, and unlike the conventional 8-figure coil, the H-coils that deliver the magnetic pulses are placed in a hood that is fitted to the head of the patient during treatment. The H-coils generate magnetic pulses that can penetrate 3-6 cm beneath the skull to stimulate deeper regions and neural pathways of the brain and produce antidepressant effects of greater magnitude compared to conventional rTMS. Each dTMS session includes a series of 2-second stimulations with a frequency of 18-20 Hz followed by a 20-second pause. One treatment session is thus equivalent to 40-55 stimulations, with a total of approximately 1700-2000 magnetic pulses delivered in 15-20 minutes. The acute treatment is administered 5 days a week for 4-5 weeks and is usually followed by maintenance phase in which treatment is delivered less often for up to 12 weeks (Roth 2007, Levkovitz 2015, Kedzoir 2016, Nordenskjold 2016).

Reported side effects include scalp discomfort, transient headache and dizziness, insomnia, perceiving an odd smell, numbness in the right cervical zone, and very rarely convulsions. The TMS machine produces loud snapping noises during stimulation and the patients are given earplugs for protection against hearing damage. However, some patients may still complain of hearing problems immediately following treatment (Bewernick 2015, Nordenskjold 2016).

An absolute contraindication to the use of any TMS is the presence of metallic or ferromagnetic objects in the head or eye, cochlear implants, implanted pacemakers, or other implants. Relative contraindications include history of previous epilepsy, skull trauma, cerebral damage of any etiology, severe headache or migraine, hearing loss, substance abuse, pregnancy, severe or recent heart disease, and systemic disease (Nordenskjold 2016, Valero Cabre 2017).

In 2013, the Brainsway Deep TMS system (Brainsway Ltd., (Har Hotzvim. Jerusalem, Israel), have received 510(k) clearances by the United States Food and Drug Administration (FDA) for the treatment of depressive episodes in adult patients suffering from Major Depressive Disorder who failed to achieve satisfactory improvement from previous anti-depressant medication treatment in the current episode. The Brainsway dTMS system is composed of an electromagnetic coil (H1 Coil), TMS neurostimulator, cooling system, a positioning device, and a cart.

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Medical Technology Assessment Committee (MTAC)

Repetitive transcranial magnetic stimulation (rTMS)

06/01/2009: MTAC REVIEW

Evidence Conclusion: Active rTMS vs. sham treatment for treatment-resistant depression

Efficacy: There is insufficient evidence on the long-term efficacy of rTMS for treatment-resistant depression. In the RCTs, patients were generally evaluated at the end of the treatment period, 4 weeks or less. A pooled analysis of the 4 studies that followed patients for an additional 1-2 weeks also found a significantly higher response rate with rTMS vs. sham treatment. There is sufficient evidence from a meta-analysis of 21 RCTs (Lam et al., 2008) that there is a higher short-term clinical response rate with rTMS compared to sham treatment (NNT=6). *Safety:* In the Lam meta-analysis, there was a low rate of withdrawals due to adverse effects overall, 2% of patients in the active rTMS group and 1.5% in the sham group. Janicak et al. (2008), in a study funded by Neuronetics, compiled safety data from one sham-controlled RCT and two unpublished open-label studies and found few treatment-related adverse effects. No deaths or seizures were reported among the 218 patients receiving active treatment A total of 41 serious adverse events were reported. 36 of the 41 were assessed by study investigators as unrelated to the study device. The 5 related events included 3 related to a manufacturing defect in a component of the study device, 1 was left-sided facial numbness and the fifth, deemed probably related, was not specified.

rTMS vs. other established treatment for treatment-resistant depression: There is insufficient evidence to draw conclusions about the safety and efficacy of rTMS for treatment-resistant depression compared to electroconvulsive therapy. One RCT comparing rTMS to ECT in this population was identified (Rosa et al., 2006). The study did not find a significant difference in the rate of clinical remission with rTMS compared to ECT. There were a relatively small number of patients enrolled, a relatively high drop-out rate and no analysis of statistical power, so conclusions cannot be made about equivalence of the treatments. There is insufficient evidence to draw conclusions about the safety and efficacy of rTMS for treatment-resistant depression compared to additional trials of antidepressants. No trials were identified comparing monotherapy with rTMS or antidepressants in this population. One RCT compared the combination of rTMS and escitalopram to escitalopram (plus sham rTMS) (Bretlau et al., 2008). The study, which included patients who failed at least one previous trial of antidepressants, used the difference in depression scores as the primary outcome, rather than the more clinically significant outcomes, clinical response or remission. With an appropriate statistical analysis, adjusting for multiple comparisons, there was a significant benefit of the combined active treatment group at the end of the three-week rTMS period, but no difference after an additional 9 weeks of medication treatment.

Articles: Active rTMS vs. sham treatment for treatment-resistant depression

The Pubmed searched yielded three meta-analyses of RCTs comparing rTMS for major depression to sham treatment. Only one of the three meta-analyses (Lam et al., 2008) focused on treatment-resistant depression, the FDA-approved indication and was critically appraised. No major sham-controlled RCTs were published after the meta-analysis literature search date (May 15, 2008). The search of the Cochrane database yielded a systematic review of rTMS for depression, but this review had not been updated since 2001 and was therefore excluded. A study that compiled safety data from several trials (Janicak et al., 2008) was reviewed, but an evidence table was not created. rTMS vs. other established treatment for treatment-resistant depression. One RCT comparing rTMS to ECT for patients with treatment-resistant depression (Rosa et al., 2006) was identified and critically appraised. Another RCT comparing rTMS and ECT had as its entry requirement, referral for ECT. The investigators did not specify that patients needed to have failed at least one treatment, so this study was excluded from further review. One RCT comparing rTMS to antidepressants for medication-resistant depression (Bretlau et al., 2008) was identified and critically appraised. Two other RCTs that evaluated the combination of rTMS and antidepressants as first-line treatment were excluded. The references for the studies that were reviewed are as follows: Bretlau LG, Lunde M, Unden M et al. Repetitive transcranial magnetic stimulation (rTMS) in combination with escitalopram in patients with treatment-resistant major depression. Pharmacopsychiatry 2008; 41: 41-47. See Evidence Table 1. Janicak PG, O'Rearson JP, Sampson SM et al. Transcranial magnetic stimulation in the treatment of major depressive disorder: A comprehensive summary of safety experience from acute exposure, extended exposure and during reintroduction treatment. J Clin Psychiat 2008; 69: 222-232. Lam RW, Chan P, Wilkins-Ho M et al. Repetitive transcranial magnetic stimulation for treatment-resistant depression: A systematic review and meta-analysis. Can J Psychiatr 2008; 53: 621-631. See Evidence Table 2. Rosa MA, Gattaz WF, Pascual-Leone A et al. Comparison of repetitive transcranial magnetic stimulation and electroconvulsive therapy in unipolar non-psychotic refractory depression: a randomized, single-blind study. Int J Neuropsychopharm 2006; 9: 667-676. See Evidence Table 1.

The use of Repetitive transcranial magnetic stimulation (rTMS) for the treatment of treatment-resistant major depression does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

04/18/2011: MTAC REVIEW

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Repetitive Transcranial Magnetic Stimulation (rTMS)

Evidence Conclusion: *rTMS vs. sham rTMS*: A recent RCT evaluated the safety and efficacy of daily left prefrontal cortex rTMS compared to sham rTMS for the treatment of antidepressant medication resistant depression in 190 patients with unipolar depression. The primary outcome was remission defined as a Hamilton Scale for Depression (HAM-D) score ≤3 or 2 consecutive HAM-D scored less than 10. Thirteen patients in the active rTMS group and five patients in the sham rTMS group experienced remission [Odds ratio 4.18, 95% CI (1.32-13.24), NNT=12]. There was no significant difference in adverse events by treatment arm. Results from this trial suggest that rTMS is more effective than placebo at treating medication resistant depression; however, this trial does not address the duration of the effect (George 2010). rTMS vs. venlafaxine ER the efficacy of rTMS over the right prefrontal dorsolateral cortex versus venlafaxine ER for the treatment of resistant depression was assessed in a recent RCT that followed 60 patients for 4-weeks. The primary outcome measure was change in Montgomery-Åsberg Depression Rating Scale (MADRS) score. Clinical response (more than a 50% reduction of the MADRS score) and remission (MADRS score ≤10 points) were also evaluated. There was no significant difference in mean change in MADRS score, clinical response, or remission rates between the two groups (Bares 2009).

Conclusion: There is insufficient evidence to determine the long-term safety and efficacy of rTMS for the treatment of depression in patients who have failed at least one prior antidepressant medication. Results from one RCT suggest that rTMS may be effective at treating medication resistant depression; however, this trial does not address the durability of the effect. Additionally, studies addressing the efficacy of rTMS differ with regards to the duration of treatment and treatment parameters. More research is necessary to identify the ideal duration of treatment and treatment parameters.

Articles: Studies were selected for review if they included at least 25 subjects and assessed either the safety or efficacy of transcranial magnetic stimulation for the treatment of depression. Studies were excluded if they addressed the safety or efficacy of TMS for the treatment of conditions other than depression; if they compared different TMS applications to each other; or if they lacked a valid comparison group. Two recent meta-analyses were also identified, but not selected for review. One meta-analysis that examined the efficacy of slow frequency (≤1 Hz) rTMS for the treatment of depression was not selected as the trials included were all published before the 2009 review (Schutter 2010). The other meta-analysis was not selected for review because of methodological limitations (Slotema 2010). Additionally, the majority of the articles included in these meta-analyses were also included in a previously reviewed meta-analysis. Two RCTs were selected for review. The following studies were critically appraised: Bares M, Kopecek M, Novak T, et al. Low frequency (1-Hz), right prefrontal repetitive transcranial magnetic stimulation (rTMS) compared with venlafaxine ER in the treatment of resistant depression: A double-blind, single-center, randomized study. *J Affect Disord 2009;* 118:94-100. See Evidence Table. George MS, Lisanby SH, Avery D, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-Controlled randomized trial. *Arch Gen Psychiatry 2010;* 67:507-516. See Evidence Table.

The use of Repetitive transcranial magnetic stimulation (rTMS) for the treatment of treatment-resistant major depression does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

08/17/2015: MTAC REVIEW

Repetitive Transcranial Magnetic Stimulation (rTMS)

Evidence Conclusion: The BCBS TEC assessment, published in January of 2014, established that the available evidence on the use of TMS therapy for depression does not meet the TEC criteria. More specifically, the TEC assessment was not able to make conclusions with regard to the effect of TMS on health outcomes, net health outcomes, and, as a result, was unable demonstrate that the technology was as beneficial as any established alternative and that results were attainable outside the investigational setting (BCBS 2014). Subsequent to the TEC assessment, a group of European experts made a conflicting conclusion regarding the efficacy of TMS for the treatment of depression. In their analysis of the literature, the European experts made a level A recommendation establishing the efficacy of high frequency rTMS of the left DLPFC in depression (Lefaucheur, André-Obadia et al. 2014).

Effectiveness: In the first meta-analysis, Gaynes and colleagues pooled data from 18 trials with the overall aim to evaluate the efficacy of rTMS in patients with treatment resistant depression. In all three primary outcomes (severity of depression symptoms, response rate, and remission) the investigators reported that rTMS was superior to sham leading to the conclusion that rTMS is a reasonable, effective treatment option in patients with treatment-resistant depression (Gaynes, Lloyd et al. 2014). The second meta-analysis, carried out by Kedzior and colleagues, focused more on the durability of the antidepressant effect. In their analysis, data from 16 studies involving 495 patients demonstrated only a small antidepressant effect during follow up (Kedzior, Reitz et al. 2015). Safety: The literature reports several common events to be associated with TMS therapy including problems at the site of coil placement, tension like headaches and light-headedness with the most serious event

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reported being seizure. Overall, however, the technique appears to be relatively safe and reasonably well tolerated. Collectively, the body of published evidence relating to TMS therapy for depression is plagued with heterogeneity with a wide range of aims, outcomes and varying populations. To add to this, the technology is inherently limited by the lack of any established consensus regarding both the frequency and intensity of stimulation. Historically, TMS therapy for depression has failed MTAC criteria due to insufficient evidence. The current evidence remains conflicting and does not provide clear and convincing evidence that rTMS therapy is an effective and sustainable treatment option for depression. *Conclusion:* There is insufficient evidence to support the superiority of rTMS over antidepressants. There is evidence to support the short-term efficacy of rTMS over sham therapy. rTMS appears to be a relatively safe and well tolerated treatment.
Articles: The literature search identified an evidence-based guideline on the therapeutic use of rTMS in a variety of different conditions. (Lefaucheur, André-Obadia et al. 2014). In addition, a 2014 TEC (technology evaluation center) assessment produced by the Blue Cross and Blue Shield (BCBS) Association in association with Kaiser Permanente was identified (BCBS 2014). As a result, the literature search focused on updating the evidence base established by the guideline and TEC assessment (March 2014 through July 2015). The search yielded just over 200 publications including a variety of case series/reports, clinical trials, review articles, and meta-analyses. No studies were identified comparing rTMS as a monotherapy with antidepressants. The following studies were selected for critical appraisal: Gaynes BN, Lloyd S, Lux L, et al. Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis. *J Clin Psychiatry*. 2014; 75(5):477-489. Kedzior KK, Reitz SK, Azorina V, et al. Durability of the antidepressant effect of the high-frequency repetitive transcranial magnetic stimulation (rTMS) in the absence of maintenance treatment in major depression: a systematic review and meta-analysis of 16 double-blind randomized, sham-controlled trials. *Depression and Anxiety*. 2015; 32:193-203.

The use of Repetitive transcranial magnetic stimulation (rTMS) for the treatment of major depression does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

07/09/2018: MTAC REVIEW
Deep Repetitive Transcranial Magnetic Stimulation (dTMS)
MTAC Discussion and Outcome
Randomized controlled trial (Levkovitz et al, 2015. Evidence table 1***)***

This was multicenter sham-controlled double-blind randomized trial that examined the safety and efficacy of dTMS using H-coil versus a sham therapy in adult patients with a first or recurrent depression episode fulfilling the DSM-IV criteria for MDD. The study enrolled 233 patients 22-68 years of age who had failed 1-4 adequate antidepressant treatments for the current episode. Symptom severity was equivalent to a score of at least 20 on the Hamilton Depression Rating Scale (HDRS) with 21 questions (HAMD-21).
The patients were randomly assigned to receive an active dTMS using the H-coil or a sham treatment that used a placebo coil placed next to the H1-coil. The coil was selected for each patient with a pre-programed card that was placed in a card reader attached to both-coils to maintain blinding of both the provide and the patient. All antidepressant medications were discontinued before the trial was begun.
Treatment was administered 5 days a week for 4 weeks, followed by twice-weekly treatment for up to 12 weeks. The treatment target was the dorsolateral prefrontal cortex on the left side with an intensity of 120% of the motor threshold with 2-s stimulations with 18 Hz followed by a 20-s pause, repeated 55 times over a total of ~20 minutes. The primary outcome was score change on the HAMD-21 after 4 weeks of therapy. Secondary outcomes were response and remission at 5 weeks, and adverse events. Response was defined as a reduction of ≥50% in the total HDRS-21 score compared to baseline; and remission was defined as a total HDRS-21 score <10.
233 patients were enrolled in the trial, N=212 were included in the ITT analysis, 181 (77%) in the per-protocol analysis. only 159 (68%) completed 5 weeks of the study and n=71 (30%) completed the 16 weeks.
Efficacy Levkovitz 2015 trial
The analysis showed that the treatment-group scored lower than the placebo group in the HDRS-21 from baseline to 5 weeks (primary outcome), The difference was not statistically significant according to the intention to treat analysis (ITT), but was statistically significant in the per-protocol analysis that included 77.7% of the patients enrolled (85% of those randomized to the treatment groups).
Validity of the trial
- The study was multicenter, randomized, controlled, double blinded, and had proper randomization and power analysis.
- dTMS was compared to sham therapy using an inactive coil, which is an important initial step to determine whether the treatment has a placebo effect. The trail, however, did not include a comparison arm with ECT or

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other alternative treatment to determine whether dTMS has a superior, inferior, or equivalent effect on TRD compared to other established therapies.
- The results showed no significant difference in the primary outcome between the active dTMS and sham therapy according to the ITT analysis. The difference, however, was significant in the PP analysis which does not consider the dropout due to insufficient improvement and/or compliance, or tolerance.
- There were differences between the side effects and their rates reported to the FDA vs. those in the published article.
- Patients with psychosis, bipolar disorder, OCD, PTSD, any significant neurological disorder, increased risk of seizure or suicide were excluded from the study, which limits generalization of the results.
- The drop-out rate was high; only 68% of those initially enrolled completed the 5 weeks of treatment and less than one third completed the 16 weeks of the study, mainly due to insufficient improvement in the two study groups.
- The trial was supported by Brainsway the manufacturer of the dTMS H-coil; system, which is a potential source of reporting bias.

Meta-analysis: Kedzoir et al, 2015 (Evidence table 2***)***
Kedzoir and colleagues conducted a systematic review to investigate the acute antidepressant effect of dTMS using the H-coil in patients with MDD. The review included one RCT (Levkovitz, 2015) with 181 patients, and nine observational studies with a total of 162 patients. The observational studies very small (population sizes ranged from 6-29 participants); six were conducted in Israel, 2 in Italy and one in Canada. Most of the patients had treatment resistant unipolar depression and were on concurrent antidepressants (in only 2 studies dTMS was used as a monotherapy).
The authors pooled the results of the observational studies, and descriptively presented the results of the only one published RCT. The primary outcome was the change in standardized Hamilton Rating Scale for Depression scores, response rate, remission rate, and acceptability.
Validity of Kedzoir et al's meta-analysis
- The meta-analysis had generally valid methodology and analysis. However, due to the lack of published RCTs, the authors pooled the results of 9 small observational studies with a total of 162 patients. The observational studies did not include a control or comparison group that received a sham treatment, ECT or any alternative therapy and the results were based on pre-post comparisons.
- The calculated overall effect sizes may be inflated by the possible placebo effect of the TMS.
- The studies included in the meta-analysis used different definitions for remission rates, which as well as the response rates varied widely between the studies. Response rates tended to be higher among patients on concurrent antidepressants and to increase with time, while remission rates tended to decrease over time, but did not seem to be affected by the concurrent use of antidepressants.
- The small sample sizes of the studies included, the short follow-up duration, and lack of control or comparison group, do not allow making any conclusion on the efficacy of dTMS, the durability of the reported results, or comparative effectiveness to ECT or other alternative therapies.

Conclusion:
- There is insufficient evidence to determine the comparative efficacy and safety of dTMS to ECT or other alternative therapies.
- There is limited evidence from one RCT showing that dTMS may have a superior short-term benefit compared to sham therapy.

The use of Repetitive transcranial magnetic stimulation (rTMS) for the treatment of major depression does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

03/2023: MTAT Review
Repetitive Transcranial Magnetic Stimulation (rTMS) for the Treatment of Bipolar Depression/Disorder (BPD)
Evidence Conclusion:
The Medical Technology Assessment Team (MTAT) reviewed the evidence assessment provided by SCPMG Evidence-Based Medicine Services on March 31, 2023, which concluded:
- In patients with BPD, there is very low-certainty evidence from one systematic review/metaanalysis (SR/MA) of RCTs and one additional RCT on the efficacy and safety of rTMS. The very low certainty of the evidence is due to the very low confidence in the effect estimate; and the true effect is likely to be substantially different from the estimate of effect.

The MTAT discussion with clinical expert input noted that despite the very low-certainty rating, the

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current body of evidence did not report significant harms, with a very low rate of hypomania or mania switch. It was also noted that there is a high burden of suffering and poor quality of life for select BPD patients who are refractive to multiple treatment regimens and intolerant to electroconvulsive therapy (ECT). In these patients, rTMS may provide some benefit as an alternative treatment option. Discussions and development of recommendations on the management and potential use of rTMS for BPD are underway within SCPMG Psychiatry.

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
90867	Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; initial, including cortical mapping, motor threshold determination, delivery and management
90868	Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; subsequent delivery and management, per session
90869	Therapeutic repetitive transcranial magnetic stimulation (TMS) treatment; subsequent motor threshold re-determination with delivery and management

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed	Date Last Revised
07/15/2009	06/01/2009, Reinstituted criteria annual review for Medicare 4/4/2011 MDCRPC, 5/3/2011 MDCRPC, 2/7/2012 MDCRPC, 12/4/2012 MDCRPC, 09/01/2015MPC, 07/05/2016MPC, 05/02/2017MPC, 03/06/2018MPC, 03/05/2019MPC, 03/03/2020MPC, 03/02/2021MPC, 03/01/2022MPC, 03/07/2023MPC	03/12/2024

MDCRPC Medical Director Clinical Review and Policy Committee
MPC Medical Policy Committee

Revision History	Description
09/08/2015	Revised LCD L34886 and L35008 Non-Covered Services.
10/03/2017	MPC approved to adopt MCG hybrid criteria for rTMS
10/10/2017	Migraine Headaches removed from indication
09/20/2018	Added MTAC review and denial language for dTMS
11/06/2018	MPC approved coverage for deep TMS
03/05/2019	MPC approved the recommendation to add the indication to include 18 y/o and older
03/03/2020	MPC approved the amended criteria to the existing hybrid TMS criteria (B-KP-801-T) to include additional indications for Behavioral Health Exclusions, Continued Therapy and Extension Therapy.
11/20/2023	Added March 2023 MTAT review for Repetitive Transcranial Magnetic Stimulation (rTMS) for the Treatment of Bipolar Depression/Disorder (BPD)
03/12/2024	MPC approved the revised clinical criteria for Transcranial Magnetic Stimulation (TMS) effective August 1st, 2024. Requires 60-day Notice.

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Clinical Review Criteria
Radiofrequency Ablation

- Barrett's Esophagus
- Lung Cancer
- Renal Tumors
- Primary HCC and Metastatic Liver Cancer
- Uterine Fibroids

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article	None
KPWA Policy	Due to the absence of a NCD, LCD, or other coverage guidance, KPWA has chosen to use their own Clinical Review Criteria, "***Radiofrequency Ablation***" for medical necessity determinations. Use the Non-Medicare criteria below.

For Non-Medicare Members

Service	Criteria Used
Barrett's Esophagus	Radiofrequency ablation is considered medically necessary for the treatment of members with Barrett's esophagus (BE) who have histological confirmation of low-grade dysplasia by two or more endoscopies three or more months apart.
Lung Cancer	There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.
Renal Tumors Primary HCC and Metastatic Liver Cancer	Medical necessity review is no longer required for this service.
Transcervical Ablation Uterine Ablation of Leiomyomas (0404T)	MCG* A-1039 This is not covered per MCG* For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.

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Laparoscopic Radiofrequency Ablation of Uterine Fibroids (58674)	There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

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The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage

Evidence and Source Documents

Radiofrequency Ablation for the Treatment of Barrett's Esophagus
Radiofrequency Ablation in the Treatment of Lung Cancer
Radiofrequency Ablation of Renal Tumors
Radiofrequency Ablation of Primary HCC and Metastatic Liver Cancer
Radiofrequency Volumetric Thermal Ablation (RFVTA) of Uterine Fibroids Using the AcessaTM System

Medical Technology Assessment Committee (MTAC)

Radiofrequency Ablation for the Treatment of Barrett's Esophagus

BACKGROUND

Barrett's esophagus is a disease wherein the stratified squamous epithelium lining the esophagus gets replaced by metaplastic columnar epithelium. The disease affects more Caucasians than Blacks and is diagnosed around 55 years (Spechler & Goyal, 1996) and its prevalence varied widely from 0.4% to 20% (Gerson, Shetler, & Triadafilopoulos, 2002; Ormsby et al., 2000; Ward et al., 2006). Barrett's esophagus is caused by chronic gastro esophageal reflux disease (GERD). While Body mass index (BMI), is believed to be associated with increased risk of Barrett's esophagus (Kamat, Wen, Morris, & Anandasabapathy, 2009), studies have found that abdominal obesity is a risk factor for Barrett's esophagus (Corley et al., 2007; Edelstein, Farrow, Bronner, Rosen, & Vaughan, 2007; Kramer et al., 2013). It is not well known if germline mutations are associated with the disease.

Initially, Barrett's esophagus manifests with no symptoms or patients show signs of GERD. The most common symptoms of GERD are pyrosis (heart burn), regurgitation and dysphagia. Other manifestations of GERD are chronic cough, bronchospasm and laryngitis, chest pain resembling angina pectoris. GERD is complicated by erosive esophagitis, esophageal ulceration, stricture and hemorrhage (Spechler & Goyal, 1996), and Barrett's esophagus. The annual cancer incidence varied from 0.1 to 0.4% (Desai et al., 2012; Hvid-Jensen, Pedersen, Drewes, Sørensen, & Funch-Jensen, 2011; Rugge, Fassan, Cavallin, & Zaninotto, 2012; Shakhatreh et al., 2014). Studies have shown that the risk of developing cancer is proportional to dysplasia status and length of Barrett's esophagus (Pohl et al., 2016; Sikkema et al., 2011; Thota et al., 2015; Van der Veen, Dees, Blankensteijn, & Van Blankenstein, 1989). Patients with high-grade dysplasia have higher risk (4-8%) of progression to adenocarcinoma while patients with Barrett's esophagus, low-grade dysplasia and indefinite for dysplasia have a risk ranging from 0.2 to 1.2% (Singh et al., 2014; Verbeek et al., 2012). However, mortality due to esophageal adenocarcinoma is lower than that of other causes (Sikkema, De Jonge, Steyerberg, & Kuipers, 2010). Diagnostic is based on endoscopy and biopsy showing columnar epithelium and intestinal metaplasia respectively. Histology classification has described four types of Barrett's esophagus (BE); these include non-dysplastic (ND), low-grade for dysplasia (LGD), indefinite for dysplasia (ID), high-grade dysplastic (HGD).

General management includes proton pump inhibitor (PPI). Fundoplication may be an alternative for PPI resistance. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit cyclooxygenase (COX) have been described; however, these drugs have potential side effects. Surveillance has been

promoted by many guidelines (Association, 2011; Fitzgerald et al., 2014; Shaheen, Falk, Iyer, & Gerson, 2016) but its benefit is not well documented. In addition, surveillance modality depends on the type of dysplasia. Treatment of dysplasia is of greatest importance. Several approaches have been described and include endoscopic ablative therapies, endoscopic resection or the combination of both, and esophagectomy. Endoscopic resection encompasses removal of both mucosa and submucosa (Pech, May, Gossner, Rabenstein, & Ell, 2004) and can lead to stricture. Endoscopic ablative therapies consist of radiofrequency ablation (RFA), photodynamic therapy, and endoscopic spray cryotherapy.

RFA uses radiofrequency energy and produces thermal injury to destroy the mucosa. Energy used comes from a balloon equipped with a series of electrodes to ablate the mucosa (Sharma et al., 2007). The radiofrequency energy can either be delivered circumferentially or focally. There are two different devices and accessories, both manufactured by BARRX. The balloon based HALO360 device is used to treat circumferential areas of BE. The system includes a high-power energy generator, a sizing balloon catheter and several balloon-based ablation catheters. There are 60 tightly spaced, bipolar independent electrodes encircling the balloon through which the energy is delivered. A preselected amount of energy is delivered in less than a second at 350 W. This allows for full thickness ablation of the epithelium without damage to the submucosa. The HALO [90] ablation system is used to treat more focal areas and uses a radiofrequency generator and an endoscope mounted electrode. Both procedures can be done on an outpatient basis. Barrx90 ULTRA, Barrx60, and Channel RFA device are alternative options for focal ablations.

02/01/2010: MTAC REVIEW
Radiofrequency ablation for the treatment of Barrett's Esophagus
Evidence Conclusion: The literature search revealed only one published randomized controlled trial (Shaheen et al, 2009) that compared radiofrequency ablation of Barrett's esophagus to a sham endoscopic procedure. The trial had valid design and analysis; it was multicenter, appropriately randomized, controlled, blinded, had sufficient statistical power, and with low dropout rate. However, radiofrequency ablation was compared to a sham procedure and not to another established alternative procedure with a curative intent for BE with dysplasia e.g. endoscopic resection, esophagectomy, or photodynamic therapy. Moreover, the trial had only one year of follow-up which is insufficient to determine the long-term efficacy, and safety of the procedure. Due to the short follow-up duration, the authors used neoplastic progression and eradication of dysplasia and metaplasia as surrogates for death from cancer. The trial randomized 127 patients (in a 2:1 ratio) with low- or high-grade dysplasia to undergo either radiofrequency ablation or sham endoscopic therapy. Randomization was stratified according to grade of dysplasia (LGD or HGD) and length of BE lesion (<4 or 4-8cm). Those in the ablation group underwent step-wise circumferential and focal ablation using HALO 360 and HALO 90 systems (BARRX Medical Inc, Sunnyvale, CA). Patients in the two groups underwent endoscopic surveillance for the study period; biopsies were obtained throughout the BE length every 3 months in patients with HGD or 6 months among those with LGD. After 12 months of follow-up, the results of the trial showed that more than three fourths of patients treated with radiofrequency ablation had complete eradication of intestinal metaplasia and dysplasia (77 % of all BE was completely reversed into normal epithelium among those who received RFA, vs. 2% in the control; 90% of patients with LGD, and 81.5% with HGD had complete eradication of the dysplasia vs. 23% and 19% of the controls respectively). The ablation therapy was also associated with a significant decrease in the risk of cancer but, as acknowledged by the authors this should be interpreted with caution due to the small number of cases. RFA therapy was not without risk as 5 (6%) cases developed esophageal stricture that required endoscopic dilatation, and 3 (3.5%) had other serious events as bleeding and chest pain.
Conclusion:

- There is fair evidence from one RCT with short-term follow-up that radiofrequency ablation using the HALO systems is superior to sham therapy (no therapy) in the treatment of BE with dysplasia.
- There is insufficient evidence to determine that RFA to has better outcomes and less harms than alternative therapies with curative intent for BE with dysplasia.
- There is insufficient evidence to determine the long-term efficacy, and safety of radiofrequency ablation therapy in the management of patients with Barrett's esophagus with dysplasia, and whether the risk of ablation is less than the risk of progression of BE.
- There is insufficient evidence to determine that radiofrequency ablation therapy eliminates the necessity for of further endoscopic surveillance of patients with Barrett's esophagus with dysplasia.

- There is insufficient evidence to determine that radiofrequency ablation therapy reduces or eliminates cancer risk in patients with Barrett's esophagus with dysplasia.

Articles: The search yielded around forty articles. Many were reviews, letters, and editorials. There was one randomized controlled trial and number of case series and reports. The RCT and the majority of the case series were conducted by the same group of investigators. The RCT with the following citation was critically appraised. Shaheen NJ, Sharma P, Overholt B, et al. Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med 2009; 360:2277-2288. See Evidence Table

The use of Radiofrequency ablation for the treatment of Barrett's esophagus with dysplasia does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

09/19/2016: MTAC REVIEW
Radiofrequency ablation for the treatment of Barrett's Esophagus
Evidence Conclusion: RFA vs alternative treatment Systematic review comparing radiofrequency ablation and complete endoscopic resection in treating dysplastic Barrett's esophagus: a critical assessment of histologic outcomes and adverse events (Chadwick et al, 2014) (evidence table 1) The first study is a systematic review aiming to compare the efficacy and safety of complete endoscopic mucosal resection (EMR) and radiofrequency ablation (RFA) in the treatment of dysplastic BE. It was reported that dysplasia was eradicated in 95% and 92% of patients treated with EMR and RFA respectively. Intestinal metaplasia (IM) eradication was similar between both groups. After (23 and 21 months for EMR and RFA respectively) months of follow-up for patients, who were treated with EMR, dysplasia eradication was achieved in 85% of patients versus 79% among RFA group. In EMR group, additional treatments were reported in 7 studies. In EMR group, overall short-term adverse events were 12.5% and most frequently acute bleeding. In RFA group, overall short-term adverse events were 2.5% and most frequently acute bleeding (1%). In EMR group, overall long-term adverse events were 38% and most frequently stricture compared to 4% in RFA group. Buried BE was 3.8% in EMR group vs. 0% in RFA group (not reported in table). Progression to cancer appeared to be low in both groups. This indicates that both treatments are effective in the management of HGD BE but more events that are adverse are observed with EMR. However, the review is mostly based on observational studies. Ten studies were directly or indirectly industry funded; only 3 RCTs were represented in the review. Individual studies were small. Follow-ups periods were short (<1 year) and varied greatly limiting accurate assessment of cancer progression and incidence of recurrence. Fair evidence shows that both treatments are effective in managing HGD BE but RFA has less adverse events.
Radiofrequency ablation vs endoscopic surveillance for patients with Barrett's esophagus and low-grade dysplasia a randomized clinical trial (Phoa et al 2014) (evidence table 2) This RCT investigated whether endoscopic radiofrequency ablation could decrease the rate of neoplastic progression. Compared to control group, patients who were treated with RFA, were less likely to progress to high grade dysplasia or cancer. At the end of endoscopic treatment, (After RFA), 92.6% and 88.2% of complete eradication of dysplasia and IM were observed respectively. During follow-up, patients who were treated with RFA were more likely to obtain complete eradication of dysplasia; the risk of complete eradication of dysplasia was increased by 70.5%. Complete eradication of intestinal metaplasia was maintained in 54of60patients (90.0%) receiving ablation compared with 0 of 68 patients receiving control (risk difference, 90% [95% CI, 82.4%-97.6%]; P < .001). Adverse events are represented by abdominal pain, bleeding, stricture, laceration, retrosternal pain while no adverse events were reported for endoscopic surveillance. The results indicate that in patients with low-grade dysplasia, RFA reduced the risk of progression to high-grade dysplasia or adenocarcinoma by 25% corresponding to an NNT of 4.0. Study had a valid methodology in general. However, it had some limitations: external validity is compromised (referral centers), study was underpowered for cancer-related death outcome which is the primary end point. Endoscopic rescue therapy was performed to decrease residual Barrett tissue. Based on the Cochrane collaboration's tool for risk of bias assessment, the overall risk of bias is low with unclear information on blinding. Fair evidence supports efficacy of RFA over endoscopic surveillance for low grade dysplasia. **Endotherapy versus surgery for early neoplasia in Barrett's esophagus: a meta-analysis (Wu et al., 2014)** (evidence table 5) This meta-analysis aimed to compare the efficacy and safety of endotherapy and surgery for early neoplasia in BE. A systematic literature search was performed up to December 2012 and included 870 patients. No significant difference between endotherapy and esophagectomy in the outcomes presented in the table below. However, endotherapy was associated with a higher neoplasia recurrence rate and fewer major adverse events. Limitations include: a small number of studies including retrospective studies; patients were not comparable in

some studies leading to bias of the results. Different endotherapies including EMR, PDT, RFA and argon plasma coagulation were used. The type of surgery and the experiences of surgeons were different. Publication bias might also exist. Low evidence supports similar efficacy between endotherapy and surgery in the treatment of early Barrett's neoplasia with fewer adverse events. Efficacy of RFA (non-comparative studies. **Efficacy and durability of radiofrequency ablation for Barrett's esophagus: systematic review and meta-analysis** (Orman et al, 2013) (evidence table 3) This systematic review aimed to determine the efficacy and durability of RFA for patients with dysplastic and nondysplastic BE. The authors found 91% of patients achieved CE-IM while 78% achieved CE-D and that in 13% of cases, IM recurred after successful treatment. Most common adverse events were stricture (5%) and pain (3%). Although the study has valid methodology, limitations included the poor quality of included studies and external validity. Settings include referral centers with capability in RFA. Heterogeneity was high. Adverse events may have been underestimated due to the retrospective design of a number of studies. Individual studies were small in size. Follow-ups periods were short. RFA was not compared to alternative treatment limiting accurate assessment. The results indicate that CE-IM and CE-D were achieved in most of the patients undergoing RFA with low IM recurrence and low adverse events.

Several prospective studies have assessed the efficacy of RFA. Their findings can be found in the following table. However, none of these studies compare RFA to alternative treatment.

Author, year	N	Intervention	Protocol	BE baseline	Median Follow-up (mos)	Findings	Adverse events
(Phoa et al., 2014)	132	ER combined with RFA	Visible lesions were removed with ER followed by serial RFA every 3 months. Follow-up endoscopy was scheduled at 6 months after the first negative post-treatment endoscopic control and annually thereafter	BE≤12 cm with HGD and/or EC	27	CE-neo:92% CE-IM: 87% Recurrence: neo and IM 4% & 8% respectively	Mucosal lacerations (8%) and stenosis (6%).
(He et al., 2015)	96	RFA	RFA was used at baseline to treat all unstained lesions (USL), and then biopsy (and focal RFA if USL persisted) was performed every 3 months until all biopsies were negative for MGIN, HGIN, and ESCC	moderate/high grade intraepithelial neoplasia [MGIN/HGIN] and early flat-type esophageal squamous cell carcinoma [ESCC]	12	73% & 84% of complete response at 3 and 12 months respectively. Progression in 2%	Stricture (21%)
(Haidry et al., 2014)	508	RFA/EMR	Visible lesions were removed by EMR. Thereafter, patients had RFA 3-monthly until all BE was ablated or cancer developed	HGD or IMC	6 years	CE-D: 77% to 92% CE-IM:56% to 83% (p<0.0001) Progression to OAC at 12 months (3.6% vs. 2.1%, p=0.51) Risk of IM recurrence at 5 years: 32%	
(Small et al., 2015)	246	EMR and/or ablation therapy		HGD/IMC		83.7% with HGD 75.7% with IMC	

BE, Barrett's esophagus; ER, endoscopic resection; EMR, endoscopic mucosal resection

Low grade dysplasia **Meta-analysis of endoscopic therapy for low-grade dysplasia in Barrett's oesophagus (Almond et al 2014)** (evidence table 4) This systematic review aimed to identify systematically all reports of endoscopic treatment of LGD, and to assess outcomes in terms of disease progression, eradication of dysplasia and intestinal metaplasia, and complication rates. The search was performed from January 1988 to January 2013. 37 studies reporting outcomes of endoscopic therapy for 521 patients with LGD. Study quality was assessed using Jadad scale for controlled trials and the Newcastle–Ottawa scale for

uncontrolled trials. The results indicated that 67.8% and 88.9% achieved CE-IM and CE-D respectively. The overall incidence of progression to cancer is 3.90. The authors concluded that RFA does not eradicate the risk of progression to cancer, but it appears to be safe and effective at eliminating LGD. Fair evidence supports the efficacy and safety of RFA in the treatment of low-grade dysplastic BE. However, studies with longer follow-up are needed.

Conclusion:

- Fair evidence shows that Radio frequency ablation (RFA) and endoscopic mucosal resection are both effective in managing HGD BE but RFA has less adverse events.
- Fair evidence supports efficacy of RFA over endoscopic surveillance for low grade dysplasia.
- Low evidence supports similar efficacy between endotherapy and surgery in the treatment of early Barrett's neoplasia
- There is fair evidence that RFA is effective and safe for the treatment of low-grade dysplasia; however, studies with long follow-up are needed.
- There is sufficient evidence to determine whether RFA is effective and safe for the treatment of high-grade dysplastic Barrett's esophagus.

Articles: The literature revealed a number of articles, but the following articles were selected for critical appraisal: Systematic review comparing radiofrequency ablation and complete endoscopic resection in treating dysplastic Barrett's esophagus: a critical assessment of histologic outcomes and adverse events (Chadwick et al, 2014) See Evidence Table 1. Radiofrequency ablation vs endoscopic surveillance for patients with Barrett's esophagus and low-grade dysplasia a randomized clinical trial (Phoa et al 2014) See Evidence Table 2. Efficacy and durability of radiofrequency ablation for Barrett's esophagus: systematic review and meta-analysis (Orman et al, 2013) See Evidence Table 3. Meta-analysis of endoscopic therapy for low-grade dysplasia in Barrett's oesophagus (Almond et al 2014) See Evidence Table 4. Endotherapy versus surgery for early neoplasia in Barrett's esophagus: a meta-analysis (Wu, Pan, Wang, Gao, & Hu, 2014) See Evidence Table 5.

The use of Radiofrequency ablation for the treatment of Barrett's esophagus with dysplasia does meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Radiofrequency Ablation in the Treatment of Lung Cancer

BACKGROUND

Lung cancer is the leading cause of cancer related mortality in the United States. It has two main types; the non-small cell lung cancer (NSCLC) which accounts for approximately 80-85% of cases, and the small cell lung cancer (SCLC). After the initial diagnosis of the disease is made, it is essential to have an accurate TNM staging in order to determine the appropriate therapy. The standard treatment of patients with stage I or II NSCLC is surgical resection, and in order to achieve a potential cure from the disease, the cancer must be completely resectable through pneumonectomy or lobectomy, and the patient should be able to tolerate the surgery and have adequate pulmonary function. Patients with more advanced or metastatic lung disease, or who cannot tolerate surgery, due to age or the presence of other co-morbidities, are poor surgical candidates. They are traditionally offered treatment with conventional external beam radiotherapy which is considered the most reasonable alternative. However, its results have not been satisfactory, and it has lower overall long-term survival than complete surgical resection. This radiation therapy may also be associated with regional complications as radiation pneumonitis, fibrosis, and esophagitis, and is not indicated for pulmonary metastases. Chemotherapy was found to have only a modest therapeutic effect and is usually used as palliative therapy. This has led the researchers to develop minimally invasive techniques as stereotactic radiotherapy, brachytherapy, photodynamic therapy, bronchial artery infusion of chemotherapy, cryotherapy and radiofrequency ablation (RFA) (D'Amico 2003, Qiao 2003, Pennathur 2007). Radiofrequency ablation is a relatively new minimally invasive therapy that potentially leads to localized tissue destruction. It works by transferring radiofrequency (RF) energy from a generator through an electrode, to the target tissues. The waves are converted into heat, resulting in thermal damage, and coagulative necrosis of the tissues. For solid organ tumor ablation, thin RF electrodes are introduced laparoscopically or percutaneously to the target lesion under ultrasound, CT, or MRI guidance. A power of 5-120W is delivered to the electrodes, and an alternating current of 450-1,200 kHz passes from the tip to the surrounding tissue. When the temperature of the tumor cells is raised above 70oC cell destruction occurs. Several radiofrequency ablation devices were cleared by the FDA as tools for general ablation of soft tissue by thermal necrosis. The devices were also cleared for ablation of liver lesions, and bone metastases. According to the FDA, they have not been cleared

for lung tumor ablation as their safety and effectiveness have not been fully established. In December 2007, the FDA issued a public health notification to alert the health practitioners of the deaths associated with lung tumor ablation using the radiofrequency devices (FDA Web site).

06/04/2008: MTAC REVIEW
Radiofrequency Ablation in the Treatment of Lung Cancer
Evidence Conclusion: There is limited evidence on the efficacy and safety of radiofrequency ablation for the treatment of lung cancer in patients who are not candidates for surgical resection. The body of evidence consists of small observational case series with no control or comparison groups that compare the RF ablation with conventional or other noninvasive techniques used for the treatments of patients with non-operable lung cancer, or those who cannot tolerate surgery. The published studies were heterogeneous; there were differences in the eligibility criteria of the studies, patient characteristics, stage of the disease, cancer type, number and sizes of the lesions, as well as other tumor characteristics. There were also variations in the ablation approaches, types of devices used to deliver the therapy, follow-up, endpoints, and outcome measures. Moreover, the follow-up duration in the majority of the studies was too short to determine the long-term safety and effectiveness of the therapy. Overall, the results of the published studies indicate that the median survival of patients receiving the therapy ranged from 8.6 months to 33 months. The one-year survival rate ranged from 63-85%, the two-year survival was 55-65% and the three-year survival rate was 15-46%. Complete tumor necrosis ranged from 38% to 95%, and local disease recurrence varied from 3% to 38.1%. The studies indicate the RF ablation has better outcomes with tumors smaller than 3 cm in diameter vs. those >3cm in diameter, as this would allow oversizing of the ablation areas. The adverse effects associated with FR ablation included pneumothorax that often-needed aspiration, pleural effusion, hemoptysis, pain, as well as other complications some of which required hospitalization of the patients. The authors of the published studies presented the results for all patients combined, with no adjustments for confounding factors as age of the patients, presence of other co-morbidities and/or malignancies, or the use of other adjuvant therapy. Moreover, in the absence of comparison groups, it is hard to determine whether radiofrequency ablation leads to better local control or improved survival outcomes than external beam radiation therapy or any other noninvasive treatment. In conclusion there is insufficient published evidence to determine the efficacy and safety of radiofrequency ablation for the treatment of lung cancer.
Articles: The search yielded over 300 articles. Many were review articles or publications not related to the current review. No meta-analyses of empirical studies randomized, or non-randomized controlled studies were identified. The majority were observational prospective case series with population sizes ranging from <10 to 60 patients. There was a larger (N=153) retrospective observational study that evaluated the long-term efficacy and safety of the therapy. Prospective series with at least 50 patients, and/or with longer-term follow-up, as well as the larger retrospective series were selected for critical appraisal. *The following studies were critically appraised:* DE Baire T, Palussiere J, Auperin A, et al. Midterm local efficacy and survival after radiofrequency ablation of lung tumors with minimum follow-up of 1 year. Prospective evaluation. Radiology 2006.240:587-596. See Evidence Table. Ambrogi MC, Lucchi M, Dini P, et al. Percutaneous radiofrequency ablation of lung tumors: results in mid-term. Eur J Cardiothorac Surg. 2006. 30:177-183. See Evidence Table. Gadaleta C, Catino A, Mattioli V. Radiofrequency thermal ablation in the treatment of lung metastases. In Vivo. 2006; 20:765-768. See Evidence Table. Simon CJ, Dupuy DE, DiPetrillo TA, et al. Pulmonary radiofrequency ablation: Long-term safety and efficacy. Radiology 2007.243:268-275. See Evidence Table.

> The use of Radiofrequency ablation in the treatment of lung cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Radiofrequency Ablation of Renal Tumors
BACKGROUND
With the widespread use of body imaging techniques as magnetic resonance imaging (MRI), computed tomography (CT), there is an increasing number of pre-symptomatic, incidentally detected small renal masses or lesions with unclear clinical significance. The standard treatment for renal masses is radical nephrectomy. Other available treatment options for these small, incidentally discovered masses include watchful waiting or partial nephrectomy. Recently, with the current trend of minimally invasive surgery, nephron-sparing approaches have gained more acceptance. Among these are radiofrequency (RF) ablation, cryoablation, microwaves, and high intensity focused ultrasonography (HIFU). These techniques are still under development and only target selected, small renal tumors with a diameter of 4 cm or less. RF ablation works

by transferring RF energy from a generator through an electrode, to the target tissues. The waves are converted into heat, resulting in thermal damage, and coagulative necrosis of the tissues. For solid organ tumor ablation, thin RF electrodes are introduced laparoscopically, or percutaneously to the target lesion under ultrasound, CT, or MRI guidance. A power of 5-120W is delivered to the electrodes, and an alternating current of 450-1,200 kHz passes from the tip to the surrounding tissue. When the temperature of the tumor cells is raised above 70°C cell destruction occurs. The size of the lesion depends on the thermal properties of the tissue, the time, and the amount of the energy delivered. Radiofrequency ablation has been used for selected liver and bone tumors. It is approved by the FDA for ablation of aberrant atrioventricular conduction pathways in patients with Wolf-Parkinson-White syndrome, and for treating soft-tissue lesions in the liver. Its use for human renal tumors is still under investigation, and its efficacy and safety as well as its dosimetry have not been fully established.

12/11/2002: MTAC REVIEW
Radiofrequency Ablation of Renal Tumors
Evidence Conclusion: There is insufficient published evidence to determine the efficacy and safety of radiofrequency ablation for the treatment of renal tumors.
Articles: The search yielded one review article, two case reports and three case series with 10-15 patients each. There were no meta-analyses or randomized controlled studies.

> The use of radiofrequency ablation in the treatment of renal tumors does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Radiofrequency Ablation of Primary HCC and Metastatic Liver Cancer
BACKGROUND
The liver is a common site for primary and secondary malignancies. Hepatocellular carcinoma (HCC), the most common primary tumor is the fifth most common cancer in the world, and the third most common cause of cancer-related mortality. It is responsible for more than half a million deaths across the globe each year. Treatment options for patients diagnosed with primary and secondary malignancies are limited. Less than 15% are candidates for surgical resection at presentation because of inadequate liver functional reserve, extrahepatic disease, anatomic constraints of the tumor, or medical comorbidities. The use of external beam radiation is limited due to the intolerance of normal liver parenchyma to tumoricidal radiation doses (the dose required to destroy solid tumors (>70 Gy) is much higher than the liver tolerance dose of 35 GY). In addition, systematic chemotherapy was found to have little impact on survival, and negative impact on the health-related quality of life due to the toxicity to other organs and systems. These limitations have led to the emergence of other therapies, such as radiofrequency ablation (RFA), cryosurgical ablation (CSA), percutaneous ethanol injections (PEI), hepatic arterial infusion chemotherapy, transarterial chemo-embolization (TACE), and selective intrarterial radioembolization therapy (Steel 2003, Salem 2005, Ibrahim 2008, Bult 2009, Riaz 2009, Bhardwaj 2010). Ablative techniques improve the ability to treat patients with unresectable hepatic tumors. Thermal ablative techniques, such as RFA, destroy tumors via a source that changes temperature to levels that are associated with cell death while causing minimal damage to adjacent, normal tissue. Chemical ablative techniques, such as PEI, involve the injection of cancer killing chemicals such as pure alcohol (ethanol) or acetic acid directly into the tumor. The choice of technique depends on equipment availability and physician preference. PEI is a chemical ablative technique where absolute or 95% ethanol is injected into tumor tissue resulting in coagulative necrosis through cytoplasmic dehydration, denaturation of cellular proteins, and small vessel thrombosis. When the consistency of the tumor is ‘soft’ within a ‘hard’ cirrhotic liver (most HCCs), the distribution of ethanol is relatively uniform; however, when the tumor is ‘hard’ within a ‘soft’ normal liver (most metastases), the distribution is not as uniform. For this reason, PEI works better for HCC than for metastases. Complications of PEI include: hyperthermia, pain, elevated serum liver function tests, needle-tract seeding, pleural effusion, biliary stricture, portal vein thrombosis, and bleeding in the biliary tract (Clark 2007, Yamane 2009). The most commonly used ablative technique in the United Stated is RFA. RFA causes tumor destruction through the use of alternating high-frequency electric current in the radiofrequency range (460-500 kHz). This current is delivered through an electrode placed in the center of a lesion. Ions within the cell follow the alternating current creating frictional heat producing local tissue temperatures that can exceed 100°C. This ionic agitation leads to tissue destruction via tissue boiling and creation of water vapors. Once temperatures greater than 60°C are reached, protein denaturation, tissue coagulation, and vascular thrombosis result in a zone of complete ablation. Partial tissue destruction can

occur up to 8 mm in diameter from the zone of complete ablation. RFA can be delivered either percutaneously, laparoscopically, or through open approaches (laparotomy). Complications from RFA include pleural effusion, hepatic abscess, biliary injury, liver failure, intra-abdominal hemorrhage, pneumothorax, and hypoxemia. The most troubling complications arise when a probe is placed too close to the diaphragm or intra-abdominal organ, resulting in ablation of the surrounding viscera with the accompanying complications of perforation, diaphragmatic injury, or pulmonary damage. Limitations of RFA include: treating lesions in perihilar areas or near large vascular structures, and real time monitoring of the ablative zone is difficult due to air released during heating (Yamane 2009, Arciero 2006). RFA has received FDA approval for generic tissue ablation and the ablation of unresectable colorectal cancer metastases.

08/11/1999: MTAC REVIEW
Radiofrequency Ablation of Primary HCC and Metastatic Liver Cancer
Evidence Conclusion: The best published scientific evidence evaluating percutaneous radiofrequency (RF) ablation of liver cancer consists of one case series of 39 patients with primary hepatocellular carcinoma and 11 patients with other primary tumors who had liver metastases. The majority of patients had 3-4 treatments with one or more nodules being ablated at each session. Five patients experienced mild pain during the procedure; no other complications were reported. The 5-year survival rate among those with primary hepatocellular carcinoma was 40%; the period of follow-up for persons with liver metastases was too short for the calculation of a 5-year survival rate. Because the survival rate of patients treated with RF ablation was not directly compared to that of a control group, it is not possible to determine whether this treatment improves survival among patients with liver cancer.
Articles: Rossi S, DiStasi M, Buscarini E, Quartetti P, Garbagnati F, Squassante L, Paties CT, Silverman DE, Buscarini L. Percutaneous RF interstitial thermal ablation in the treatment of hepatic cancer. AJR Am J Roentgenol 1996; 167: 759-68. See Evidence Table.

The use of radiofrequency ablation in the treatment of primary HCC does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

08/08/2001: MTAC REVIEW
Radiofrequency Ablation of Primary HCC and Metastatic Liver Cancer
Evidence Conclusion: Only one study on radiofrequency ablation was a controlled trial. The remainder were case series. The trial reported on a clinically intermediate outcome, liver necrosis, not survival. The case series reports had survival information, but this was not presented in a standardized format (e.g. 1-year survival, 3-year survival). Instead, they reported on survival after a certain mean or median follow-up time (patients had different amounts of follow-up time) which is more difficult to interpret. For primary HCC, in the one trial comparing RF ablation to an alternative technique, PEI, both techniques resulted in high rates of complete necrosis and the difference in rates was not statistically significant (Livraghi). PEI required more sessions and RF ablation had more adverse effects (there was 1 major and 4 minor complications with RF ablation, none with PEI). In the case series reviewed (Curley), there was a 72% survival rate after a median of 19 months of follow-up (all patients had at least 12 months follow-up). Livraghi (2001) (not critically appraised for this review) reported on a case series of patients with HCC treated with PEI. The 1-year survival rate for patients with a single HCC 5 cm or smaller was 98, 93 and 64%, respectively for Child's A, B and C cirrhosis. For metastatic hepatic cancer, de Barre found that 81% patients survived after a mean follow-up of 14 months; 62% of these who survived had hepatic disease or distant metastases. 2-year or longer follow-up data were not available. This does not appear to be a dramatic increase in survival compared to untreated metastatic liver cancer (mean survival 6 to 21 months), but there is not strong evidence to support this claim. No studies compared RF ablation treatment to another treatment for metastatic liver cancer such as cryosurgery. In a case series on cryosurgery for hepatic colorectal metastases (Ruers, 2001) (not critically appraised for this review), the 1-year survival was 76% and the 2-year survival was 61%. The effectiveness of RF ablation may differ depending on the type of metastatic tumor.
Articles: The search yielded 85 articles, many of which were review articles, opinion pieces, dealt with technical aspects of the procedures or addressed other, similar treatments. There were no randomized controlled trials or meta-analysis. There was one non-randomized controlled trial and the rest of the empirical articles were case series. Articles on HCC and metastatic liver cancer were analyzed separately. Two studies on primary hepatocellular carcinoma were reviewed (the non-randomized trial and a recent case series with a moderate sample size by a different research group): Livraghi T, Goldberg SN, Lazzaroni S, Meloni F, Solbiati

L, Gazelle GS. Small hepatocellular carcinoma: Treatment with radiofrequency ablation versus ethanol injection. Radiology 1999; 210: 655-661. See Evidence Table. Curley SA, Izzo F, Ellis LM, Vauthey JN, Vallone P. Radiofrequency ablation of hepatocellular cancer in 110 patients with cirrhosis. Ann Surg 2000; 232: 381-91. *One study on metastatic liver cancer was reviewed (the largest case series with the longest follow-up):* de Barre T, Ellas D, Dromain C, El Din MG, Kuoch V, Ducreux M. et al. Radiofrequency ablation of 100 hepatic metastases with a mean follow-up of more than 1 year. AJR 2000; 175: 1619-25. See Evidence Table.

The use of radiofrequency ablation in the treatment of primary HCC does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

06/21/2010: MTAC REVIEW
Radiofrequency Ablation of Primary HCC and Metastatic Liver Cancer
Evidence Conclusion: While there are many studies comparing RFA with resection and other ablative techniques, such as PEI, for the treatment of liver cancer, the data are difficult to compare since the studies are heterogeneous in study design, patient selection, data collection, tumor characteristics, primary cause of liver disease, route of access, electrode types used, and periinterventional systemic treatment. **Primary Liver Cancer** *RFA vs. Resection* The study selected for critical appraisal was a randomized controlled trial that compared the results of RFA with resection for the treatment of solitary and small HCC. Overall and disease-free survival rates were not statistically different for patients with solitary HCC < 5 cm in diameter treated with either RFA or resection. Additionally, patients treated with RFA had fewer major complications than patients treated with resection (0.04% vs. 56%, p<0.05). Treatment groups were comparable at baseline for all characteristic measured with the exception of serum alanine aminotransferase (ALT). Patients in the RFA group had higher serum ALT concentrations compared to patients in the resection group. Factors that limit the validity of the study include: uneven dropout rates, use of additional techniques, and lack of generalizability (Chen 2006). Another nonrandomized study comparing RFA with resection demonstrated similar survival outcomes between RFA and resection for tumors <5 cm (Montorsi 2005). One recent retrospective study suggested that overall and disease-free survival was higher for patients treated with resection compared to patients treated with RFA. However, in a subgroup analysis by tumor size, there was no significant difference in survival between RFA and resection for patients with tumors ≤3 cm. Results from this study should be interpreted with caution as this study contained significant selection bias; most patients who underwent RFA had more advanced tumors and worse liver function than those who received resection (Guglielmi 2008). *RFA vs. PEI There* are several published randomized controlled trials and meta-analyses comparing the efficacy of RFA versus PEI. Two of the most recent meta-analyses were selected for appraisal (Germani 2010, Bouza 2009). Results were consistent across the two analyses. Compared to patients treated with PEI, patients treated with RFA had higher three-year overall survival rates (73% RFA vs. 58% PEI, p<0.001) and lower rates of local recurrence (7% RFA vs. 22% PEI, p<0.001). Patients treated with RFA experienced more complications (19% RFA vs. 11% PEI, p<0.001) than those treated with PEI; however, there was no difference in the rate of major complications (4% RFA vs. 3% PEI, p=0.22).The most frequent complication reported in both groups was severe pain. All studies included in the analysis were classified to be trials with high-risk of bias. *RFA + PEI vs. RFA alone* There have been several published studies comparing PEI + RFA versus RFA alone. A randomized controlled trial was selected for review (Zhang 2007). Results from this trial suggest that overall survival is higher for patients with HCC treated with PEI + RFA versus RFA only (p=0.04). In a subgroup analysis by tumor size, survival was significantly better for those treated with PEI + RFA who had tumors between 3.1 and 5.0 cm compared to those treated with RFA only (p=0.03). There was no significant difference in survival for patients with tumors ≤3 cm or tumors 5.1-7.0 cm. The local recurrence rate was higher for those treated with RFA alone compared to those treated with PEI + RFA (p=0.01). There was no significant difference in overall, intrahepatic, or extrahepatic recurrence rates. There were no procedure related mortalities or major complications. Pain and fever were the most commonly seen minor complications. Data after 2-years should be interpreted with caution as less than 45% of patients were followed for 3-years. Results are not generalizable to women as less than 15% of the patients enrolled in the study were women. Additionally, the predominant cause of HCC in the study was hepatitis B while the predominant cause of HCC in Japan, Europe, and the United States is hepatitis C and alcohol abuse. *Secondary Liver Cancer RFA vs. Resection* No randomized controlled trials evaluating RFA compared to resection for unresectable liver metastases from colorectal cancer were identified. Results from a retrospective cohort study indicate that patients treated with resection had the highest overall and disease-

free survival rates and the lowest rates of recurrence compared to patients treated with RFA alone or RFA + resection. Results from this study should be interpreted with caution as this study contained significant selection bias. Patients who were treated with RFA were not eligible for resection (Abdalla 2004). The majority of other studies (Park 2007, Aloia 2006, Hur 2009) comparing RFA and resection reached similar conclusions regarding survival and recurrence rates; however, a few studies have found that survival rates were comparable (Oshowo 2003). It is hard to compare results across studies as the primary cause of the disease differs, techniques differ, and disease characteristics differ. Additionally, none of the treatment groups were comparable at baseline. Patients treated with RFA were not eligible for resection. *Conclusion:* There is fair evidence that overall and disease-free survival rates were not statistically different for patient with solitary HCC <5 cm in diameter treated with either RFA or surgical resection. There is fair evidence that patients with HCC treated with RFA have better survival and lower recurrence rates than patients treated with PEI. There is fair evidence that for patients with HCC and tumors between 3.1 and 5.0 cm in diameter the combined treatment of PEI plus RFA versus RFA alone increases survival; however, long term follow-up is needed. There is insufficient evidence to determine the efficacy of RFA compared to surgical resection for patients with liver metastases. **Articles:** The literature search yielded around 250 articles pertaining to the use of RFA. The majority of these articles were case series and cohort studies. Only one randomized controlled trial (Chen 2006) was identified that compared RFA with resection for small HCC. There were several RCTs and meta-analyses comparing RFA with PEI. The two most recent meta-analyses (Bouza 2009, Germani 2010) were selected for review. There were several studies comparing the combined use of PEI and RFA. Many of these studies did not have a control group or did not assess survival as an outcome. An RCT that compared PEI + RFA with RFA alone was selected for review (Zhang 2007). No randomized controlled trials or meta-analyses were found pertaining to the use of RFA for metastatic liver cancer. The literature consisted mainly of case series and cohort studies. A retrospective cohort study (Abdalla 2004) that compared resection to RFA was selected for review. The following studies were critically appraised. Chen MS, Li JQ, Zheng Y et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. *Ann Surg 2006;* 243:321-328. See Evidence Table. Bhardwaj N, Strickland AD, Ahmad F et al. Liver ablation techniques: a review. *Surg Endosc 2010;* 24:254-265. Bouza C, López-Cuadrado T, Alcázar R et al. Meta-analysis of percutaneous radiofrequency ablation versus ethanol injection in hepatocellular carcinoma. *BMC Gastroenterol 2009;* 9:31-39. See Evidence Table. Germani G, Pleguezuelo M, Gurusamy K et al. Clinical outcomes of radiofrequency ablation, percutaneous alcohol ablation and acetic acid injection for hepatocellular carcinoma: A meta-analysis. *J Hepatol 2010;* 52:380-388. See Evidence Table. Zhang YJ, Liang HH, Chen MS et al. Hepatocellular carcinoma treated with radiofrequency ablation with or without ethanol injection: A prospective randomized controlled trial. *Radiology 2007;* 244:599-607. See Evidence Table. Abdalla EK, Vauthey JN, Ellis LM et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. *Ann Surg 2004;* 239:818-827. See Evidence Table.

The use of radiofrequency ablation in the treatment of primary HCC does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Laparoscopic Radiofrequency Volumetric Thermal Ablation (RFVTA) of Uterine Fibroids Using the AcessaTM System

BACKGROUND

Uterine fibroids, also known as uterine myomas or leiomyomas, are non-cancerous tumors that grow within the wall of the uterus. They are the most common pelvic neoplasms in women, occurring among 20-40% of those in the reproductive age and 70%-80% by the age of 50. Uterine myomas are commonly classified into 3 subgroups according to their location: subserosal (projecting outside the uterus), intramural (within the myometrium) and submucosal (projecting into the cavity of the uterus. (A more recent classification was developed by International Federation of Gynecology and Obstetrics [FIGO]). Uterine fibroids also vary in size and number ranging from one tiny seedling to multiple bulky mases that can significantly enlarge the uterus. The majority of uterine leiomyomas are asymptomatic and can go unnoticed or are incidentally detected on clinical examination or imaging. However, 20-50% are symptomatic causing abnormal uterine bleeding (AUB) including menorrhagia, dysmenorrhea, pelvic pressure, back pain, and fertility issues (Brucker 2014, Chittawar 2015, Vilos 2015, Lee 2016).

Uterine fibroids are currently the leading indication of hysterectomy worldwide. Hysterectomy is the most effective and definitive treatment for symptomatic fibroids, however, many women desire to preserve their fertility and/or conserve their uterus. Myomectomy is the alternative procedure for these women; it can be performed by conventional laparotomy or by minimal access techniques such as laparoscopy, robotic-assisted laparoscopy, hysteroscopy, or other modified techniques depending on the number, size, and location of the fibroids. Each technique has its benefits and associated harms, but myomectomy in general carries the risk of fibroid recurrence and potential need for future hysterectomy. The recurrence rate ranges from 10-50% depending on age, number of fibroids, uterine size, and childbirth after myomectomy. Conventional laparotomy has been the approach of choice for many surgeons, but it is associated with intra- and post-operative blood loss requiring blood transfusion in approximately 20% of cases. Laparoscopic myomectomy performed by a highly skilled laparoscopic surgeon is associated with less blood loss, diminished postoperative pain, faster recovery, and shorter hospital stay compared to abdominal myomectomy. However, the multilayer suturing may be challenging, and the procedure takes longer to perform and requires surgical expertise and specialized equipment. In addition, there may be a limit to the size and number of lesions removed laparoscopically. There is also a concern about the risk of uterine rupture occurring in the second or third trimester of pregnancy after laparoscopic myomectomy. A recently raised concern is the risk of power morcellation in cases of undiagnosed uterine malignancy while removing the fibroids laparoscopically as this may result in disruption and wide dissemination of an unrecognized sarcoma (Brucker 2014, Chittawar 2015, Vilos 2015 Kramer 2016).
Alternative non-surgical or minimally invasive management options for uterine fibroids include medical treatment (hormonal and non-hormonal); magnetic resonance guided focused ultrasound surgery (MRgFUSD), uterine artery embolization (UAE), laparoscopic occlusion of uterine arteries, and radiofrequency (RF) myolysis or ablation of the myomas (Chittawar 2015, Vilos 2015).

Myolysis was introduced in the 1980s as a conservative option for treating myomas. It uses a focused energy to cause tissue destruction. Energy sources include laser, bipolar, monopolar, cryoprobe, or thermal radiofrequency ablation (RFA). In general, a radiofrequency system consists of a generator, an electrode, electrode return pads, and cables connecting these elements. The generator produces high frequency, low voltage, alternating current that is transmitted via an electrode with an insulated shaft. Placing the electrode into the target tissue results in transmission of the current through the tissue. The current then travels to the electrode return pads and back to the generator completing the circuit. The heat produced by ionic movement within the cells adjacent to the exposed portion of the electrode, spreads and produces volumetric ablation through coagulative necrosis (Lee 2016)

In 2002 Lee BB, first reported on the use of RF ablation under laparoscopic intraabdominal ultrasound guidance to treat patients with symptomatic myomas. A number of observational small feasibility studies using different systems were published along the years (Chudnoff 2013, Chittawar 2015, Kramer 2016, and FDA website accessed April 2017). The Acessa™ System (Halt Medical, Inc., Brentwood, CA) is an ultrasound guided system for performing radiofrequency volumetric thermal ablation (RFVTA) of fibroids in the outpatient setting. The system consists of several components including a dual function RF generator, a disposable 3.4 mm diameter hand piece with a deployable 7-needle electrode array, a handpiece cable, two disposable dispersive electrode pads, pad cable, power cord, and a foot pedal. It is designed to deliver up to 200W of RF power in 3 operational modes: Temperature Control, Manual Control, and Coagulation Mode. Additional equipment needed for the RFA procedure using the Acessa™ system include a standard laparoscopic tower (insufflator, camera box, light source and printer), laparoscope 5 or 10 mm, ultrasound machine with laparoscopic transducer, and two video monitors one for the laparoscopic image and one for the ultrasound image (Chudnoff 2013, lee 2016 and Acessa website accessed April 2017).

The procedure is performed under general anesthesia and laparoscopic intra-abdominal ultrasound guidance. The laparoscopic ultrasound probe is used to determine the location and size of all fibroids present. The RFA handpiece tip is then inserted percutaneously through a 2-mm skin incision and directed into each myoma with laparoscopic and ultrasound guidance to verify the appropriate placement of the device within each myoma. The electrode array is then deployed, the appropriate duration of ablation is determined, and the treatment applied. Once the ablation is completed, the generator is switched to coagulation mode to seal the tract during withdrawal of the handpiece and provide hemostasis. Irregular myomas and those ≥ 4 cm in diameter require multiple overlapping ablations to ensure adequate ablation of the myoma periphery. After

ablation, the myomas are not replaced by fibrous tissue, but are gradually reabsorbed by the surrounding myometrium. Complete reabsorption depends on the completeness of ablation, location of the myoma and weal as its size (Vilos 2015, Lee 2016).

More recently a transvaginal approach was introduced for delivering the energy without the need for general anesthesia. The procedure was examined in an observational study in China and used a different radiofrequency generator (Jiang 2014).

06/21/2017: MTAC REVIEW

Evidence Conclusion: Comparative studies the only randomized controlled trial identified by the literature search was a single center study that compared the laparoscopic ultrasound guided radiofrequency volumetric thermal ablation (RFVTA) of uterine fibroids versus laparoscopic myomectomy (LM). It is an industry sponsored ongoing post-market RCT trial with a 5-year follow-up plan. The perioperative results of the trial as well as follow-up data at 12 and 24 months were reported in three publications (Brucker 2014, Hahn 2015, and Kramer 2016) (Evidence Table 1). The trial compared RFVTA to LM which is more invasive treatment, rather than to a minimally invasive procedure such as uterine artery embolization (UAE). The primary outcome was the mean time to hospital discharge which may not be the ideal primary outcome as patients undergoing LM may require one day stay in the hospital. In this trial all 25 patients in the LM group were hospitalized overnight to monitor for potential post-procedure bleeding. Patient symptoms and safety of the procedure were secondary outcomes based on subjective responses to validated questionnaire. The study was not blinded, which is a potential source of bias, and it was only powered to detect significant differences between the two treatments for the primary outcome and not for the patient outcomes that matter. The perioperative results show significantly less time spent in hospital and less bleeding with RFVTA compared to LM (Brucker 2014 Evidence Table 1).

Outcons in the two intervention groups (Brucker 2014)

Outcomes	LM group* N=25	RFVTA N=25	P value
Time to hospital discharge in hours, Mean	29.9 ± 14.2	10.0 ± 5.5	<0.001
Median	22.6	7.8	
Range	16.1-68.1	4.2-25.5	
Intraoperative blood loss in ml, Mean	51 ± 57	16 ± 9	Not provided
Median	35	20	
Range	10-300	0-30	

Patients were kept overnight in the hospital for observation

At 12-months women in the two treatment groups reported significant reduction in their symptom severity and improvement health related quality of life (HR-QoL) compared to baseline. The reported improvements were better with LM compared to RFVTA, but the differences between the two groups were not statistically significant. The only statistically significant difference between the two groups was the degree of patient satisfaction (very vs. moderately satisfied) favoring the myomectomy group. Two women in the ablation group underwent hysterectomy and one underwent myomectomy (Hahn 2015). The interim analysis at 24 months also showed significant improvement in the patient-reported symptom severity for both interventions compared to baseline. However, the improvement reported in health-related quality of life reached a statistically significant level only among patients in the LM group (Kramer 2016). The authors concluded that both interventions have similar clinical benefits, and that 12-and 24-months data suggest equivalence in safety and patient-reported efficacy of RFVTA and LM. However, the study was not designed nor powered as an equivalent trial and the numbers were too small to provide sufficient statistical power to detect significant differences. A lack of significant statistical difference does not necessarily indicate equivalence. The trial was randomized and controlled, but not without limitations. It was a single-center, relatively small, and unblinded trial. 14% of the study population was not included in the 12- and 24-months analysis which was based on per-protocol rather than on intention to treat (ITT) analysis, and on patient-reported outcomes. The study was

conducted in Germany among 100% white women, with symptomatic fibroids <10 cm diameter, and other strict inclusion/exclusion criteria, that may limit generalization of the results. In addition, there were some baseline differences between the two study groups as regard age, number, size, and location of fibroids. The authors indicated that randomization occurred intraoperatively after laparoscopic ultrasound mapping of the uterus to classify the fibroid and define its size and location, and did not indicate whether any patient was excluded from randomization based on the ultrasound results, which may be a potential source of selection bias. **Non-comparative studies** the literature search identified two small low-quality feasibility studies and a one non-comparative observational study (Halt trial), the pivotal study that led to the FDA clearance of the Acessa System in 2012. Halt trial (Chudnoff 2013, Guido 2013, Berman 2014). (See Evidence Table 2) was a prospective multicenter study that examined the efficacy and safety of laparoscopic ultrasound-guided RFVTA of uterine myomas in symptomatic women. The study enrolled 137 women with documented fibroids and menstrual blood loss between 150 and 500mL from 11 centers in the US and Latin America (additional inclusion /exclusion criteria are provided in the evidence table). The primary outcomes were the volume of menstrual bleeding compared to baseline, surgical re-intervention and device related adverse events at 12 months, Secondary outcomes included uterine volume measurements, patient-reported Uterine Fibroid Symptom and Health Related Quality of Life (QoL) scores and general health outcome scores at 3-6 and 12 months. Guido, 2013 and Berman, 2014 reported on the effect of the RFVTA on symptom severity qualitative clinical outcomes at 2- and 3 years after the intervention based on the patients' responses to validated questionnaires.

Rate of reduction in menstrual blood from baseline to 12 months

Outcome	
Decrease of menstrual blood from baseline to 12 months	n/N 104/127 81.9%
% women with ≥ 50% reduction in menstrual flow from baseline to 12 m	42% (95% CI, 31.6-48.7%)
% women with ≥ 40% reduction in menstrual flow from baseline to 12 m.	48.8% (95% CI, 40.1-57.5%)
% women with ≥ 30% reduction in menstrual flow from baseline to 12m.	59.1% (95% CI, 50.5-67.6%)
% women with ≥ 22% reduction in menstrual flow from baseline to 12 m.	67.7% (95% CI, 59.6-75.8%)

The results suggest that menstrual blood loss was significantly reduced from baseline to 12 months post-procedure. By the end of 12 months after the procedure there was one surgical intervention for persistent bleeding and one serious adverse event. Between 12 and 24 months 6 more women underwent surgical intervention for fibroid-related bleeding and one experienced severe adverse event during and after a Cesarean section delivery. By 36 months a total of 14 women (11.0%) had repeat surgical re-interventions for fibroid symptoms (11 hysterectomies, 2 myomectomies, and 1 uterine artery embolization). The results also show significant improvement in patient-reported symptom severity and health related QoL at 3 months compared to baseline, and that all quality of life and health state scores remained stable over 12, 24, and 36 months of follow-up. 5 patients (4%) experienced treatment-related adverse events including pelvic abscess, laceration in sigmoid colon, vaginal bleeding, severe lower abdominal pain and superficial uterine serosal burn. One woman got pregnant and delivered a healthy full-term baby by C-section, but experienced severe bleeding during the surgery and 48 hours later. Halt trial was sponsored by Halt Medical, the manufacturer of Acessa™ System. It was not a comparative trial and only aimed at examining the safety and efficacy of the procedure. The study was multicenter and included a diverse population, but had strict inclusion /exclusion criteria as regards the size of the leiomyomas, size of the uterus, minimum preoperative hemoglobin and other variables including limiting the procedure to women who did not desire future childbearing, all of which may limit generalization of the results.

Conclusion

- There is insufficient published evidence to determine that laparoscopic ultrasound guided radiofrequency volumetric thermal ablation (RFVTA) of symptomatic uterine myoma has superior or equivalent results as other therapies/interventions used among women with symptomatic fibroids who desire to conserve their uterus. The only comparative study published to date, was small, unblinded, and only powered to detect

significant difference in the length of post procedural hospital stay with RFVTA versus laparoscopic myomectomy. It was not powered to detect differences in the clinical outcomes or quality of life. A lack of significant differences does not necessarily indicate equivalence.

- There is insufficient evidence to determine the safety of the laparoscopic ultrasound RFVTA or the durability of the observed benefit over the years. The comparative study was too small and with insufficient follow-up period. The other studies examining the safety of the procedure were all observational; the largest and longest of which was the pivotal Halt trial which reported significant benefit and durability of the effect of the intervention for up to three years. However, similar to the other published observational studies on this technology, it had its limitations; had no control or comparison group, and the majority of outcomes were subjective. The three-year follow-up of Halt trial shows an increasing rate of repeat surgeries along the years. By the end of the third year, 14 (12%) of the women who entered the 3-year follow-up had repeat surgeries 11 (79%) of which were hysterectomies

Articles: The literature search for studies on laparoscopic radiofrequency volumetric thermal ablation of uterine fibroids identified 4 studies with population sizes ranging from 31 to135, reported in 9 publications. Only one study was randomized and controlled with its results were published in three articles (Brucker 2014, Hahn 2015, and Kramer 2016). The others were observational, non-comparative studies including a very small short feasibility study (Garza 2011), a small study (N-35) with 12 months follow-up (Robles 2013) and the pivotal Halt trial (published in 4 articles (Chudnoff 2013, Guido 2013, Galen 2013, and Berman 2014). The RCT and the HALT trial were selected for critical appraisal. Berman JM, Guido RS, Garza Leal JG, et al. Three-year outcome of the Halt trial: a prospective analysis of radiofrequency volumetric thermal ablation of myomas. *J Minim Invasive Gynecol*. 2014 Sep-Oct; 21(5):767-774. Brucker SY, Hahn M, Kraemer D, et al. Laparoscopic radiofrequency volumetric thermal ablation of fibroids versus laparoscopic myomectomy. *Int J Gynaecol Obstet*. 2014 Jun; 125(3):261-265.Chudnoff SG, Berman JM, Levine DJ, et al. Outpatient procedure for the treatment and relief of symptomatic uterine myomas. *Obstet Gynecol*. 2013 May; 121(5):1075-1082. Galen DI, Isaacson KB, Lee BB. Does menstrual bleeding decrease after ablation of intramural myomas? A retrospective study. *J Minim Invasive Gynecol*. 2013 Nov-Dec; 20(6):830-835. Guido RS, Macer JA, Abbott K, et al. Radiofrequency volumetric thermal ablation of fibroids: a prospective, clinical analysis of two years' outcome from the Halt trial. *Health Qual Life Outcomes*. 2013 Aug 13; 11:139. Hahn M, Brucker S, Kraemer D, et al. Radiofrequency Volumetric Thermal Ablation of Fibroids and Laparoscopic Myomectomy: Long-Term Follow-up from a Randomized Trial. *Geburtshilfe Frauenheilkd.* 2015 May; 75(5):442-449. Krämer B, Hahn M, Taran FA, et al. Interim analysis of a randomized controlled trial comparing laparoscopic radiofrequency volumetric thermal ablation of uterine fibroids with laparoscopic myomectomy. *Int J Gynaecol Obstet*. 2016 May; 133(2):206-211.

The use of Laparoscopic Radiofrequency Volumetric Thermal Ablation (RFVTA) of Uterine Fibroids Using the AcessaTM System does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Barrett's Esophagus- Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
43229	Esophagoscopy, flexible, transoral; with ablation of tumor(s), polyp(s), or other lesion(s) (includes pre- and post-dilation and guide wire passage, when performed)
43270	Esophagogastroduodenoscopy, flexible, transoral; with ablation of tumor(s), polyp(s), or other lesion(s) (includes pre- and post-dilation and guide wire passage, when performed)
With Diagnosis Codes	
K22.70	Barrett's esophagus without dysplasia
K22.710	Barrett's esophagus with low grade dysplasia
K22.711	Barrett's esophagus with high grade dysplasia
K22.719	Barrett's esophagus with dysplasia, unspecified

Lung Cancer - Considered Not Medically Necessary:

CPT® or HCPC Codes	Description
32998	Ablation therapy for reduction or eradication of 1 or more pulmonary tumor(s) including pleura or chest wall when involved by tumor extension, percutaneous, including imaging guidance when performed, unilateral; radiofrequency

Transcervical Uterine Ablation of Leiomyomas - Considered Not Medically Necessary:

CPT® or HCPC Codes	Description
0404T	Transcervical uterine fibroid(s) ablation with ultrasound guidance, radiofrequency

Laparoscopic Radiofrequency Ablation of Uterine Fibroids—Considered Not Medically Necessary:

CPT® or HCPC Codes	Description
58674	Laparoscopy, surgical, ablation of uterine fibroid(s) including intraoperative ultrasound guidance and monitoring, radiofrequency

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Dates Reviewed	Date Last Revised
07/17/2008	Added to annual review on 04/04/2011 MDCRPC, 02/07/2012 MDCRPC,12/04/2012 MDCRPC, 10/01/2013 MPC, 08/05/2014 MPC, 06/02/2015MPC, 04/05/2016MPC, 02/07/2017MPC, 12/05/2017MPC ,11/06/2018MPC, 11/05/2019MPC, 11/03/2020MPC, 11/02/2021MPC, 11/01/2022MPC, 11/07/2023MPC	10/03/2023

MDCRPC Medical Director Clinical Review and Policy Committee

MPC Medical Policy Committee

Revision History	Description
09/08/2015	Revised LCD L34886 and L35008 Non-Covered Services.
05/03/2016	Combined RFA Barrett's Esophagus and Lung Cancer into one policy
10/04/2016	Added MTAC Review
11/01/2016	MPC approved criteria of medical necessity for Barrett's Esophagus
08/01/2017	Added MTAC Review for RFVTA
12/05/2017	Adopted KPWA Policy for Barrett's Esophagus and Uterine Fibroids for Medicare
08/28/2018	Removed non-covered LCD for lung cancer
11/17/2020	Removed references to vertebral augmentation for painful spinal metastases as there is already separate criteria for vertebroplasty
04/05/2022	MPC approved to adopt MCG* A-1039 Transcervical Uterine Ablation of Leiomyomas. This service continues to be considered not medically necessary.
10/03/2023	MPC approved to maintain a position of noncoverage for Laparoscopic RFA by adopting KP criteria of insufficient evidence (CPT 58674). 60-day notice not required.

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Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Rhinoplasty

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	Plastic Surgery (L37020)
Local Coverage Article	Billing and Coding: Plastic Surgery (A57222) Cosmetic vs. Reconstructive Surgery (A52729) Medicare retired Article for Cosmetic vs. Reconstructive Surgery (A52729). These services still need to meet medical necessity as outlined in the LCA and will require review. LCAs are retired due to lack of evidence of current problems, or in some cases because the material is addressed by a National Coverage Decision (NCD), a coverage provision in a CMS interpretative manual or an article. Most LCAs are not retired because they are incorrect. Therefore, continue to use LCA A52729 for determining medical necessity.

For Non-Medicare Members

Kaiser Permanente has elected to use the (MCG)* Rhinoplasty (KP-0184 10172023) for medical necessity determinations. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.

***MCG Manuals are proprietary and cannot be published and/or distributed**. However, on an individual member basis, Kaiser Permanente can share a copy of the specific criteria document used to make a utilization management decision. If one of your patients is being reviewed using these criteria, you may request a copy of the criteria by calling the Kaiser Permanente Clinical Review staff at 1-800-289-1363 or access the MCG Guideline Index using the link provided above.

If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

The nose is responsible for almost 2/3 of the resistance to airflow during breathing, with most of the resistance occurring in the anterior part of the nose, called the nasal valve, comprised of the external and internal valves. External valve collapse may be idiopathic or associated with a history of trauma or previous surgery; common causes of internal valve collapse are septal deviation and previous surgery. Restoration of the normal aperture of

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the internal and external components of the nasal valve are important treatment strategies for the correction of nasal obstruction.

Haye's Technology Assessment

Absorbable Nasal Implant (Latera, Stryker) for the Treatment of Nasal Valve Collapse
May 10, 2022; Annual Review May 04, 2023

Health Technology

Rationale
Absorbable nasal implants are synthetic grafts designed to provide reinforcement to weakened nasal cartilage, thereby obviating the impact of lateral wall insufficiency on risk for developing nasal valve collapse (NVC) (Stryker, 2021).

Technology Description
Only 1 absorbable nasal implant cleared for marketing in the United States was identified: the Latera absorbable nasal implant (Stryker, 2021). Latera is a cylindrically shaped device composed of a bioresorbable poly-L-lactide acid and poly-D-lactic acid (PLLA-PDLA; mix of chiral isomers/molecular orientations) copolymer with dimensions 1 millimeter (mm) × 20 or 24 mm. One end is forked for anchoring purposes (i.e., above the maxilla), while the other end is narrower to increase flexibility. The implant is made to support the upper and lower cartilage on the sides of the nose (K192661; Stryker, 2021).

Insights
Clinical evidence suggests absorbable nasal implants are technically feasible to implant and are associated with reductions in nasal airway obstruction symptoms and pain; however, evidence is of generally very poor quality and there is a paucity of studies with control groups to inform whether absorbable nasal implants have clinical performance that is better, worse, or similar to competing technologies, such as nonabsorbable nasal implants. Additionally, many patients received adjunctive treatment with the nasal implants, which confounds interpretation of results. There is no applicable Centers for Medicare & Medicaid Services (CMS) National Coverage Determination (NCD) for absorbable nasal implants for NVC; payers generally consider them experimental or investigational and therefore noncovered.

Hayes. Hayes Technology Assessment. Absorbable Nasal Implant (Latera, Stryker) for the Treatment of Nasal Valve Collapse. Dallas, TX: Hayes; May 10, 2022. Retrieved September 25, 2023, from https://evidence.hayesinc.com/report/eer.latera4372

References

ECRI. Latera Absorbable Nasal Implant (Stryker Corp.) for treating nasal valve collapse. Clinical Evidence Assessment. 2022 Sept. Retrieved September 25, 2023, from: https://www.ecri.org/components/ProductBriefs/Pages/24952.aspx#

Applicable Codes

Rhinoplasty:
Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® Codes	Description
30400	Rhinoplasty, primary; lateral and alar cartilages and/or elevation of nasal tip
30410	Rhinoplasty, primary; complete, external parts including bony pyramid, lateral and alar cartilages, and/or elevation of nasal tip
30420	Rhinoplasty, primary; including major septal repair
30430	Rhinoplasty, secondary; minor revision (small amount of nasal tip work)
30435	Rhinoplasty, secondary; intermediate revision (bony work with osteotomies)
30450	Rhinoplasty, secondary; major revision (nasal tip work and osteotomies)

Nasal Mesh Implant (Latera®) Requires Medical Director Review:
Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

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CPT® Codes	Description
30468	Repair of nasal valve collapse with subcutaneous/submucosal lateral wall implant(s)

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
06/04/2013	06/04/2013[MPC], 03/03/2015[MPC], 01/05/2016[MPC], 11/01/2016[MPC], 09/05/2017[MPC], 08/07/2018[MPC], 08/06/2019[MPC], 08/04/2020[MPC], 08/03/2021[MPC], 08/02/2022[MPC], 08/01/2023[MPC]	10/03/2023

[MPC] Medical Policy Committee

Revision History	Description
09/08/2015	Revised LCD L35008
12/2/2015	Added LCA
12/19/2017	Added the Plastic Surgery LCD
08/04/2020	Added Medicare LCA A57222
10/03/2023	Updated the criteria to clarify the language in the policy regarding photographic requests.

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Clinical Review Criteria
Robotic Assisted Surgeries (RAS)

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Criteria

For Medicare Members

Source	Policy
Local Coverage Determinations (LCD)	07/14/2016 Noridian **RETIRED** Non-Covered Services (L34886) and Billing and Coding: Non-Covered Services (A57642). These services still need to meet medical necessity as outlined in the LCD and will require review. LCDs are retired due to lack of evidence of current problems, or in some cases because the material is addressed by a National Coverage Decision (NCD), a coverage provision in a CMS interpretative manual or an LCD. Most LCDs are not retired because they are incorrect. The criteria should be still referenced when making an initial decision. However, if the decision is appealed, the retired LCD cannot be specifically referenced. Maximus instead looks for “medical judgment” which could be based on our commercial criteria or literature search.

For Non-Medicare Members

Kaiser Permanente will not separately reimburse for the use of robotic surgical systems, including but not limited to the CPT/HCPCS codes listed in this document.

Please refer to Kaiser Permanente payment policy for reimbursement clarifications.

For high-tech radiology (imaging) procedures being requested for the purpose of robotic assisted surgery please refer to the **High-End Imaging Site of Care Policy**.

If requesting review for this service, please send the following documentation:

- Last 6 months of clinical notes from requesting provider &/or specialist.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Robotic assisted surgery involves use of a computerized system operated by a surgeon at a computer console connected with robotic arms. The system is used to assist in laparoscopic surgical procedures. Robotic assisted

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surgery may allow for finer more precise control of the instruments by the surgeon, though surgery may take longer. Laparoscopic surgery is associated with improved postsurgical pain and recovery and with lower risk of infection and blood loss for some procedures compared with open surgery.

In 2000, the da Vinci robot was approved by the Food and Drug Administration (FDA) for general laparoscopic surgery. Numerous other indications for the da Vinci system have since been approved by the FDA, including urological procedures, gynecologic laparoscopic procedures, general thoracoscopic procedures, and others. In 2007, the American Medical Association determined that an additional CPT code for robotic-assisted procedures was not necessary.

Robotic assisted surgery has been used in the following procedures:
Prostatectomy; Hysterectomy; Nephrectomy; Cardiac Surgery; Adjustable Gastric Band; Adnexectomy; Adrenalectomy; Cholecystectomy; Colorectal Surgery (Colorectal Resection, Colectomy, Mesorectal Excision); Cystectomy; Esophagectomy; Fallopian Tube Reanastomosis; Fundoplication; Gastrectomy; Heller Myotomy; Ileovesicostomy; Liver Resection; Lung Surgery; Myomectomy; Oropharyngeal Surgery; Pancreatectomy; Pyeloplasty; Rectopexy; Roux-en-Y Gastric Bypass; Sacrocolpopexy; Splenectomy; Thymectomy; Thyroidectomy; Trachelectomy; and Vesico-vaginal Fistula.

In March 2013, the American Congress of Obstetricians and Gynecologists released a statement that said in part, "There is no good data proving that robotic hysterectomy is even as good as—let alone better—than existing, and far less costly, minimally invasive alternatives."

The Health Care Authority in Washington State conducted an evidence review for each procedure listed above and found the evidence to be minimal in most cases. The outcome of their review was to not pay additionally for the use of the robotic device use.

Applicable Codes

Not separately reimbursed:

CPT® Codes	Description
20985	Computer-assisted surgical navigational procedure for musculoskeletal procedures, image-less (List separately in addition to code for primary procedure)
0054T	Computer-assisted musculoskeletal surgical navigational orthopedic procedure, with image-guidance based on fluoroscopic images (List separately in addition to code for primary procedure)
0055T	Computer-assisted musculoskeletal surgical navigational orthopedic procedure, with image-guidance based on CT/MRI images (List separately in addition to code for primary procedure)
HCPC Codes	**Description**
S2900	Surgical techniques requiring use of robotic surgical system (list separately in addition to code for primary procedure)

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
03/04/2014	03/04/2014[MPC], 04/01/2014[MPC], 02/03/2015[MPC], 12/01/2015[MPC], 10/04/2016[MPC], 08/01/2017[MPC], 07/10/2018[MPC], 07/09/2019[MPC], 07/07/2020[MPC], 07/06/2021[MPC], 07/05/2022[MPC], 07/11/2023[MPC]	07/25/2023

[MPC] Medical Policy Committee

Revision History	Description

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09/08/2015	Revised LCD Non-Covered Services L34886
05/04/2020	Updated the Non-Medicare statement to match the Kaiser Permanente Payment Policy for Robotic Assisted Surgery
07/07/2020	Added Medicare LCA (A57642)
07/06/2021	Removed retired Medicare LCD (L35008) and LCA (A57642) for non-covered services. Added statement that policy does not apply to Medicare members.
07/25/2023	Added retired Medicare LCD (L35008) and LCA (A57642) for non-covered services. Removed statement that policy does not apply to Medicare members for clarity to reference Medicare.

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Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Sacral Nerve Stimulator for Fecal and Urinary Incontinence

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Sacral Nerve Stimulator for Urinary Incontinence (230.18)
Local Coverage Determinations (LCD)	None
Local Coverage Article	Sacral Nerve Stimulation for Urinary and Fecal Incontinence (A53017)

For Non-Medicare Members

Kaiser Permanente has elected to use the MCG* Implanted Electrical Stimulator, Sacral Nerve (A-0645) for medical necessity determinations. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.

__The MCG are proprietary and cannot be published and/or distributed__. However, on an individual member basis, Kaiser Permanente can share a copy of the specific criteria document used to make a utilization management decision. If one of your patients is being reviewed using these criteria, you may request a copy of the criteria by calling the Kaiser Permanente Clinical Review staff at 1-800-289-1363 or access the MCG Guideline Index using the link provided above.

If requesting these services, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Fecal incontinence is the inability to control the loss of fecal matter from the bowel. Management of fecal incontinence includes conservative therapy, such as dietary and lifestyle changes, antidiarrheal medications, biofeedback therapy, absorbent pads, and anal plugs, as well as surgical interventions, such as direct sphincter repair and implantation of an artificial sphincter (Mowatt 2007, Tan 2011).

Sacral nerve stimulation is a treatment option for patients who have failed or could not tolerate conservative therapy. It involves applying electrical stimulation to a sacral nerve via an electrode that is placed through the corresponding sacral foramen. In order to be a candidate for sacral nerve stimulation, patients must undergo a testing phase known as peripheral nerve evaluation to determine if the treatment might prove effective. The peripheral nerve evaluation determines the feasibility of electrode implantation and involves a 2 to 3-week period of stimulation with a temporary electrode to assess the potential benefits of the therapy. If significant benefit is achieved, patients may undergo permanent implantation. The exact mechanism of action through which sacral nerve stimulation provides its therapeutic effect is unclear (Mowatt 2007, Pettie 2012, Tan 2011).

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The InterStim® Therapy System (Medtronic Inc., Minneapolis, MN) is a sacral nerve stimulation device that has been approved by the FDA to treat chronic fecal incontinence in patients who have failed or could not tolerate conservative treatments.

Evidence and Source Documents

Bladder Pacemaker /Sacral Nerve Stimulation for Treatment of Urinary Incontinence
Sacral Nerve Stimulator for Fecal Incontinence

Medical Technology Assessment Committee (MTAC)

Bladder Pacemaker /Sacral Nerve Stimulation for Treatment of Urinary Incontinence

BACKGROUND

Urinary incontinence (UI) refers to an involuntary leak of urine. There are several types of UI. Stress UI, the most common form, is an involuntary leak on effort or exertion and urge UI is an involuntary leak accompanied or immediately preceded by a sense of urgency. Mixed UI is a combination of stress and urge UI. A related condition is urinary retention, the inability to completely empty the bladder. Another diagnosis is overactive bladder syndrome (OAB), an urge that occurs with us without a leak of urine, and usually occurs with increased urinary frequency and nocturia. The condition is often categorized as either OAB dry (without incontinence) or OAB wet (with incontinence). The prevalence of urinary incontinence in women is approximately 50% when defined as any urine loss and is 8-36% when limited to bothersome urine loss. About half of all cases are stress incontinence. Urinary incontinence that is severe enough it cannot be easily concealed can have a major impact on quality of life, especially if it includes urinary urgency. Severe urinary incontinence has been found to increase the risk of urinary tract infections in post-menopausal women, and the risk of falls and hip fractures in elderly women (Gray, 2005). Treatments for urge incontinence include the use of absorbent pads, bladder training/pelvic floor muscle exercises, treatment with medications (anti-cholinergic agents, antispasmodics, tricyclic antidepressants), topical estrogen, pelvic floor electrical stimulation, and surgery. The most common treatment for urinary retention is self-catheterization. Sacral nerve stimulation using an implantable device (bladder pacemaker) is proposed as an additional alternative to surgery for patients with urge incontinence, urgency-frequency symptoms or urinary retention. (It is not proposed for stress incontinence, the most common form of urinary incontinence). The InterStim Therapy for Urinary Control is an FDA-approved device developed by Medtronic. Consistent with the protocol in clinical trials, patients undergo percutaneous test stimulation in an outpatient setting before implantation. This involves insertion of an electrode into a sacral foramen. An external device produces continuous stimulation. The implantable InterStim system uses an implanted lead stimulating the appropriate sacral nerve root, most commonly S3. The proximal part of the lead is tunneled under the skin and connected to the neurostimulator which is placed in a subcutaneous pocket in the lower abdomen. The physician can use a microprocessor-based console programmer to set stimulation settings. There is also a handheld programmer that patients can use to turn the stimulator on and off, and to adjust the voltage output amplitude. The battery operating the device is expected to last 7 to 9 years. It is challenging to evaluate the efficacy of treatments for urinary incontinence because there is no gold standard for outcome assessment. In addition, there is a high placebo effect in randomized incontinence studies; as many as 30-40% of patients in placebo groups report success. The high placebo effect has been attributed to several factors including the strong subjective component in voiding dysfunction, and potentially therapeutic effects of study design components such as keeping a voiding diary and interacting with study personnel (Dmochowski, 2001). Because of the high placebo effect, in order to show that an intervention is effective, it is necessary to show that it has an impact beyond that of a placebo. Sacral nerve stimulation for urinary incontinence was reviewed by MTAC in February 1999 and February 2001. The technology did not meet MTAC evaluation criteria. An evidence update was conducted outside of MTAC in October 2002. The GHP Urology Department has requested an updated review.

01/2001: MTAC REVIEW

Bladder Pacemaker /Sacral Nerve Stimulation for Treatment of Urinary Incontinence

Evidence Conclusion: The Schmidt et al. study found a significant improvement in urinary incontinence symptoms at 6 months among patients who received an InterStim device compared to patients receiving standard medical treatment. This study has several threats to validity including substantial selective loss to follow-up, self-report data and lack of blinding or intention-to-treat analysis. Moreover, the research team had with financial ties to the manufacturer of the device. Due to the potential biases in this study, the existing data are insufficient to permit conclusions about the effectiveness of this technology.

Articles: Eleven articles were identified. Six articles were not directly relevant, did not include clinical outcomes or were review articles; five articles presented empirical data on clinical outcomes. Articles were selected based on study type. There were three randomized controlled trials (RCTs) and two case series. The three RCTs were done by a single group of investigators. Only one of the 3 RCTs were examining urinary incontinence as the

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outcome. An evidence table was created for this RCT: Schmidt RA, Jonas U, Oelson KA, Janknegt RA, Hassouna MM, Siegel SW, Kerrebroek for the Sacral Nerve Stimulation Study Group. J Urol 1999; 162: 352-57. See Evidence Table.

The use of sacral nerve stimulation for the treatment of urinary incontinence does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

10/2002: MTAC REVIEW
Bladder Pacemaker /Sacral Nerve Stimulation for Treatment of Urinary Incontinence
Evidence Conclusion: The RCT that generated the three reports was done by the same multinational research team and was funded by Medtronic, the device manufacturer. All of the three first authors had financial relationships with Medtronic. The articles reviewed included the identical intervention for urology patients with different presenting symptoms (urge incontinence, urgency-frequency and non-obstructive urinary retention) and were limited by the same biases. The RCT compared implantation of the Interstim device to standard medical treatment for 6 months, among patients who demonstrated during a 3-7-day testing period that they responded to the Interstim device. All found that sacral nerve stimulation was superior to standard medical care during the 6 months before patients in the control group were offered implantation. Bias was introduced because 1) only patients who were shown to respond to the device were included (about 45% of otherwise eligible patients); 2) Treatment was not blinded and did not allow for a placebo effect of the Interstim device and; 3) The intervention was compared to standard medical treatment, which the patients had already failed. A more valid comparison would be to implant the device in all eligible patients and randomly assign patients to receive active stimulation or no stimulation (this type of placebo control group was used in studies of biventricular pacing).
Articles: The search yielded 17 articles, many of which were review articles, opinion pieces, dealt with technical aspects of the procedures or addressed other, similar treatments. There were three articles on a single randomized controlled trial and five case series. The three RCT articles reported on different patient populations enrolled in the same trial (those with urge incontinence, urgency-frequency and non-obstructive urinary retention) and were all critically appraised. The Schmidt study was included in the February 2001 MTAC review. Evidence tables were created for the following articles: Schmidt RA, Jonas U, Oleson KA et al. Sacral nerve stimulation for treatment of refractory urinary urge incontinence. *J Urol* 1999; 162: 352-357. See Evidence Table. Hassouna MM, Siegel SW, Lycklama AAB et al. Sacral neuromodulation in the treatment of urgency-frequency symptoms: A multicenter study on efficacy and safety. *J Urol* 2000; 163: 1849-1854. See Evidence Table. Jonas U, Fowler J, Chancellor B et al. Efficacy of sacral nerve stimulation for urinary retention: Results 18 months after implantation. *J Urol* 2001 165: 15-19. See Evidence Table.

The use of sacral nerve stimulation for the treatment of urinary incontinence does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

10/01/2007: MTAC REVIEW
Bladder Pacemaker /Sacral Nerve Stimulation for Treatment of Urinary Incontinence
Evidence Conclusion: The RCT that generated the three reports was done by the same multinational research team and was funded by Medtronic, the device manufacturer. All of the three first authors had financial relationships with Medtronic. The articles reviewed included the identical intervention for urology patients with different presenting symptoms (urge incontinence, urgency-frequency and non-obstructive urinary retention) and were limited by the same biases. The RCT compared implantation of the InterStim device to standard medical treatment for 6 months, among patients who demonstrated in a 3-7-day testing period that they responded to the device. All found that sacral nerve stimulation was superior to standard medical care during the 6 months before patients in the control group were offered implantation. Bias was introduced because 1) only patients who were shown to respond to the device were included (about 45% of otherwise eligible patients); 2) treatment was not blinded and did not allow for a placebo effect of the InterStim device and; 3) the intervention was compared to standard medical treatment, which the patients had already failed. A more valid comparison would be to implant the device in all eligible patients and randomly assign patients to receive active stimulation or no stimulation (this type of placebo control group was used in studies of biventricular pacing). An alternative study design to evaluate the effectiveness of InterStim among patients who respond to a test trial would be to compare InterStim to a different treatment that patients had not already failed. Especially in a non-blinded study with some subjective outcomes, bias can be introduced if one group perceives that they are receiving a new and innovative treatment and the other group is receiving the same treatment they have already received. There are no new RCTs to supplement the above data.
Articles: The ideal study would be a randomized controlled trial comparing InterStim therapy to a placebo and/or established alternative intervention. At the time of the 2002 evidence review, conducted outside of the MTAC meeting, there were several RCTs by the same group of investigators. The RCTs compared InterStim to standard medical therapy. No new RCTs evaluating the efficacy and/or safety of the InterStim device were identified. There

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was one additional publication on the original RCT, evaluating psychosocial outcomes in a subset of the study population (Das et al., 2004; Urol). One new RCT was identified on a related topic, comparing two methods for predicting which patients would proceed to device implantation (Borawski et al., 2007). The study did not compare the effectiveness of InterStim treatment compared to placebo or an alternative treatment and was thus not reviewed further. In addition, there were several new case series with sample sizes of approximately 30 patients. Since higher grade evidence has been published, the small case series were not reviewed. *The RCTs on InterStim that have been critically appraised are:* Schmidt RA, Jonas U, Oelson KA et al. for the Sacral Nerve Stimulation Study Group. J Urol 1999; 162: 352-57. See Evidence Table. Hassouna MM, Siegel SW, Lycklama AAB et al. Sacral neuromodulation in the treatment of urgency-frequency symptoms: A multicenter study on efficacy and safety. J Urol 2000; 163: 1849-1854. See Evidence Table. Jonas U, Fowler J, Chancellor B et al. Efficacy of sacral nerve stimulation for urinary retention: Results 18 months after implantation. J Urol 2001 165: 15-19. See Evidence Table.

The use of sacral nerve stimulation for the treatment of urinary incontinence does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Sacral Nerve Stimulator

2/11/2013: MTAC REVIEW

Evidence Conclusion: Based on evidence from one randomized controlled trial and several observational studies, the Kaiser Medical Technology Assessment Team found that the evidence on the safety and efficacy of sacral nerve stimulation for treating severe fecal incontinence is of insufficient quality and quantity to determine whether sacral nerve stimulation is medically appropriate for the treatment of fecal incontinence. The best evidence comes from the randomized controlled trial conducted by Tjandra and colleagues (see below) (Kaiser 2011).

Results from a RCT that included 120 patients with severe fecal incontinence suggest that compared to optimal medical therapy patients who were treated with sacral nerve stimulation had significantly fewer incontinence episodes per week, days with incontinence, days with straining, and significantly better quality of life at 12 months. Adverse events included pain at implant site, seroma, and excessive tingling in the vaginal region. All patients in the sacral nerve stimulation group needed the program readjusted. The mean number of readjustments per person was three. Adjustments included changes in the electrode used for stimulation as well as changes in amplitude and rate. This study had several limitations: power was not assessed, results are only applicable to patients with severe incontinence, and patients included in the study were refractory to medical therapy and pelvic floor exercises, which was the control group treatment (Tjandra 2008).

Outcomes at 12 months (Tjandra 2008)

	SNS	Control	P-value
	mean ± standard deviation		
Incontinence episodes/week	3.1±10.1	9.4±11.8	<0.05
Days with incontinence/week	1.0±1.7	3.1±1.8	<0.05
Days with straining/week	1.4±2.0	4.5±2.3	<0.05
Days using pads/week	2.2±3.0	3.2±3.1	0.085
Fecal incontinence quality of life (FIQL) index*			
Lifestyle	3.3±0.7	2.3±0.9	<0.05
Coping/behavior	2.7±0.9	1.9±0.9	<0.05
Depression/self-perception	3.3±0.8	2.6±0.8	<0.05
Embarrassment	2.8±0.9	1.8±0.6	<0.05

Abbreviations: SNS= sacral nerve stimulation.
* FIQL score range= 1 to 4 with a higher score indicating better quality of life.

Conclusion: There is limited evidence on the safety and efficacy of sacral nerve stimulation for the treatment of fecal incontinence.

Articles: In February 2011, Kaiser Permanente's Medical Technology Assessment Team reviewed implantable sacral nerve stimulators for fecal incontinence. The randomized controlled trial that was included in the Kaiser technology assessment was also selected for review as this was the highest quality study assessing the effects of sacral nerve stimulation for the treatment of fecal incontinence. Since the Kaiser Technology Assessment, several observational studies were identified that evaluated the effects of sacral nerve stimulation. None of these studies were selected for review as they did not compare sacral nerve stimulation to other treatments.

The following study and technology assessment were selected for review: Kaiser Permanente. Implantable sacral nerve stimulators for severe fecal incontinence. February 2011;
http://pkc.kp.org/national/cpg/intc/topics/03_19_125.html
Accessed November 6, 2012.

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The use of Sacral Nerve Stimulation for Fecal Incontinence meets the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® Codes	Description
64561	Percutaneous implantation of neurostimulator electrode array; sacral nerve (transforaminal placement) including image guidance, if performed
64581	Open implantation of neurostimulator electrode array; sacral nerve (transforaminal placement)
64590	Insertion or replacement of peripheral or gastric neurostimulator pulse generator or receiver, direct or inductive coupling
HCPC Codes	**Description**
C1767	Generator, neurostimulator (implantable), nonrechargeable
C1778	Lead, neurostimulator (implantable)
C1820	Generator, neurostimulator (implantable), with rechargeable battery and charging system

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
3/5/2013	03/05/2013[MDCRPC], 11/03/2013 [MPC], 09/02/14 [MPC], 11/04/2014 [MPC] ,09/01/2015 [MPC], 07/05/2016[MPC], 06/06/2017[MPC], 04/03/2018[MPC], 04/02/2019[MPC], 04/07/2020[MPC], 04/06/2021[MPC], 04/05/2022[MPC], 04/04/2023[MPC]	04/18/2023

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
11/04/2014	MPC approved to adopt MCG* Implanted Electrical Stimulator, Sacral Nerve (A-0645) for medical necessity determinations for non-Medicare members
12/09/2015	Added LCA and CPT codes
04/07/2020	Added CPT codes 64590 and 64595
04/18/2023	Updated Medicare Billing and coding A53017

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Clinical Review Criteria
Seat Lift Chair (Mechanism Only)

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Seat Lift (280.4)
Local Coverage Determinations (LCD)	Seat Lift Mechanism (L33801)
Local Coverage Article	Seat Lift Mechanisms – Policy Article (A52518)

For Non-Medicare Members

I. A seat lift mechanism is covered if **All of the following** criteria are met:
   A. Has DME benefit
   B. The patient must have severe arthritis of the hip or knee or have a severe neuromuscular disease.
   C. The seat lift mechanism must be a part of the physician's course of treatment and be prescribed to effect improvement, or arrest or retard deterioration in the patient's condition.
   D. The patient must be completely incapable of standing up from a regular armchair or any chair in their home. (The fact that a patient has difficulty or is even incapable of getting up from a chair, particularly a low chair, is not sufficient justification for a seat lift mechanism. Almost all patients who are capable of ambulating can get out of an ordinary chair if the seat height is appropriate and the chair has arms.)
   E. Once standing, the patient must have the ability to ambulate.

II. Coverage of seat lift mechanisms is limited to those types which operate smoothly, can be controlled by the patient, and effectively assist a patient in standing up and sitting down without other assistance. Excluded from coverage is the type of lift which operates by a spring release mechanism with a sudden, catapult-like motion and jolts the patient from a seated to a standing position.

III. Coverage is limited to the seat lift mechanism, even if it is incorporated into a chair (E0627). Payment for a seat lift mechanism incorporated into a chair (E0627) is based on the allowance for the least costly alternative (E0628, E0629).

IV. The physician ordering the seat lift mechanism must be the treating physician or a consulting physician for the disease or condition resulting in the need for a seat lift. The physician's record must document that all appropriate therapeutic modalities (e.g., medication, physical therapy) to enable the patient to transfer from a chair to a standing position have been tried and failed.

This criteria set is not applicable to seat lift mechanisms for wheelchairs. Please see the Mobility Assistive Devices criteria.

If requesting this service (*or these services*), please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist including details outlined in criteria above

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Background

The seat-lift mechanism is a device that is installed in a chair to help the patient to stand when they are unable to do so from a low chair that has arm rests to support the patient to a standing position. It should be one of those devices that operates smoothly, can be controlled by the patient, and effectively assists a patient standing up and sitting down without assistance.

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
E0627	Seat lift mechanism, electric, any type
E0629	Seat lift mechanism, nonelectric, any type
E0172	Seat lift mechanism placed over or on top of toilet, any type

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Creation Date	Review Dates	Date Last Revised
05/01/1998	08/03/2010[MDCRPC],06/07/2011[MDCRPC],04/03/2012[MDCRPC], 02/05/2013[MDCRPC], 12/03/2013[MPC], 10/07/2014[MPC], 08/04/2015[MPC], 06/07/2016[MPC], 04/04/2017[MPC], 02/06/2018[MPC], 01/08/2019[MPC], 01/07/2020[MPC], 01/05/2021[MPC], 01/04/2022[MPC], 01/10/2023[MPC], 01/09/2024[MPC]	02/16/2022

[MDCRPC] Medical Director Clinical Review and Policy Committee

[MPC] Medical Policy Committee

Revision History	Description
02/16/2022	Updated applicable codes

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Clinical Review Criteria
Sensory Integration Therapy (SIT)

- For children with developmental and behavioral disorders

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	Medicare Benefit Policy Manual, Chapter 15, Coverage of Outpatient Rehabilitation Therapy Services
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article	None

For Non-Medicare Members

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist

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Background

The sensory integration (SI) framework was first described by an occupational therapist Jean Ayres, PhD, in the early 1970s and refers to the body's way of handling and processing sensory inputs from the environment. This was based on a theory that the sensory system develops over time just like other higher order learning skills (such as cognition, language, and academic performance) and that deficits can occur in the process of developing a well-organized sensory system. A well-organized sensory system can integrate input from multiple sources primarily the three basic senses: vestibular, proprioceptive, and tactile. The vestibular system responds to gravity and movement, and the proprioceptive system receives inputs from joints and muscles. When these systems interact with the tactile sensation, sensory integration takes place. Normally, effective sensory integration occurs automatically, unconsciously, and without effort, but for some children it does not develop as efficiently as it should. Any dysfunction or disorder in the SI process may lead to problems in learning, response to sensory input, behavior, or motor development. According to Ayres' theory these could be manifested as coordination problems; unusually high or low activity level; delays in speech, language, or motor skills; delays in academic achievements; under-reactivity to sensory stimulation; sensitivity to touch, movements, sounds, or sights; poor organization of behavior; lack of self-control; poor self-concept; and other signs and symptoms (Ayres 1972, 1977).

Based on her theory, Ayres developed the sensory integration therapy (SIT) with the goal of improving the way the brain processes and adapts to sensory information, as opposed to teaching specific skills. The therapy involves activities that are believed to organize the sensory system by providing vestibular, proprioceptive, and tactile

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sensory input. Techniques used include vestibular stimulation such as swinging in a hammock, using swing balls, bounce pads or scooter boards; tactile stimulation achieved by brushing parts of the child's body or the use of weighted vests and other clothing (Ayres 1977).

Since that sensory integration dysfunction was described, sensory-based therapies have been increasingly used by occupational therapists and other health professionals to treat children with a range of symptoms and disabilities including autism, attention deficit hyperactivity disorder, fragile-x syndrome, brain injuries and others (Zimmer 2014). SIT is usually provided by certified therapists with special training and mentorship in the theory, techniques, and assessment tools unique to sensory integration theory. It is delivered in one-on-one sessions individualized to the child, one to three times a week, for several months or years. In these therapy sessions, the therapists combine primitive forms of sensation with motor activities according to a manualized protocol (Schaaf 2014).

Some authors distinguish sensory integration therapy from sensory-based interventions (SBIs) which are adult-directed sensory strategies that are applied to the child, most often in the school environment, to improve behaviors associated with modulation disorders. SBIs require less engagement of the child and are integrated into his/her daily routine to improve behavioral regulation (Case-Smith 2014).

SIT is controversial and a topic for debate by many professionals in medicine, psychology, and education (May-Benson 2010). According to a Policy Statement from the American Academy of Pediatrics on SIT (Zimmer et al, 2012) proponents of SI theory believe that inappropriate or deficient sensory processing is a developmental disorder responsive to therapy and that treatment can improve developmental outcomes. A definition of sensory processing disorder has been proposed but is not universally accepted. Standardized measures such as the Sensory Profile have been developed to classify a child's sensory deficit. However, the possible diagnosis of a sensory processing disorder remains a challenging clinical issue, and it is unclear whether children who present with findings described as sensory processing difficulties have an actual disorder of the sensory pathway of the brain or that the deficits observed are associated with other developmental and behavioral disorders. The symptoms described in children with sensory processing disorders, overlap the behavioral differences seen in children with autism spectrum disorders, attention-deficit hyperactivity disorder, and developmental coordination disorders. Evaluating the effectiveness of sensory integration therapy presents another challenge due to the wide spectrum of symptom severity and presentation of the disorder, variations in response due to several factors, and lack of consistent outcome measures (Zimmer 2012).

SIT is a therapy and thus it is not regulated by the FDA. SIT has been reviewed by MTAC earlier in 2005 and did not meet the committee's evaluation criteria. It is being re-reviewed based on requests for its coverage.

Medical Technology Assessment Committee (MTAC)

Sensory Integration Therapy

11/28/2005: MTAC REVIEW

Evidence Conclusion: The results of Vargus' (1999) meta-analysis show that sensory integration therapy was not more effective than other alternative therapies in improving psychoeducational, behavior, language, motor, and sensory perceptual functions among the groups studied. The studies included in the meta-analysis did not provide sufficient data on the ages of participants, the types of disabilities, or details on therapies provided. There were also variations and differences in the characteristics of the participants, intervention methods, hours of therapy received, ratio of therapists to children, evaluation of the therapy, duration between therapy and re-testing, and outcomes measured. The authors of the meta-analysis were thus unable to determine the effect of sensory integration therapy among different ages or among individuals with different types of disabilities.
Humphries and colleagues (1992) compared sensory integrative therapy among children with learning disabilities and sensory integration dysfunction to another active treatment (perceptual-motor training), and to no treatment. There were some significant baseline differences between the study groups, and both the sensory integrative therapy and the perceptual-motor therapy were performed by the same occupational therapists, which may be a potential source of bias. Their results show significant pretest-posttest differences between the three groups in the motor functions but not in the psychoeducational variables. The difference in the motor performance between the two active therapies was statistically insignificant. In conclusion, the current literature does not provide a clear definition or description of the sensory integration therapy and does not provide evidence that the therapy is more effective than an alternative therapy or no treatment for children with learning disabilities, or neurodevelopmental delay.
Articles: The search yielded 126 publications, the majority of which were review articles. There were four systematic reviews; two meta-analyses: Ottenbacher 1982 and Vargus 1998; an article combining the results of only two studies (Kaplan 1993); and a number of controlled trials. Many of the studies revealed by the search were

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conducted in the 1970s and 1980s, their sample sizes varied from 10 to 92 participants, and the majority were poorly controlled. The search on the use of sensory integration therapy for autistic children revealed one small case series with 10 children. The most recent meta-analysis and a randomized controlled trial (RCT) were critically appraised. The RCT selected was included in the meta-analysis but was reviewed, as it was the largest trial identified and had a relatively better-quality design. *Evidence tables were made for the following studies:* Vargas S, Camilli G. A meta-analysis of research on sensory integration treatment. Am J Occup Ther. 1999; 53:198-198. See Evidence Table 1. Humphries T, Wright M, Snider L, McDougal B. A comparison of the effectiveness of sensory integrative therapy and perceptual-motor training in treating children with learning disabilities. J Dev Behav Pediatr. 1992; 13:31-40. See Evidence Table 1.

The use of Sensory integration therapy in the treatment of neuro-developmentally delayed children does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

12/06/2015: MTAC REVIEW
Sensory Integration Therapy
Evidence Conclusion: The results of the meta-analysis (Vargus, et al, 1999) reviewed earlier for MTAC suggested that the benefits of sensory integration therapy on psychoeducational and motor functions was significantly better than no treatment among the individuals studied, but it was not superior to other alternative treatments. The authors cautioned about interpreting the results and concluded that there was insufficient evidence to determine the effectiveness of the SI approach. The search for more recent evidence after that last review identified a pilot trial that investigated the effectiveness of SI interventions in children with autism spectrum disorders, a RCT that compared SIT to usual care in children with autism, and a larger RCT that compared SIT to two other active treatments and a control among children with mild mental retardation. Schaaf and colleagues, 2014 (Evidence table 1), randomly assigned 32 children aged 4-8 years, with autism and sensory difficulties to either an occupational therapy/sensory intervention (OT/SI) group or a control group. The study was randomized, and controlled, with proper randomization procedure, and power analysis. However, it was very small and parents who rated their child's goals and other outcomes were not blinded to the treatment allocation, which is a source of bias. In addition, the OT/SI was not compared to an alternative occupational therapy with the same intensity and duration of intervention. The overall results showed significant positive improvement in Goal Attainment Scores (GAS) in the two study groups, but children in the OT/SI group scored significantly higher than the controls.
The only other statistically significant differences between the two groups were for the less care-giver assistance during self-care, and social activities observed in the treatment group. There were no statistically significant differences between the study groups in adaptive behaviors. The authors concluded that the results of the study provide preliminary support for the efficacy of manualized SI intervention. They however, noted that the results should be interpreted with caution until they are replicated in future larger studies. Pfeiffer and colleagues, 2011 (Evidence table 2), conducted a pilot trial to identify appropriate outcome measures, and address the effectiveness of sensory integration (SI) interventions in children with autism spectrum disorders (ASD). They randomized 37 children with ASD, 6-12 year of age to undergo either a fine motor (FM) or sensory integration therapy. Pretests and posttests measured social responsiveness, sensory processing, functional motor skills, and social-emotional factors. The study was randomized, controlled, and blinded. However, it was a small pilot trial with no power analysis or follow-up after the therapy ended. Its overall results showed significant positive improvement in GAS in the two study groups. Children in the SIT group had more significant changes in GAS and improvement in mannerism vs. those in the FM group. The differences in the other outcomes were statistically insignificant. The authors discussed limitations to the study and suggestions for future studies. They explained that standardized measures for determining progress are often inappropriate for children on the autistic spectrum because of the wide variety in behavior and developmental levels among the children, and their ability to complete the test while maintaining its validity. The authors also indicated that another challenge for using a standardized measure is the fact that the SIT forms, activities, and goals are individualized to the specific needs of each child, resulting in a wide range of goals and outcomes among the participants within a study. Wuang and colleagues, 2009 (Evidence table 3) compared the effect of SIT, neurodevelopmental treatment (NDT), and perceptual-motor (PM) approach, and no treatment in 160 children 7-8 years of age with mild mental retardation. 120 were randomly assigned to one of the three active treatments and 40 children who fulfilled the inclusion criteria but could not attend the sessions because of its timing, were not randomized, did not receive any intervention during the study period, but were used as controls.
Each of the active interventions was delivered in a 1-hr. session 3 days per week for 40 weeks, and the children were assessed with measures of sensorimotor function at baseline and after completion of the study. The results show that postintervention, the active treatment groups significantly outperformed the control group on almost all measures. The SIT group demonstrated a greater pretest-posttest change on fine motor, upper-limb coordination, and SI functioning. The PM group showed significant gains in gross motor skills, whereas the NDT group had the smallest change in most measures. The study had its advantages and limitations discussed in evidence table 3. Among the limitations is the inclusion of a selected group of patients, non-adjusting for confounding factors, and a lack of long-term follow-up. The authors recommended that the results be replicated in more studies with long- term

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follow-up. A 2012 Policy Statement by the American Academy of Pediatrics on sensory integration therapies for children with developmental and behavioral disorders states that is unclear whether children who present with sensory-based problems have an actual "disorder" of the sensory pathways of the brain or whether these deficits are characteristics associated with other developmental and behavioral disorders. Because there is no universally accepted framework for diagnosis, sensory processing disorder generally should not be diagnosed. Other developmental and behavioral disorders must always be considered, and a thorough evaluation should be completed. Difficulty tolerating or processing sensory information is a characteristic that may be seen in many developmental behavioral disorders, including autism spectrum disorders, attention-deficit/hyperactivity disorder, developmental coordination disorders, and childhood anxiety disorders. Occupational therapy with the use of sensory-based therapies may be acceptable as one of the components of a comprehensive treatment plan. However, parents should be informed that the amount of research regarding the effectiveness of sensory integration therapy is limited and inconclusive. Important roles for pediatricians and other clinicians may include discussing these limitations with parents, talking with families about a trial period of sensory integration therapy, and teaching families how to evaluate the effectiveness of a therapy (Zimmer 2012).

Conclusion: The evidence remains insufficient to support the effectiveness of sensory integration therapy in improving the behaviors and functional skills in children with developmental and/or behavioral disorders. Due to the individual nature of SIT and the large variation in individual therapists and patients, large multicenter randomized controlled trials among a more diverse population, with blinded assessment, and long-term follow-up are needed to determine the effectiveness the efficacy of this therapy and durability of outcomes.

Articles: The search for studies published after the 2005 MTAC review, revealed over 150 publications, the majority of which were unrelated to the current review. There were three systematic reviews without meta-analyses, two small RCTs among children with autism spectrum disorders (ASD), one quasi-randomized trial among children with mild mental retardation, a number of small non-randomized comparative studies, observational studies with no controls, case series, and case reports on sensory integration therapy for children. The three randomized controlled trials were selected for critical appraisal. Pfeiffer BA, Koenig K, Kinnealey M, et al. Effectiveness of sensory integration interventions in children with autism spectrum disorders: a pilot study. Am J Occup Ther. 2011 Jan-Feb; 65(1):76-85. See Evidence Table 1. Schaaf RC, Benevides T, Mailloux Z, et al. An intervention for sensory difficulties in children with autism: a randomized trial. J Autism Dev Disord. 2014 Jul; 44(7):1493-506. See Evidence Table 2. Wuang YP, Wang CC, Huang MH, et al. Prospective study of the effect of sensory integration, neurodevelopmental treatment, and perceptual-motor therapy on the sensorimotor performance in children with mild mental retardation. Am J Occup Ther. 2009 Jul-Aug; 63(4):441-452. See Evidence Table 3.

The use of Sensory Integration Therapy does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

04/11/2022: MTAC REVIEW
Sensory Integration Therapy

Evidence Conclusion: The evidence remains insufficient to determine the safety and effectiveness of sensory integration therapy in improving the behavior and functional skills in children with ASD or other developmental and/or behavioral disorders. The published trials evaluating the effectiveness of ASI as described by Ayres, in improving the behavior and functional skills in children with developmental and/or behavioral disorders are limited by their small number, sample sizes, variable outcome measures, lack of blinding when parent-reported outcome measures used, and the short study durations. Due to these limitations, the published trials and the qualitative systematic reviews only provide low strength evidence suggesting that SIT may lead to some improvement in subsets of sensory and motor skills in selected children with ASD. None of the three published RCTs had a long-term follow-up to determine the safety of the intervention on the child and /or therapist, as well as durability of the observed effects. Large double-blinded, multicenter RCTs in children diagnosed with developmental disorders and sensory processing problems; that adhere to the core principles of ASI, using the Fidelity Measure of ASI; with an active comparator and blinded assessment of objective outcomes sensitive to the changes expected following ASI intervention; and with long-term follow-up, are needed to determine the safety, effectiveness, and durability of outcomes of the therapy.

Articles: PubMed and Cochrane database were searched from November 2014 through February 2022, using the search terms: sensory integration, sensory integrative dysfunction; sensory processing disorder, sensory integration therapy, SIT, learning disability, ASD, autism, neuro-developmental delay, and Ayres sensory integration, with variations.The search was limited to English-language publications in peer-reviewed journals, among human populations, and children 0-18 years. Experimental studies, abstracts, case reports, case series with less than 25 patients, reviews, comments, and editorials were excluded. Preference was given to meta-analyses and randomized controlled trials reporting clinical outcomes. Reference lists and PubMed related articles were also examined for

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additional articles. To identify ongoing clinical trials, a search of the National Institute of Health Clinical Trials website https://clinicaltrials.gov/ was conducted using the same methodology. See Evidence Tables.

The use of Sensory Integration Therapy does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Non-Medicare - Considered Not Medically Necessary:

CPT® Codes	Description
97533	Sensory integrative techniques to enhance sensory processing and promote adaptive responses to environmental demands, direct (one-on-one) patient contact, each 15 minutes

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
10/30/2005	10/30/2005[MDCRPC], 01/06/2015[MPC], 11/03/2015 [MPC], 09/06/2016[MPC], 07/11/2017[MPC], 06/05/2018[MPC], 06/04/2019[MPC], 06/02/2020[MPC], 06/01/2021[MPC], 06/07/2022[MPC], 06/06/2023[MPC]	06/07/2022

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
06/07/2022	Added April 2022 MTAC review; MPC approved to adopt MTAC's recommendation of non-coverage and continue existing the policy of insufficient evidence

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KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria

Serum Biomarker Tests for Multiple Sclerosis

- gMS®Dx Testing
- gMS®Pro EDSS Testing

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Cytogenetic Studies (190.3)
Local Coverage Determinations (LCD)	None
Local Coverage Article	None

For Non-Medicare Members

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist

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Background

Multiple sclerosis (MS) is a chronic illness of the central nervous system. Diagnosis of MS can be very difficult as there are no clinical findings that are unique to MS. The revised McDonald's Criteria, which incorporated clinical, radiologic, and laboratory findings are often used to diagnose MS. However, because the use of these criteria frequently results in delayed diagnosis, researchers have been trying to find reliable biomarkers that would help to establish a diagnosis (Harris 2009).

The **gMS®Dx test**, a new blood-based test for MS biomarkers, was developed by Glycominds to help physicians identify patients with a high probability of developing MS. The biomarker used in the gMS®Dx test is based on IgM antibodies against the a-glucose antigen (GAGA4). The test is designed to be used in patients as a part of the MS diagnostic work-up and is recommended for use in suspected MS patients for which the diagnosis of MS has not yet been confirmed. The results of the test are reported as negative (patient may still have MS or other neurological disease, continue with routine testing), positive (patient has a high likelihood of having MS), high positive (patient has a very high likelihood of having MS) (Glycominds 2012). One advantage of the gMS®Dx test is that blood samples are relatively easy to obtain and are minimally invasive. A limitation of using biomarkers for diagnosing MS is that they may be affected by other systematic events such as viral infections (Harris 2009). An additional limitation of the gMS®Dx test is that the biologic basis for the MS biomarker is unclear (Freeman 2009).

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Multiple sclerosis (MS) is a complex disease with heterogeneous clinical presentation and disease course. Because prognosis is so hard to predict there has been interest in indentifying biomarkers that are associated with disease progression (Harris 2009).

Glycominds has developed the **gMS®Pro EDSS test**, a blood-based test that uses biomarkers to identify patients at high risk for severe disease progression. The biomarkers used in the gMS®Pro EDSS test are based on IgM antibodies against the a-glucose antigen (GAGA2, GAGA3, GAGA4, GAGA6). The aim of this test is to help clinicians choose the most appropriate disease treatment. The test is designed for use in patients at their first episode and for patients with relapse-remitting multiple sclerosis during their first decade of the disease. The results of the test are reported as negative (patient has a low risk to fast disability progression as measured by EDSS) or positive (patient has a high risk to fast disability progression as measured by EDSS) (Glycominds 2012). One advantage of the gMS®Pro EDSS test is that blood samples are relatively easy to obtain and are minimally invasive. A limitation of using biomarkers for diagnosing MS is that biomarkers may be affected by other systematic events such as viral infections (Harris 2009). An additional limitation of the gMS®Pro EDSS test is that the biologic basis for the MS biomarkers is unclear (Freeman 2009).

Medical Technology Assessment Committee (MTAC)

gMS®Dx and gMS®Pro EDSS

06/18/2012: MTAC REVIEW

Evidence Conclusion: Diagnostic accuracy**:** Results from a recent observational study with several limitations suggest that the gMS®Dx test has a sensitivity or 33.7% (95% CI, 30.2 to 37.3) and a specificity of 98.5% (95% CI, 91.7 to 100) for differentiating relapsing remitting multiple sclerosis (RRMS)/secondary progressive multiple sclerosis (SPMS) from other neurological disorders (Brettschneider 2009). Impact on diagnosis: There is insufficient evidence to determine whether the gMS®Dx test will impact diagnosis. Impact on patient management: There is insufficient evidence to determine whether the gMS®Dx test will change patient's management. Conclusion: Diagnostic accuracy: Weak evidence suggest that the gMS®Dx test has a sensitivity or 33.7% and a specificity of 98.5% for differentiating RRMS/SPMS from other neurological disorders. Impact on diagnosis: There is insufficient evidence to determine whether the gMS®Dx test will impact diagnosis. Impact on patient management: There is insufficient evidence to determine whether the gMS®Dx test will change patient's management.

gMS®Pro EDSS testing

06/18/2012: MTAC REVIEW

Evidence Conclusion: Accuracy: A prospective cohort study that included 286 patients with clinically isolated syndrome (CIS) evaluated the prognostic value of the gMS®Pro EDSS test. Results from this study suggest that that the gMS®Pro EDSS test does not significantly predict prognosis, conversion to McDonald MS, or EDSS progression in patients with CIS. Results from this study should be interpreted with caution as this is an exploratory analysis (Freedman 2011). Results from a retrospective study of 100 RRMS patients taken at their first presentation of RRMS suggest that using a panel of 4 different antibodies had a sensitivity of 37.9% and a specificity of 83.3% for predicting early relapse in patients with RRMS following their first presentation. Results from this study should be interpreted with caution as this is a retrospective exploratory analysis (Freedman 2009). Impact on patient management: No studies were identified that address the impact of gMS®Pro EDSS on patient's management. Conclusion: Accuracy: There is insufficient evidence to determine the accuracy of the gMS®Pro EDSS test. Impact on patient management: There is insufficient evidence to determine whether the gMS®Pro EDSS test will change patient's management.

Articles: gMS®Dx test: Several observational studies were identified that addressed the diagnostic accuracy of the gMS®Dx test. The largest study was selected for review. No studies were identified that addressed the impact of the test on diagnosis or patient's management. The following study was selected for review: Brettschneider J, Jaskowski TD, Tumani H, et al. Serum anti-GAGA4 IgM antibodies differentiate relapsing remitting and secondary progressive multiple sclerosis from primary progressive multiple sclerosis and other neurological diseases. J Neuroimmunol. 2009; 217:95-101. **gMS®Pro EDSS test**: Two studies were identified that addressed the accuracy of the gMS®Pro EDSS test. No studies were identified that addressed the clinical utility of the gMS®Pro EDSS test. The following study was selected for review: Freedman M, Metzig C, Kappos L, et al. Predictive nature of IgM anti-alpha-glucose serum biomarker for relapse activity and EDSS progression in CIS patients: a BENEFIT study analysis. Mult Scler. 2011. [Epub ahead of print] See Evidence Table. Freedman MS, Laks J, Dotan N, Altstock RT, Dukler A, Sindic CJ. Anti-alpha-glucose-based glycan IgM antibodies predict relapse activity in multiple sclerosis after the first neurological event. Mult Scler. 2009; 15:422-430. See Evidence Table.

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The use of gMS®Dx and gMS®Pro EDSS testing does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Considered Not Medically Necessary:

CPT® or HCPC Codes	Description
No specific codes for this service. Often submitted with unlisted code 84999.	

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[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description

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KAISER PERMANENTE®

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Clinical Review Criteria
Supervised Exercise Therapy on Patients with Intermittent Claudication from Peripheral Vascular Disease (SET for IC in PAD)

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Supervised Exercise Therapy (SET) for Symptomatic Peripheral Artery Disease (PAD) (20.35)
Local Coverage Determinations (LCD)	None
Local Coverage Article	None

For Non-Medicare Members

Kaiser Permanente considers medical supervision of peripheral vascular rehabilitation programs medically necessary for the treatment of persons with symptomatic peripheral artery disease (PAD) (i.e., intermittent claudication).

Program Description

- Up to 36 sessions over a 12-week period are considered medically necessary if **ALL of the following** components of a supervised exercise therapy (SET) program are met:
  - consist of sessions lasting 30-60 minutes comprising a therapeutic exercise-training program for PAD in members with claudication; *and*
  - be conducted in a hospital outpatient setting, or a physician's office; *and*
  - be delivered by qualified auxiliary personnel to ensure benefits exceed harms, and who are trained in exercise therapy for PAD; *and*
  - be under the direct supervision of a physician, physician assistant, or nurse practitioner/clinical nurse specialist trained in both basic and advanced life support techniques; *and*
  - Member must have a face-to-face visit with the physician responsible for PAD treatment to obtain the referral for SET program. At this visit, the member must receive information regarding cardiovascular disease and PAD risk factor reduction, which could include education, counseling, behavioral interventions, and outcome assessments.

Kaiser Permanente considers medical supervision of peripheral vascular rehabilitation programs experimental and investigational for persons with absolute contraindications to exercise and for all other indications because the value of such supervision for other indications is not well documented by the available peer-reviewed published medical literature.

Kaiser Permanente considers the PADnet System and testing program experimental and investigational for evaluation of peripheral artery disease and other indications because of insufficient evidence of its effectiveness.

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Background

Atherosclerosis is a systemic disease that affects arteries of different sizes including large and medium arteries. Atherosclerosis narrows the lumen of the arteries because of an accumulation of fibrous material in the inner layers of the arteries. When the arteries of the lower extremities are affected, the disease is called lower extremity peripheral artery disease (PAD) (Linda Harris et al., 2019).

The prevalence of lower extremity PAD is less than 12% but increases after the age of 40. Risk factors for peripheral artery disease are the same as those for coronary disease. These include smoking, hypertension, hypercholesterolemia, diabetes, and metabolic syndrome. Other factors include age, gender, ethnicity, family history and genetic influences, and homocysteinemia (Hageman, Fokkenrood, Gommans, van den Houten, & Teijink, 2018) (Linda Harris et al., 2019).
Symptoms of peripheral artery disease include lower extremity pain, nonhealing wound or ulcer, skin discoloration or gangrene. Lower extremity pain includes pain in the calf, thigh, buttock, or foot. The pain is associated with activity and relieved with rest (intermittent claudication). The pain can be atypical or occurs at rest (ischemic rest pain). Intermittent claudication, the most common symptom, is defined as a leg pain that occurs during walking, forces the patient to stop walking, and resolves after 10 minutes of rest, after which the patient can resume walking with pain occurring again after walking the same distance. Claudication can be unilateral or bilateral. Ischemic rest pain is due to diffuse ischemia and is limited to the forefoot and toes. The pain can be diffuse and severe with numbness, paralysis of the extremity, pallor, coolness, and lack of pulses (David Neschis et al., 2019).

Diagnosis is made with history of risk factors, symptoms of PAD, and physical examination. However, ankle-brachial index (ABI) ≤0.9 establishes the diagnosis in individuals with atypical symptoms or ambiguous pulse examination (David Neschis et al., 2019).

The objective of the treatment is to control the claudication and reduce the risk of cardiovascular disease complications. Treatment can be medical or surgical. Initial treatment includes cardiovascular risk modification, exercise, and pharmacotherapy. In the absence of improvement after initial treatment, revascularization (percutaneous intervention, surgical bypass) is recommended. For patients with lifestyle-limiting claudication, cilostazol (100 mg twice daily) may be indicated (Mark Davies et al., 2019).

Nevertheless, it seems that exercise, particularly supervised exercise therapy, is the mainstay of the treatment for improving walking performance and quality of life (Hageman, Fokkenrood, Gommans, van den Houten, & Teijink, 2018).

Supervised exercise therapy (SET) consists of several sessions, on a treadmill, lasting 45 to 60 minutes per session. Each session comprises 35 minutes of intermittent walking including 5 to 10 minutes of warm-up and cool-down periods. In addition, five minutes are added to the walking time to allow the patient to achieve 50 minutes of intermittent walking. SET consists of three weekly sessions lasting more than three months. During the exercise, medical professionals such as physiologist, physical therapist, or nurse supervise the sessions on person to person basis and monitor patient's claudication threshold and cardiovascular system. If there is suspicion of angina, or the patient is unable to continue the exercise, he or she is referred to a physician (Mark Davies et al., 2019).

Medical Technology Assessment Committee (MTAC)

Supervised Exercise Therapy on patients with intermittent claudication from peripheral vascular disease (SET for IC in PAD)

Date: 10/14/2019

Evidence Conclusion:

- Moderate-quality evidence indicates that supervised exercise therapy may be more effective than usual care or placebo or walking advice in terms of walking performances in patients with intermittent claudication due to atherosclerosis who are fit for exercise on the short-term.
- Moderate evidence suggests that supervised exercise therapy may improve quality of life compared to usual care, or placebo in patients with intermittent claudication due to peripheral artery disease on the short-term.
- The evidence is insufficient to draw conclusion on the effectiveness of supervised exercise therapy vs medications.

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Date Sent: 3/29/24
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- Moderate-quality evidence indicates that SET may be more effective than unsupervised exercise therapy on the short-term. However, there is no difference in quality of life between the groups.

Articles: PubMed was searched through September 2019 with the following search terms: Supervised Exercise Therapy AND (intermittent claudication OR peripheral vascular disease) with the filter meta-analysis. Randomized controlled trials were also searched for. The search was limited to English language publications and human populations. The reference lists of relevant studies were reviewed to identify additional publications. The search yielded twenty-six items, but 17 were selected after reading their titles. Of the 17 articles, two were thoroughly reviewed. See Evidence Table.

The use of Supervised Exercise Therapy on patients with intermittent claudication from peripheral vascular disease (SET for IC in PAD) does meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
93668	Peripheral arterial disease (PAD) rehabilitation, per session

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed	Date Last Revised
10/14/2019	11/05/2019[MPC] ,11/03/2020[MPC], 11/02/2021[MPC], 11/01/2022[MPC], 11/07/2023[MPC]	01/07/2020

[MPC] Medical Policy Committee

Revision History	Description
11/05/2019	MPC approved to adopt clinical criteria for commercial members
01/07/2020	MPC approved proposed criteria for commercial members

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Date Sent: 3/29/24
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Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Sex-Hormone Binding Globulin (SHBG)

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Criteria

For Medicare and Non-Medicare Members

Medical necessity review no longer required.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Causes of abnormal SHBG include the following:

- Increased SHBG concentrations: aging, hyperthyroidism, high estrogen concentrations, liver disease, HIV, anti-seizure drugs
- Decreased SHBG concentrations: moderate obesity, insulin resistance, type 2 diabetes, hypothyroidism, growth hormone excess, exogenous androgens/anabolic steroids, glucocorticoids, progestins, nephrotic syndrome
- Free testosterone — If serum free testosterone concentration is measured, the following points should be kept in mind:
  - Serum free testosterone should be performed by equilibrium dialysis and only in those few laboratories that specialize in endocrine testing.
  - The free testosterone concentration, as calculated from the total testosterone, SHBG, and albumin concentrations, may also be reliable, but there are many different equations for this calculation and they give vastly different results, some of which reflect the results obtained by equilibrium dialysis better than others. Consequently, it is essential that the result be compared with the normal range for the laboratory that performed the assay.
  - Free testosterone measured by an analog method, which is the assay most commonly offered by hospital and commercial laboratories, does not correlate with the results of equilibrium dialysis. This test gives misleading information and should never be ordered.
  - The problem with the analog method was illustrated in a study in which sera from patients who had a variety of SHBG concentrations were assayed by each of the above methods. The results using each of the assays correlated well with the results using each of the other methods, except for free testosterone by the analog method, in which the results were both systematically lower than in the other methods and varied as a function of SHBG.
  - Bioavailable testosterone, ie, the total of free testosterone and that bound weakly to albumin, which is not precipitated by ammonium sulfate, also appears to accurately reflect androgen status.

When during the day should the serum testosterone concentration be measured? — Interpretation of serum testosterone measurements in young men should take into consideration its diurnal fluctuation, which reaches a maximum at about 8 AM and a minimum, approximately 70 percent of the maximum, at about 8 PM. It is easier to distinguish subnormal from normal when normal is higher, so the measurements should always be made in the

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morning, ideally between 8 to 10 AM. Food, especially glucose ingestion, also decreases the serum testosterone concentration, so the blood should also be drawn fasting.

How often should testosterone be measured? — The serum testosterone concentration fluctuates somewhat even early in the morning, although to a limited degree. If a single 8 to 10 AM value is well within the normal range, testosterone production can be assumed to be normal. If a single 8 to 10 AM value is low or borderline low or does not fit with the clinical findings, the measurement should be repeated once or twice before making the diagnosis of hypogonadism. If the results are equivocal, measurement of free testosterone can be considered.

Sex hormone-binding globulin (SHBG) is a serum protein that binds to circulating androgens and estrogens, specifically testosterone and estradiol, with high affinity and serves as a transporter/reservoir. It is believed that SHBG regulates the access and action of these hormones. Initially it was thought that when bound to SHBG these sex hormones were biologically inactive. However, emerging evidence suggests that even sex hormones bound to SHBG may be biologically active. SHBG is produced mainly in the liver; however, other tissues including the placenta, testis, brain, and endometrium also produce SHBG. Age and obesity along with a variety of hormonal, nutritional, metabolic, and genetic factors have been found to influence the production of SHBG. Several conditions such as diabetes, polycystic ovarian syndrome, obesity, hypothyroidism, and hyper-insulinemia are associated with low levels of SHBG; however, causality has yet to be proven. Because of SHBG association with type 2 diabetes, there has been growing interest in the use of SHBG levels as a tool for the early identification of this disease (Brand 2010, Dahan 2006, Hoppé 2010, Xita 2010).

Medical Technology Assessment Committee (MTAC)

Sex-Hormone Binding Globulin

02/14/2011: MTAC REVIEW

Evidence Conclusion: *Men:* Two prospective cohort studies evaluated the association between SHBG levels and the risk of type 2 diabetes in men. The first study followed 1,454 men from the Troms study, a population-based prospective cohort study, who did not have diabetes at baseline for a mean of 9.1 years. Seventy-six men were diagnosed with diabetes (incidence rate of 5.8 per 1,000 person years). After controlling for age, HDL-cholesterol, systolic blood pressure, and waist circumference there was no association between SHBG and the risk of diabetes (Vikan 2010). The second study followed 1,128 men aged 40-70 years who participated in the Massachusetts Male Aging Study, a population-based prospective cohort study, for an average of 13 years. Ninety men were diagnosed with diabetes (incidence rate of 6.2 per 1,000 person years). Results from this analysis suggest that in men, even after controlling for age, BMI, high blood pressure, smoking, alcohol intake, and physical activity, SHBG levels were associated with the development of type 2 diabetes (Laksham 2010). It should be noted that the mean levels of SHBG were higher in the Vikan study compared to the Laksham study (52.7 nmol/l vs. 32.0 nmol/l). This may be due to the fact that blood sample were drawn at different times of the day. Diabetes status was determined through self-repot in both studies. Additionally, neither study adjusted for insulin levels, which have been found to inhibit SHBG production. An earlier systematic review and meta-analysis of 3 prospective cohort studies found that men with higher SHBG levels (>28.3 vs. ≤28.3 nmol/l) had a 52% lower risk of type 2 diabetes (RR 0.48, 95%CI 0.33-0.69) (Ding 2006). *Women:* One prospective cohort study was identified that evaluated the association between SHBG levels and the risk of type 2 diabetes in postmenopausal women. In this study, 1,612 women were followed for a median of 4.7 years and 116 women were diagnosed with diabetes. Results from this study suggest that in postmenopausal women SHBG levels are associated with the development of type 2 diabetes even after adjusting for age, race/ethnicity, education, income, family history of diabetes, examination site, insulin resistance, and adiposity.

Relative hazards of developing incident type 2 diabetes by quartile of baseline SHBG level

	Model 1*	Model 2†	Model 3§
		HR (95% CI)	
SHBG (nmol/l)			
Q1 (8.9-37.8)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Q2 (38.0-51.4)	0.39 (0.25-0.61)	0.49 (0.31-0.76)	0.41 (0.24-0.69)
Q3 (51.5-71.5)	0.29 (0.18-0.47)	0.44 (0.26-0.74)	0.53 (0.30-0.92)
Q4 (71.8-255.5)	0.24 (0.14-0.42)	0.43 (0.24-0.76)	0.52 (0.27-0.98)
P-trend	<0.0001	0.0004	0.017

*Adjusted for age, race/ethnicity, education, income, family history of diabetes, and examination site.
†Adjusted for model 1 plus BMI and homeostasis model assessment of insulin resistance (HOMA-IR).
§Adjusted for model 2 plus LDL, HDL, triglycerides, use of lipid-lowering medication, systolic blood pressure, total daily caloric intake, physical activity, smoking, inflammatory factors (IL-6 and CRP), age at menopause, years since menopause, type of menopause, age at first live birth, five or more live births, past use of hormone replacement therapy or oral contraceptive.

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An earlier systematic review and meta-analysis of 2 prospective cohort studies found that women with higher SHBG levels (>60.0 vs. ≤60.0nmol/l) had an 80% lower risk of type 2 diabetes (RR 0.20, 95%CI 0.12-0.30) (Ding 2006). Conclusion: Several observational studies suggest that lower SHBG levels are associated with an increased risk of developing of type 2 diabetes; however, SHBG cut points for determining increased risk have not been established. Additionally, there is insufficient evidence to determine the clinical utility of using SHBG to predict type 2 diabetes.

Articles: The literature search revealed several case-control, cross-sectional, and prospective cohort studies that examined the association between SHBG and the risk of type 2 diabetes. Three recent prospective cohort studies were selected for review. No studies were identified that addressed the clinical utility of using SHBG to predict type 2 diabetes. The following studies were critically appraised: Kalyani RR, Franco M, Dobs AS, et al. The association of endogenous sex hormones, adiposity, and insulin resistance with incident diabetes in postmenopausal women. *J Clin Endocrinol Metab 2009;* 94:4127-4135. See Evidence Table. Lakshman KM, Bhasin S, and Araujo AB. Sex hormone-binding globulin as an independent predictor of incident type 2 diabetes in men. *J Gerontol a Biol Sci Med Sci 2010;* 65A: 503-509. See Evidence Table. Vikan T, Schirmer H, Njolstad I, and Svartberg J. Low testosterone and sex hormone-binding globulin levels and high estradiol levels are independent predictors of type 2 diabetes in men. *Eur J Endocrinol 2010;* 162:747-754. See Evidence Table

The use of SHBG does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Medical necessity review no longer required:

CPT® or HCPC Codes	Description
84270	Sex hormone binding globulin (SHBG)

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
02/14/2011	04/05/2011[MDCRPC], 02/07/2012[MDCRPC],12/04/2012[MDCRPC] ,10/01/2013[MPC], 08/05/2014[MPC], 06/02/2015[MPC], 04/05/2016[MPC], 02/07/2017[MPC], 11/07/2017[MPC], 10/02/2018[MPC], 10/01/2019[MPC], 10/06/2020[MPC] , 10/05/2021[MPC] , 10/04/2022[MPC] , 10/03/2023[MPC]	10/21/2020

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
04/05/2016	Added exclusion language for symptoms of erectile dysfunction, fatigue, impotence or low libido as the medical literature does not support its use in these circumstances.
10/21/2020	Updated criteria to medical necessity review no longer required to align with current review processes.

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Clinical Review Criteria
Extracorporeal Shock Wave Therapy (ESWT)

- Chronic Plantar Fasciitis
- Lateral Epicondylitis (Tennis Elbow)
- Non-Union or Delayed Union Fractures

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article	None
Kaiser Permanente Medical Policy	Due to the absence of an active NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Clinical Review Criteria, **"Extracorporeal Shock Wave Therapy (ESWT)"** for medical necessity determinations. Use the Non-Medicare criteria below.

Non-Medicare Members

Indication	Policy
Chronic Plantar Fasciitis Lateral Epicondylitis (Tennis Elbow) Non-Union or Delayed Union Fractures	There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

If requesting review for this service, please send the following documentation:

- Last 6 months of clinical notes from requesting provider &/or specialist

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Evidence and Source Documents

Extracorporeal Shock Wave Therapy (ESWT) for Delayed or Nonunion Fractures
Extracorporeal Shock Wave Therapy (ESWT) for Chronic Plantar Fasciitis
Extracorporeal Shock Wave Therapy (ESWT) for Lateral Epicondylitis

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Background

Extracorporeal shock waves are characterized by high positive pressure with a rapid rise time and short (microsecond) duration. The shock waves are concentrated into small focal areas of 2 to 8 mm to optimize therapeutic affects and minimize the impact on adjacent tissues. There are several types of shock wave generating systems; they can involve electrohydraulic, electromagnetic or piezoelectric mechanisms. The shape of the pulses differs depending on the mechanism. In all of the systems, shock waves are concentrated by focusing reflectors on the target site. The shock waves can be further localized using imaging modalities such as ultrasound. Beneficial effects are expected to be observed between 6-12 weeks after treatment (Speed 2004; Wilner & Strash, 2004).

Extracorporeal shock wave therapy (ESWT) is used a non-invasive alternative to surgery for patients with chronic plantar fasciitis who have not responded to conservative therapy such as use of orthotics, physical therapy, night splints, heel cups and treatment with non-steroidal anti-inflammatory drugs (NSAIDs). Plantar fasciitis is believed to result from a biochemical imbalance that places abnormal tension on the plantar fascia which leads to inflammation and tension on the calcaneal periosteum. The mechanism by which ESWT relieves symptoms of plantar fasciitis is not known; however, there may be an effect through tissue disruption of the tendinous fibers followed by neovascularization and replenishment of the extracellular matrix (Atkin, 1999; Wilner & Strash, 2004).

The HealthTronics OssaTron (October 2000), Dornier Epos Ultra (January 2002), Medispec Orthospec (April, 2005) and Orthometrix Orbasone (August, 2005) devices have all been approved by the FDA for the treatment of chronic proximal plantar fasciitis in individuals aged 18 or older who have a history of unsuccessful conservative treatments. The OssaTron and Orbasone are electrohydraulic devices, the Epos Ultra uses electromagnetic technology and the Orthospec uses sound waves.

Low-intensity ultrasound treatment was approved by the FDA in 2000 for treating non-union fractures. Healing is delayed in approximately 10% of the fractures that occur in the United States. The definitions of non-unions differ, but a fracture is generally considered to be a non-union if it has not healed by 6-9 months. Factors contributing to the occurrence of delayed unions and non-unions include the location and severity of the fracture, the extent of soft tissue damage, adequacy of stabilization or fixation, and lifestyle factors such as smoking and high alcohol intake (Hadjiargyrou et al., 1998; Biederman et al., 2003).

Some investigators believe that extracorporeal shock wave treatment (ESWT) has greater potential for treating delayed union and non-union fractures than ultrasound. Shockwaves are characterized by high positive pressure with a rapid rise time and short duration. Following the high positive pressure is an exponential decrease in pressure. The low-frequency components of shock waves allow them to pass through fluid and body tissues with less energy loss than ultrasound. Thus, shock wave treatment may be better than ultrasound for penetrating tissues and delivering adequate pressure for stimulation of bone growth (Rompe et al., 2001; Speed 2004; Wilner & Strash, 2004).

ESWT has not been approved by the FDA for treating non-union or delayed union fractures. The use of shock waves for bone repair has been studied in animal models and initial clinical studies.

Extracorporeal shock wave therapy (ESWT) is used as a non-invasive alternative to surgery for patients with soft tissue conditions including lateral epicondylitis (tennis elbow). ESWT is generally reserved for patients who have not responded to conservative therapy such as physical/occupational therapy, bracing or splinting, local steroid injections and non-steroidal anti-inflammatory drugs (NSAIDs).

Lateral epicondylitis is characterized by pain at the epicondyle on the lateral side of the elbow. The etiology is not well known, but it is generally believed to be due to musculotendinous lesions. The onset of pain can occur abruptly after an unaccustomed activity or can develop gradually in individuals who perform activities requiring repetitive and vigorous use of the forearm. Pain is often mild at first but can worsen over time (Buchbinder 2004; Melikyan, 2003).

Medical Technology Assessment Committee (MTAC)

Extracorporeal Shock Wave Therapy (ESWT) for Chronic Plantar Fasciitis

BACKGROUND

Plantar fasciitis is the most common cause of inferior heel pain characterized by deep pain in the plantar aspect of the heel particularly on arising from the bed in the morning. While the pain may subside with activity, in some

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patients it persists, interrupting the activities of daily living. Approximately 10% of people develop this condition throughout their lifetime (Riddle and Schappert 2004). While the etiology has not fully been established, it is believed to result from a biomechanical abnormality that places tension on the plantar fascia and leads to inflammation and tension on the calcaneal periosteum. Several risk factors such as bone spurs, pronated foot type, obesity, limb-length discrepancy and weight-bearing appear to increase the risk of plantar fasciitis (Theodore, Buch et al. 2004). In the past, conservative therapies for plantar fasciitis, such as rest and stretching, have been successful (Digiovanni, Nawoczenski et al. 2006). Orthotics, physical therapy, night splints, heel cups and treatment with non-steroidal anti-inflammatory drugs (NSAIDs) have also been used in acute cases. While conservative therapies are successful in 85%-90% of patients (Gill 1997), there remain some persistent cases of plantar fasciitis. Extracorporeal shock wave therapy (ESWT) is a noninvasive intervention for patients with chronic plantar fasciitis who have not responded to conservative therapy. Thought to be an alternative to surgical intervention, the mechanism by which ESWT relieves symptoms of plantar fasciitis is not fully understood. The shock waves are believed to stimulate an extracellular response causing neovascularization, promoting tissue repair and regeneration (Atkin, 1999; Wilner & Strash, 2004). Shock waves are characterized by high positive pressure with a rapid rise time and short (microsecond) duration and are concentrated into small focal areas to optimize therapeutic effects and minimize the impact on adjacent tissues. With a variety of devices on the market, shock waves might involve electrohydraulic, electromagnetic or piezoelectric mechanisms and, in each case, the shape of the pulse differs. Beneficial effects are expected to be observed between 6-12 weeks after treatment (Speed 2004; Wilner & Strash, 2004). Please only refer to the criteria listed above for coverage determinations conservative management). These include the HealthTronics OssaTron (October 2000), Dornier Epos Ultra (January 2002), Medispec Orthospec (April 2005) and Orthometrix Orbasone (August 2005).

12/2001: MTAC REVIEW
Extracorporeal Shock Wave Therapy (ESWT) for Chronic Plantar Fasciitis
Evidence Conclusion: There were two RCTs evaluating shock wave generating devices for chronic plantar fasciitis. The Ogden study was the only RCT evaluating the OssaTron system. The Rompe study evaluated a similar device, the Siemens Osteostar. The Ogden study had substantial threats to validity including inadequate description of randomization and statistical analysis techniques and incomplete presentation of data. In the Ogden article, a significantly higher proportion of patients in the active treatment group than the placebo group met success criteria at 12 weeks. The Rompe study was single blind and had a small sample size; selection bias is a possibility. Rompe found a significantly greater reduction in pain in the active treatment group compared to the placebo group at 6 weeks. Neither study discussed possible adverse effects of treatment or presented long-term effectiveness data. Articles: The search yielded 10 articles. There were three empirical articles on extracorporeal shock wave treatment for chronic plantar fasciitis using the OssoTron system. One of these articles was a randomized controlled trial and 2 were case series. There were 4 articles on shock wave stimulation using devices other than the OssoTron system, 3 case series and one RCT. The two RCTs were critically appraised: Ogden JA, Alvarez R, Levitt R, Cross GL, Marlow M. Shock wave therapy for chronic proximal plantar fasciitis. Clin Orthop 2001; (387): 47-59. See Evidence Table**.** Rompe JD, Hopf C, Nafe B, Burger R. Low-energy extracorporeal shock wave therapy for painful heel: A prospective single-blind study. Arch Orthop Trauma Surg 1996; 115; 75-79. See Evidence Table.

The use of OssaTron in the treatment of chronic plantar fasciitis does not meet the *Kaiser Permanente Medical Technology Assessment Criteria for effectiveness.*

12/11/2001: MTAC REVIEW
Extracorporeal Shock Wave Therapy (ESWT) for Chronic Plantar Fasciitis
Evidence Conclusion: A new, valid randomized controlled trial (Buchbinder et al.) did not find that treatment with extracorporeal shock wave therapy using a device made by Dornier MedTech America was more effective than placebo treatment for plantar fasciitis. The Buchbinder et al. study was stronger methodologically than previous RCTs (Ogden et al., Rompe et al.) that had suggested that extracorporeal shock wave therapy might be effective. Unlike the earlier studies, Buchbinder et al. was double blind, adequately described the statistical procedures used and did an intention to treat analysis. Buchbinder et al. provides reasonably strong evidence that extracorporeal shock wave therapy does not improve pain and function 12 weeks after treatment in patients with plantar fasciitis. **Articles:** The search yielded five articles, two of which were included in the previous MTAC review. Of the three new articles, two were case series and one was a randomized controlled trial using the Dornier MedTech OPOS Ultra extracorporeal shock wave device. Buchbinder R, Ptasznit R, Gordon J. et al. Ultrasound-guided extracorporeal shock wave therapy for plantar fasciitis. JAMA 2002: 288: 1364-1372. See Evidence Table.

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The use of ESWT in the treatment of chronic plantar fasciitis does not meet the *Kaiser Permanente Medical Technology Assessment Criteria for effectiveness.*

12/08/2004: MTAC REVIEW
Extracorporeal Shock Wave Therapy (ESWT) for Chronic Plantar Fasciitis
Evidence Conclusion: There is conflicting evidence from four double-blind, sham-controlled randomized controlled trials. According to primary outcome assessment at 12 weeks, two of the RCTs reviewed (Buchbinder; Haake) did not find that ESWT was significantly more effective than a sham intervention at 12 weeks while the other two (Theodore; Ogden) did find a significant benefit of ESWT. It is not clear why findings varied. Clinical experts have stated the belief that efficacy is dependent on machine types and study protocols. Three studies used Dornier shock wave devices and the fourth (Ogden) used the OssaTron device. Three studies (all except Buchbinder) only included patients who had failed conservative therapy. The total number of shocks delivered was 2000-4000 in the negative studies and 1500-3800 in the positive studies. The energy of individual impulses may have been lower in the negative studies. Haake used shock waves of 0.08 mJ/mm2 and in Buchbinder, shockwaves varied between 0.02-0.33 mJ/mm2. In the positive studies, shock waves were 0.22 mJ/mm2 and 0.36 mJ/mm2. There were financial links with the device manufacturer in the positive studies, and there did not appear to be links in the negative studies. The studies either had a total of 12 weeks follow-up, or patients were unblinded at 12 months and eligible for other treatments. Therefore, high-quality comparative data on the effectiveness of ESWT beyond 12 weeks are not available. None of the studies reported serious adverse effects associated with ESWT.
Since the highest grade of evidence in previous reviews of this item was randomized controlled trials (RCTs), only RCTs and meta-analyses of RCTs were considered for the update. Ideally, RCTs of shock wave therapy for plantar fasciitis would have the following characteristics: Use a commercially available device Sham-controlled, or use of alternative treatment Double-blind Sufficient statistical power No financial conflicts of interest Long-term follow-up for efficacy and safety
Articles: The search yielded 18 articles, several of which were reviews. There were six publications reporting on five randomized controlled trials (two articles on the same study) and a meta-analysis of both controlled and uncontrolled studies. The meta-analysis was excluded because it was not limited to controlled studies, and only considered articles published through 2000, prior to the initial MTAC review. Three sham-controlled RCTs with sufficient statistical power were critically appraised. One RCT was excluded because it was not sham-controlled and another because it had a small sample size and no evaluation of statistical power. The studies reviewed include: Haake M, Buch M, Schoellner C et al. Extracorporeal shock wave therapy for plantar fasciitis: randomized controlled multicentre trial. BMJ 2003 327:75. See Evidence Table. Theodore GH, Buch M, Amendola A. et al. Extracorporeal shock wave therapy for the treatment of plantar fasciitis. Foot Ank Int 2004; 25: 290-297. See Evidence Table. Ogden JA, Alvarez RG, Levitt RL et al. Electrohydraulic high-energy shock wave treatment for chronic plantar fasciitis. J Bone Joint Surg 2004; 86-A: 2216-2228. See Evidence Table. Buchbinder R, Ptasznit R, Gordon J. et al. Ultrasound-guided extracorporeal shock wave therapy for plantar fasciitis. JAMA 2002: 288: 1364-1372. See Evidence Table.

The use of ESWT in the treatment of chronic plantar fasciitis does not meet the *Kaiser Permanente Medical Technology Assessment Criteria for effectiveness.*

04/02/2007: MTAC REVIEW
Extracorporeal Shock Wave Therapy (ESWT) for Chronic Plantar Fasciitis
Evidence Conclusion: There is some new evidence that ESWT treatment is effective in the short-term (3 months) for treating chronic plantar fasciitis that is unresponsive to conservative therapies. Both randomized controlled trials reviewed for the 2007 MTAC update found significantly greater reduction in pain after 3 months with active ESWT treatment compared to a placebo intervention. Overall, the findings from double-blind placebo-controlled RCTs are mixed. Some, including the two recent studies, have found a significant benefit with ESWT treatment whereas other studies did not. Studies have varied in the type of design used and the protocol e.g. number of sessions, energy level, number of shocks delivered, etc. The positive studies such as the two new studies, but not the negative studies, appear to have financial links with the device manufacturer, although specific biases introduced by industry funding were not identified. The absolute benefit of ESWT in statistically significant studies tended to be small, e.g. 1 point or less difference between groups on a 10-point visual analogue scale. Evidence of long-term effectiveness is lacking. None of the RCTs had blinded assessment of pain outcomes beyond 3 months. None of the studies reported serious adverse effects associated with ESWT. No Cochrane collaboration meta-analysis was identified. The Kaiser Interregional New Technology Committee (INTC) reviewed this topic in November 2006 and concluded that there was insufficient evidence of efficacy based on methodological limitations of studies and lack of long-term follow-up. New RCTs identified in the literature

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search were screened using the same criteria as in the previous MTAC review. These criteria are: Use of a commercially available device Included patients who meet FDA approved indication for treatment Sham-controlled, or use of alternative treatment Double-blind Sufficient statistical power No financial conflicts of interest Long-term follow-up for efficacy and safety

Articles: Four double-blind sham-controlled RCTs have been reviewed by MTAC (Haake et al., 2003; Theodore et al., 2004; Ogden et al., 2004; Buchbinder et al. 2002). Two additional double-blind sham-controlled RCTs conducted with patients who had failed conservative therapy for at least 6 months were identified. Both used commercially available devices. Neither study had long-term follow-up of effectiveness or had financial links with the device manufacturers. These two studies were critically appraised. Other new RCTs were excluded from further review. Two studies (Porter and Shadbolt, 2005; Wang et al., 2006) used ESWT as the initial treatment, not an FDA-approved indication. Another RCT (Rompe et al., 2005) compared two techniques for delivering ESWT; there was no comparison group that did not receive shockwave treatment. References for the critically appraised studies are as follows: Malay DS, Pressman MM, Assili A et al. Extracorporeal shockwave therapy versus placebo for the treatment of chronic proximal plantar fasciitis: Results of a randomized, double-blinded, multicenter intervention trial. J Foot & Ankle Surg 2006; 45(4): 196-210. See Evidence Table. Kudo P, Dainty K, Clarfield M et al. Randomized, placebo-controlled, double-blind clinical trial evaluating the treatment of plantar fasciitis with an extracorporeal shockwave therapy (ESWT) device: A North American Confirmatory Study. J Orthop Res 2006; 24: 115-123. See Evidence Table.

The use of ESWT in the treatment of chronic plantar fasciitis does not meet the *Kaiser Permanente Medical Technology Assessment Criteria* for effectiveness.

04/21/2014: MTAC REVIEW

Extracorporeal Shock Wave Therapy (ESWT) for Chronic Plantar Fasciitis

Evidence Conclusion: While the 2007 MTAC review identified two RCTs to support short-term effectiveness of ESWT when compared with placebo, the cumulative body of evidence (including four RCTs from previous reviews) was conflicting and lacked support of long-term effectiveness. The current literature search identified one meta-analysis pooling data from seven RCTs specifically aimed at examining the effectiveness of ESWT compared to placebo. Three additional trials were identified that compare ESWT to endoscopic plantar fasciotomy (EPF). The meta-analysis by Aqil and colleagues included seven RCTs with strict inclusion criteria. Due to differences in outcome measures and follow-up timeframes, pooled analysis of only four of the included studies was possible. Ultimately, ESWT had favorable results compared with placebo with five of the six included studies reaching significance after short term follow up (12 weeks). (Aqil, Siddiqui et al. 2013). Saxena et al. treated 25 athletes experiencing chronic plantar fasciitis with EPF, ESWT or placebo ESWT (P-ESWT). At one year follow up, the overall Visual analogue Scale (VAS) and Roles and Maudsley (RM) scores showed statistical improvement within both the EPF and ESWT groups. Treatment outcomes in the EPF group were significantly better than both ESWT and P-ESWT. The investigators report, however, that patients enrolled in ESWT were able to continue with their exercise regimen, while the EPF group were delayed in their return to athletic activity by 2.8 months on average (Saxena, Fournier et al. 2013). Radwan and colleagues randomized 65 patients to either ESWT or EPF for the treatment of resistant plantar fasciitis. At follow-up (3 weeks, 3 months and 12 months), both groups achieved progressive improvements, however, the majority of improvements in the ESWT group were seen between week three and week 12 while the EPF group saw more improvement lasting from week three to 12 months post-intervention. With that said, there were no significant differences detected between groups through the different time periods for any measured parameter except for the AOFAS maximum walking distance and gait sub-scores at three weeks (ESWT group p=005 and EPF group, p=002) (Radwan, Mansour et al. 2012). Finally, in 2010 Othman and colleagues prospectively evaluated 37 patients with chronic plantar fasciitis who self-selected either EPF or ESWT treatment after discussion of possible outcomes. Their results maintain similar trends with slightly better results seen in the EPF group but identification of the ESWT intervention as the preferred treatment option due to the benefits of no complications, no immobilization and earlier return to work (Othman and Ragab 2010). In general, study quality was good with randomization and appropriate comparison groups. For the most part, outcome measures were consistent throughout the selected literature, however, the intensity and the frequency of ESWT application varied and sample sizes were relatively small. The results from the recent meta-analysis provide evidence to suggest that ESWT is a safe and effective treatment of chronic plantar fasciitis compared to placebo in the short term. When compared to surgical intervention, however, ESWT does not perform as well. EPF produces better outcomes but is associated with morbidities such as prolonged healing, loss of time from work, nerve injury and tarsal instability. **Conclusion**: There is insufficient evidence from large, well design randomized trials that ESWT is an effective treatment for chronic plantar fasciitis. There is insufficient evidence to support the safety of ESWT as a treatment option for chronic plantar fasciitis. **Articles:** The literature search revealed over 200 publications which included systematic reviews and practice

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Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

recommendations. After articles were screened for randomization and outcome comparison one meta-analysis pooling data from RCTs and three RCTs/clinically controlled trials that compared ESWT with the surgical intervention, endoscopic plantar fasciotomy (EPF), were identified. The following articles were selected for critical appraisal: Aqil A, Siddiqui MRS, Solan M, Redfern DJ, Gulati V, Cobb JP. Extracorporeal shock wave therapy is effective in treating chronic plantar fasciitis: a meta-analysis of RCTs. Clinical Orthopedic Related Research 2013; 471:3645-3652. See Evidence Table. Saxena A, Fournier M, Gerdesmeyer L, Gollwitzer H. Comparison between extracorporeal shockwave therapy, placebo ESWT and endoscopic plantar fasciotomy for the treatment of chronic plantar heel pain in the athlete. Muscles, Ligaments and Tendons Journal 2012;2(4):312-316. See Evidence Table. Radwan YA, Mansour AMR, Badawy WS. Resistant plantar fasciopathy: shock wave versus endoscopic plantar fascial release. International Orthopaedics 2012; 36:2147-2156. See Evidence Table. Othman AMA, Ragab EM. Endoscopic plantar fasciotomy versus extracorporeal shock wave therapy for treatment of chronic plantar fasciitis. Arch Orthop Trauma Surg 2010; 130:1343-1347. See Evidence Table.

The use of ESWT in the treatment of chronic plantar fasciitis does not meet the *Kaiser Permanente Medical Technology Assessment Criteria* for effectiveness.

Extracorporeal Shock Wave Therapy (ESWT) for Lateral Epicondylitis

BACKGROUND

Extracorporeal shock waves are characterized by high positive pressure with a rapid rise time and short (microsecond) duration. The shock waves are concentrated into small focal areas of 2 to 8 mm to optimize therapeutic effects and minimize the impact on adjacent tissues. There are several types of shock wave generating systems; they can involve electrohydraulic, electromagnetic or piezoelectric mechanisms. The shape of the pulses differs depending on the mechanism. In all of the systems, shock waves are concentrated by focusing reflectors on the target site. The shock waves can be further localized using imaging modalities such as ultrasound. Beneficial effects are expected to be observed between 6-12 weeks after treatment (Speed 2004; Wilner & Strash, 2004). Extracorporeal shock wave therapy (ESWT) is used as a non-invasive alternative to surgery for patients with soft tissue conditions including lateral epicondylitis (tennis elbow). ESWT is general reserved for patients who have not responded to conservative therapy such as physical/occupational therapy, bracing or splinting, local steroid injections and non-steroidal anti-inflammatory drugs (NSAIDs). Lateral epicondylitis is characterized by pain at the epicondyle on the lateral side of the elbow. The etiology is not well known, but it is generally believed to be due to musculotendinous lesions. The onset of pain can occur abruptly after an unaccustomed activity or can develop gradually in individuals who perform activities requiring repetitive and vigorous use of the forearm. Pain is often mild at first but can worsen over time (Buchbinder 2004; Melikyan, 2003). Two ESWT devices, the Siemens Sonocur (July 2002) and the HealthTronics OssaTron (March 2003) have been approved by the FDA for the treatment of chronic lateral epicondylitis in individuals age 18 or older who have a history of unsuccessful conservative treatments. The OssaTron is an electrohydraulic device and the Sonocur uses electromagnetic technology. Extracorporeal shockwave therapy for epicondylitis was previously reviewed by MTAC in February,2005 and did not meet MTAC evaluation criteria.

02/07/2005: MTAC REVIEW

Extracorporeal Shock Wave Therapy (ESWT) for Lateral Epicondylitis

Evidence Conclusion: This review evaluated ESWT for patients with epicondylitis who had failed conservative therapy. Three double blind sham-controlled RCTs were identified, with mixed findings. The Melikyan and Haake studies did not find significant differences between the active treatment and control group on any outcome measure. Rompe found that the group receiving active ESWT had a significantly better outcome at 3 months. Pain reduction but not function was better in the treatment group at 12 months. The Melikyan study may have been underpowered (did not discuss power), but the Haake and Rompe studies were planned to have sufficient sample sizes to detect clinically significant differences. Differences in study methodology include whether the use of concurrent conservative treatments was allowed, whether local anesthesia was used during ESWT and the specific shockwave devices used. In the Haake study, patients were not restricted from using conservative treatments after ESWT. Rompe permitted use of other treatments after 3 months. Melikyan did not mention use of additional treatments. The Haake study used local anesthesia during the intervention, but Rompe and Melikyan, one positive and one negative study, did not. (Anesthesia may make it more difficult to locate the area of greatest pain). The Rompe study used the Siemens SONOCUR plus, Melikyan used the Dornier Epos Ultra and Haake used both of these. There were eight articles reporting on seven randomized controlled trials (two publications on the same study). In addition, there was a Cochrane Library review of randomized controlled trials conducted in 2001. The Cochrane review included only two trials, too few for a meaningful meta-analysis. Most of the RCTs identified were published after the Cochrane Review was completed. Individual RCTs were considered for critical

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appraisal. Ideally, RCTs of shock wave therapy for epicondylitis would have the following characteristics: Use a commercially available device, include patients who meet FDA approved indication for treatment, Sham-controlled, or use of alternative treatment, Double-blind, Sufficient statistical power, No financial conflicts of interest, Long-term follow-up for efficacy and safety
Articles: Three of the six RCTs included patients who met the FDA approval criterion of a history of unsuccessful conservative treatment. All of these were double-blind, sham-controlled, used commercially available devices and did not report significant financial conflicts of interest. These three RCTs (four articles) were critically appraised, the citations are as follows: Melikyan EY, Shahin E, Miles J et al. Extracorporeal shock-wave treatment for tennis elbow. J Bone Joint Surg (Br) 2003; 85-B: 852-855. See Evidence Table. Haake M, Konig IR, Decker T. et al. Extracorporeal shock wave therapy in the treatment of lateral epicondylitis. J Bone Joint Surg 2002; 84-A: 1982-1991. Additional data reported in Haake et al. Arch Orthop Trauma Surg 2002; 122: 222-228. See Evidence Table Rompe JD, Decking J. Schoellner C et al. Repetitive low-energy shock wave treatment for chronic epicondylitis in tennis players. Am J Sports Med 2004; 32: 734-743. See Evidence Table.

The use of extracorporeal shock wave treatment in the treatment of lateral epicondylitis does not meet the *Kaiser Permanente Medical Technology Assessment Criteria* for effectiveness.

04/02/2007: **MTAC REVIEW**
Extracorporeal Shock Wave Therapy (ESWT) for Lateral Epicondylitis
Evidence Conclusion: A Cochrane collaboration review concluded that shock wave therapy provides little or no benefit in terms of pain and function in epicondylitis. In meta-analyses of 2 to 3 studies each, shockwave therapy was not significantly better than placebo for the vast majority of outcomes. A limitation of the Cochrane review was that, due to differences in study methods, summary estimates could be obtained only for a few studies at a time, not for all of the trials they identified. Several of the RCTs included in the Cochrane review were examined in greater depth. Three double-blind sham-controlled RCTs, conducted among patients who had failed conservative therapy, were evaluated for the 2005 MTAC review. Findings were mixed. Two studies did not find significant differences between the active treatment and control group on any outcome measure; one of these may have been underpowered. The third found that the group receiving active ESWT had a significantly better outcome at 3 months, and pain reduction but not function was better in the treatment group at 12 months. One additional well-conducted RCT with patients who had failed conservative treatment was identified for this update (Pettrone et al., 2005). The Pettrone study, in which no local anesthesia was used, found that ESWT was significantly more effective than placebo at reducing pain 50% or more after 12 weeks (61% in shockwave group, 29% in placebo group). The new study appeared to be the only RCT evaluated for MTAC in which the authors received a substantial financial contribution from the manufacturer. The body of literature on shockwave therapy for epicondylitis does not permit a clear conclusion about efficacy. Findings from RCTs are contradictory, and a Cochrane review concluded that treatment provides little or no benefit. Differences in outcome may be due in part to variability in study design e.g. type of device, whether or not local anesthesia was used and whether use of any conservative treatments were permitted after ESWT. A Canadian brief technology assessment that searched the literature through March 2005 was identified (CADTH, 2007). There was no quantitative meta-analysis. The authors concluded that results from RCTs have been conflicting. A Cochrane collaboration systematic review was identified that included literature published through February 2005. The meta-analysis in the Cochrane review was of limited scope due to the inability to combine trials with varying methodology e.g. different outcome measures, time frames for analysis, etc. Due to the limited meta-analysis in the Cochrane review, individual RCTs were also examined for this MTAC update. For the previous MTAC review, the following criteria were used to identify the strongest and most relevant RCTs: Use of a commercially available device, Included patients who meet FDA approved indication for treatment, Sham-controlled, or use of alternative treatment, Double-blind, Sufficient statistical power, No financial conflicts of interest, Long-term follow-up for efficacy and safety
Articles: In 2005, the 3 RCTs that most closely met the above criteria were critically appraised. Other RCTs screened at that time did not include patients meeting the FDA-approved criterion of a history of unsuccessful conservative treatment. One new RCT was identified that was placebo-controlled, double-blind, used a commercially available device (Sonocur) and included patients who had failed conservative treatment. The Cochrane review and new RCT were critically appraised: Buchbinder R, Green SE, Youd JM. Shockwave therapy for lateral elbow pain. Cochrane Library 2007: Volume 1. Date of most recent update: March 2006. See Evidence Table.

The use of extracorporeal shock wave treatment in the treatment of lateral epicondylitis does not meet the *Kaiser Permanente Medical Technology Assessment Criteria* for effectiveness.

Extracorporeal Shock Wave Therapy (ESWT) for Delayed or Nonunion Fractures
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BACKGROUND
Healing is delayed in approximately 10% of the fractures that occur in the United States. The definitions of non unions differ, but a fracture is generally considered to be a non-union if it has not healed by 6-9 months. Factors contributing to the occurrence of delayed unions and non-unions include the location and severity of the fracture, the extent of soft tissue damage, adequacy of stabilization or fixation, and lifestyle factors such as smoking and high alcohol intake (Hadjiargyrou et al., 1998; Biederman et al., 2003). Low-intensity ultrasound treatment was approved by the FDA in 2000 for treating non-union fractures. Some investigators believe that extracorporeal shock wave treatment (ESWT) has greater potential for treating delayed union and non-union fractures than ultrasound. Shockwaves are characterized by high positive pressure with a rapid rise time and short duration. Following the high positive pressure is an exponential decrease in pressure. The low-frequency components of shock waves allow them to pass through fluid and body tissues with less energy loss than ultrasound. Thus, shock wave treatment may be better than ultrasound for penetrating tissues and delivering adequate pressure for stimulation of bone growth (Rompe et al., 2001; Speed 2004; Wilner & Strash, 2004). ESWT has not been approved by the FDA for treating non-union or delayed union fractures. The use of shock waves for bone repair has been studied in animal models and initial clinical studies. MTAC has not previously reviewed ESWT for treating delayed or non-union fractures.

02/07/2005: MTAC REVIEW
Extracorporeal Shock Wave Therapy (ESWT) for Delayed or Nonunion Fractures
Evidence Conclusion: There is insufficient evidence to determine whether extracorporeal shock wave treatment is effective for treating delayed unions and non-unions. Only case series data were available; these described the proportion of cases that healed at the end of the study period. Since the studies did not include concurrent comparison or control groups, it is not possible to know what the healing rate in these groups of patients would have been without the shock wave intervention. The authors of both studies that were reviewed called for controlled studies to be conducted. Treatment of delayed unions or non-unions are not FDA-approved indications for ESWT. The search yielded 19 articles, some of which were on related treatments or related conditions. Ideally, studies on the effectiveness of shock wave therapy would have the following characteristics: Randomized controlled trial, Use a commercially available device, Include patients who meet FDA approved indication for treatment, Sham-controlled, or use of alternative treatment, Double-blind, Sufficient statistical power, No financial conflicts of interest, Long-term follow-up for efficacy and safety
Articles: There were no randomized or non-randomized controlled studies. The empirical literature consisted of two prospective and one retrospective case series. The two prospective case series were critically appraised. The citations for the reviewed articles are as follows: Biedermann R, Martin A, Handle G et al. Extracorporeal shock waves in the treatment of nonunions. J Trauma 2003; 54: 936-942. See Evidence Table. Rompe JD, Rosendhl T, Schollner C et al. High-energy extracorporeal shock wave treatment of nonunions. Clin Orthoped Rel Res 2001; 387: 102-111. See Evidence Table.

The use of extracorporeal shock wave treatment in the treatment of delayed union or nonunion fractures does not meet the *Kaiser Permanente Medical Technology Assessment Criteria* for effectiveness.

Applicable Codes

Considered Not Medically Necessary:

CPT® Codes	Description
28890	Extracorporeal shock wave, high energy, performed by a physician or other qualified health care professional, requiring anesthesia other than local, including ultrasound guidance, involving the plantar fascia
0101T	Extracorporeal shock wave involving musculoskeletal system, not otherwise specified, high energy
0102T	Extracorporeal shock wave, high energy, performed by a physician, requiring anesthesia other than local, involving lateral humeral epicondyle
0512T	Extracorporeal shock wave for integumentary wound healing, high energy, including topical application and dressing care; initial wound
0513T	Extracorporeal shock wave for integumentary wound healing, high energy, including topical application and dressing care; each additional wound (List separately in addition to code for primary procedure)

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***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Creation Date	Review Dates	Date Last Revised
12/12/2001	04/06/2010[MDCRPC], 02/11/2011[MDCRPC], 12/06/2011[MDCRPC], 10/02/2012[MDCRPC], 08/06/2013[MPC], 06/03/2014[MPC], 04/07/2015[MPC], 02/02/2016[MPC], 12/06/2016[MPC], 10/03/2017[MPC], 08/07/2018[MPC], 08/06/2019[MPC], 08/04/2020[MPC], 08/03/2021[MPC], 08/02/2022[MPC], 08/07/2023[MPC], 03/12/2024[MPC]	08/04/2020

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
09/08/2015	Revised LCD L35008
07/18/2018	Removed coverage statement for FEHB, Changed the Medicare coverage language for code 28890
08/04/2020	Removed deleted CPT codes 0299T and 0300T; Added CPT codes 0512T and 0513T; removed Medicare LCA A57642

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Clinical Review Criteria
Sacroiliac Joint Fusion (SIJ Fusion)

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	Sacroiliac Joint Injections and procedures (L39464)
Local Coverage Article	Billing and Coding: Sacroiliac Joint Injections and Procedures A59246
Kaiser Permanente Medical Policy	Due to the absence of an active NCD, LCD, or other coverage guidance for ***Open or Percutaneous (minimally invasive) SIJ Fusion,*** Kaiser Permanente has chosen to use their own Clinical Review Criteria for medical necessity determinations. Please refer to the Non-Medicare criteria below. ***Please Note:** Noridian currently does not cover RFA ablation of the SIJ joint. Potential candidates for SIJ fusion must be evaluated on a case-by-case basis regarding this issue referenced in above LCD.

For Non-Medicare Members

A. Open sacroiliac joint fusion is medically necessary when **ALL of the following** are met:
   1. Appropriate imaging studies demonstrate localized sacroiliac joint pathology
   2. The individual is a nonsmoker, or in the absence of progressive neurological compromise will refrain from use of tobacco products for at least 6 weeks prior to the planned surgery
   3. And **ONE of the following**:
      a. Post-traumatic injury of the SI joint (e.g., following pelvic ring fracture)
      b. As an adjunctive treatment for sacroiliac joint infection or sepsis
      c. Management of sacral tumor (e.g., partial sacrectomy)
      d. When performed as part of multisegmental long fusions for the correction of spinal deformity (e.g., idiopathic scoliosis, neuromuscular scoliosis)

B. Open sacroiliac joint fusion is not covered for **ANY** other indication, including the following, because it is considered experimental, investigational or unproven:
   1. Mechanical low back pain
   2. Sacroiliac joint syndrome
   3. Degenerative sacroiliac joint
   4. Radicular pain syndromes

C. Percutaneous or Minimally Invasive sacroiliac joint fusion, using an FDA-approved implant, placed across the SI joint and intended to promote bone fusion, is considered medically necessary for the treatment of low back/buttock pain resulting from degenerative sacroiliitis or sacroiliac joint disruption when **ALL of the following** criteria are met:

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1. Adults 18 years of age or older with sacroiliac joint pain for greater than 6 months (or greater than 18 months for pregnancy induced pelvic girdle pain)

2. Significant pain originating from sacroiliac joint (e.g., pain rating of at least 5 on a 0 to 10 numeric scale)

3. Pain is located at or close to the posterior superior iliac spine (PSIS) with possible radiation into buttocks, posterior thigh, or groin and can point to the location of pain (Fortin Finger Test)

4. Sacroiliac joint diagnosed as etiology of pain by response (pain) to 3 or more provocative examination maneuvers that stress the sacroiliac joint (e.g., FABER test*, thigh thrust*, pelvic gapping test*, pelvic compression*, Gaenslen's test*) *see below for definitions*

5. Clinical documentation that pain limits activities of daily living (ADL).
    a. ADLs are defined as feeding, bathing, dressing, grooming, meal preparation, household chores, and occupational tasks that are required for daily functioning

6. Failure to respond to at least **6** months of alternative treatments consisting of **ALL of the following**
    a. Anti-inflammatory medication, one or more of the following:
        - Non-steroidal anti-inflammatory drugs (oral or topical), unless contraindicated
        - Acetaminophen
    b. A trial of Physical Therapy in the last 12 months, which should include some of the following features:
        - Supervised Physical therapy, attendance at >75% of sessions, minimum of 3 visits

        *If conservative therapy is not appropriate, the medical record must clearly document why such approach is not reasonable.

7. Trials of the following interventions:
    a. At least 2 (two) intraarticular SI joint *steroid* injections (location confirmed by either contrast spread or both A/P and lateral views). If patient fails to get 80% or greater pain relief as measured by a standard pain questionnaire, should have a second steroid injection at least one month later. *If this is unsuccessful in long-term relief, proceed to b.*
    b. Trial of at least 2 (two) *anesthetic* injections in the lateral branch (location confirmed by either contrast spread or both A/P and lateral views), with at least 80% reduction in pain as measured by a standard pain scale, for the expected duration of the anesthetic used. 2 week minimum between the 2 injections.
    c. If anesthetic injection is successful, patient should have an RFA ablation* (*RFA ablation not covered and therefore not required for Medicare patients)*. If the anesthetic injection is not successful, or if post ablation, the pain is not reduced by less than 80% after 1 month, patient should consult with an SI joint surgeon regarding other options.

8. Alternative or contributing diagnoses MUST be absent (e.g., hip osteoarthritis, L5-S1 spine degeneration, tumor, infection, fracture). Diagnostic imaging of the SI Joint should exhibit DJD or disruption but can be read as "normal" as long as the following imaging findings are met:
    a. Imaging (CT or MRI) of the sacroiliac joint excludes the presence of destructive lesions (e.g., tumor, infection) or inflammatory arthropathy of the sacroiliac joint and rules out concomitant hip pathology;
    b. Imaging of the ipsilateral hip (plan radiographs, CT or MRI) that excludes the presence of osteoarthritis
    c. Imaging of the lumbar spine (CT or MRI) that excludes neural compression or other degenerative conditions that can be causing low back or buttock pain

9. There is an absence of generalized pain behavior
    a. (e.g., somatoform disorder)
    b. or generalized pain disorders (e.g., fibromyalgia)

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NOTE: Any operative candidate should be nicotine-free for at least 6 weeks prior to elective surgery. For persons with recent nicotine use (unless there is evidence of cord compression, or other indications for urgent intervention, noted below), documentation of nicotine cessation should include a lab report (not surgeon summary) showing blood or urine nicotine level of 0, drawn within 6 weeks prior to surgery)

NOTE: BMI > 40 is a relative contraindication to SI joint fusion

* Provocative examination maneuvers definitions:

- **Faber (Patrick's) Test:** Applies tensile force on the anterior aspect of the SI joint on the side tested
  Flexion, Abduction and External Rotation (FABER). The patient is supine with one leg extended and the other flexed at the knee. The lateral malleolus of the flexed leg lies across the other leg superior to the patella. The test may also be performed so that the foot of the flexed leg is in contact with the medial aspect of the knee of the contralateral leg. The flexed leg is then allowed to fall into abduction, and from this position the examiner increases the external rotation by increasingly pressing the patient's knee down toward the examining table with one hand. The examiner must immobilize the pelvis on the extended contralateral side to prevent it from moving during the test.

- **Thigh Thrust Test (Posterior Shear Test):** *Applies anteroposterior shear stress on the SI joint*
  Patient lies in supine position with 90 degrees of flexion in the hip and knee on the side being tested. The examiner stabilized the contralateral side of the pelvis over the anterior superior iliac spine ASIS and applied a light manual pressure to the participant's flexed knee along the longitudinal axis of the femur.

- **Pelvic Gapping Test (SIJ distraction test):** Applies tensile forces on the anterior aspect of the SI joints
  Patient lies supine, and the examiner applies a vertically orientated, posteriorly directed force to both the anterior superior iliac spines (ASIS). The presumed effect is a DISTRACTION of the anterior aspect of the SIJ. A test is positive if it reproduces the patient's symptoms. This indicates SIJ dysfunction or a sprain of the anterior sacroiliac ligaments.

- **Pelvic Compression:** Applies compression force across the SI joints
  Patient is placed in a side-lying position, with the affected side up, facing away from the examiner, with a pillow between the knees. The examiner places a steady downward pressure through the anterior aspect of the lateral ilium, between the greater trochanter and ilia crest.

- **Gaenslen's test:** Applies torsional stress on the SI joints
  The patient lies supine with the affected side leg near the edge of the table. For safety, the patient's shoulders are positioned toward the middle of the table. The patient then draws the non-affected side leg into full flexion and holds the flexed knee. The examiner stabilizes the let with their hand placed over the patient's hand. This action keeps the ilium on the non-tested side in a slightly posterior and stable position during the maneuver.

If requesting these services, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist
- Last 6 months of imaging reports (if applicable)

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

The sacroiliac joint (SIJ) connects the sacrum to the pelvis (iliac bone) on each side of the lower spine and transmits the load of the body to the lower extremities. The joint is reinforced by strong ligaments that secure the fit of the joint, and help the sacrum support the weight of the spine and head. The SIJ has a unique anatomy as it is classified as one type of joint anteriorly, and as another posteriorly. In the front, it is synovial and classified as a diarthrodial joint (a freely movable type of joint), while in the back it is fibrous or ligamentous and classified as synarthrodial (an immobile or nearly immobile joint) (Vleeming 2012, Polly 2017, Thawrani 2019).

The unique anatomic and physiologic characteristics of the SIJ makes it vulnerable to unusual mechanical stress or strain. Too much motion (hypermobility), or too little motion (hypomobility) of the joint, may lead to sacroiliac joint pain or dysfunction. This may be caused by a specific traumatic event (disruption) such as a motor vehicle accident, fall, lifting, pregnancy and childbirth; or can develop over time (degeneration) because of osteoarthritis, anatomical abnormalities such as scoliosis, leg length difference as, well as a complication of lumbar or lumbosacral fixation procedures. SIJ pain may be localized to the lower buttocks or radiates into the groin, lower back and lower extremity. It is believed that the SIJ may be the source of up to 15-30% of chronic low back pain (Rashbaum 2017, Polly, 2015, 2016.2017, Dengler 2017. Thawrani 2019).

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The clinical evaluation and diagnosis of SIJ pain is challenging due to the wide variability in its clinical presentation and the overlap with the lumbar spine and hip pains. Back strain from lifting, facet syndrome, disc herniation, inflamed spinal cord roots, and sciatica can be confused with SI joint dysfunction. The joint is not easily palpated or manipulated, and there are no reliable pathognomonic or specific clinical history or physical examination findings. Imaging alone cannot accurately diagnose SJI dysfunction or differentiate between spine. hip, and SIJ pain. Assessing the pain location, patient posture/movement, and provocative manual testing are useful in making a probable diagnosis of SIJ disfunction. The most definitive evaluation is image-guided injection of anesthetic solutions into the joint which is diagnostic if there is at least 75% symptom relief (Polly 2017, Thawrani 2019).

Conservative non-surgical measures including oral analgesics, physical therapy, osteopathic and chiropractic manipulation are typically the first line therapies used for SIJ pain. Periarticular or intraarticular SIJ steroid injection and radiofrequency neurotomy of the sacral never are sometime used as last options of nonoperative management to provide short-term pain relief in some patients, but with variable success and insufficient data on the long-term effectiveness. SIJ fusion has been proposed as a potential option when the nonoperative measure have failed. Surgical fusion of the joint immobilizes the joint and eliminates its motion, which is believed to cause the inflammation and pain (Dangler 2017, Polly 2017 Tran 2019).

Traditional sacroiliac joint fusion is an open surgery that involves an incision to access the joint, removal of cartilaginous material from the joint, and use of bone grafts and screws to help the fusion. Open surgical fusion of SIJ was first reported in the early 1900s. However, it is not routinely used because of the challenges and risks associated with the procedure including the bone harvesting, potential damage to surrounding anatomic structures, intraoperative blood loss, wound size, extended hospital stays, and limits on postoperative weightbearing. Minimally invasive surgical (MIS) methods have thus been introduced over the years to provide the potential benefit of permanent stabilization of the SIJ with smaller surgical incision; less operative time, blood loss, and perioperative morbidity; and potentially faster healing (Heiney 2015.Polly 2016, Dengler 2017).

The minimally invasive SIJ fusion approach and technique differ according to the device used, but in general the steps for performing the procedure are similar. The surgery is generally performed under general anesthesia and fluoroscopy monitoring. With the patient lying face down on the operating table, a 2-3 cm incision is made in the side of the buttock and the gluteal muscles are dissected to access the ilium. A small guide pin is then inserted through the side of the ilium to create a small hole and an opening is then broached or drilled through the ilium to provide passage for the implants to reach the sacrum. If a bone graft is necessary, the SIJ is cleared of cartilage and soft tissues, and a bone graft is packed into the joint space (the bone graft is typically collected from a different area of the ilium or from shavings left behind from broaching the ilium). The implant instruments are guided through the passage in the ilium, and are put into place using screws, pins, or a mallet. For the triangular shaped titanium implants, a second and third device are implanted in the same procedure. The incision site is then irrigated, and the wound closed. Patients requiring treatment in both joints could undergo staged procedures (Rudolf 2012).

Reported adverse events associated with the procedure include neuropathic pain, neural impingement, postoperative hematoma, urinary retention, nausea, vomiting, SIJ pain, trochanteric bursitis, iliac bone fracture, malpositioning of the implant, wound problems, and the need for reoperations. A major risk of SIJ fusion is its failure to alleviate pain. It is also reported that because the SIJ is a key energy transfer mechanism, its fusion may possibly displace the pressure typically absorbed in the pelvis to the lower spine, creating pain and pressure in the lower back (adjacent segment disease). The latter complication was reported in about 5% of sacroiliac joint fusion patients within 6 months of surgery (Schell 2016).

Medical Technology Assessment Committee (MTAC)

Sacroiliac Fusion (SI Fusion) for Sacroiliac Joint Dysfunction

12/08/2014: MTAC REVIEW

Evidence Conclusion: Lower back pain is extremely common and the sacroiliac (SI) joint has been implicated as one of the potential sources dating all the way back to the early 1900s (Goldthwait and Osgood 1905). Formed by the connection of the sacrum and the right and left iliac bones, the SI joint lies at the junction of the spine and the pelvis. Held together by a collection of strong ligaments the SI joint only allows for limited rotation and translation. The SI joint plays a primary role in supporting the weight of the upper body. Pregnancy, gout, rheumatoid arthritis, psoriasis, ankylosing spondylitis, and other conditions that cause abnormal wear may aggravate the joints by placing an increased amount of stress on the SI joints. There are many different terms for SI joint problems,

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including SI joint dysfunction, SI joint syndrome, SI joint strain, and SI joint inflammation. With the most common symptoms being pain, stiffness and burning the diagnosis of SI joint conditions can prove difficult for a multitude of reasons. For starters, there are no widely accepted guidelines for diagnosis and treatment nor has any imaging modality established definitive symptoms that correlate with a visible pathology. These issues are further complicated by the large spectrum of different etiologic factors and variability that contribute to the pain. As a result, diagnosis of SI joint dysfunction relies on thorough history and physical examination. Conventional treatments for SI joint dysfunction typically consist of non-operative interventions such as injections and anti-inflammatory oral medications. However, oral steroids and physical therapy can also be helpful (Ashman, Norvell et al. 2010). In the event that conservative interventions fail, SI joint fusion has been proposed as an additional treatment option. A variety of techniques have been described over the years without the wide acceptance of a single technique. Generally speaking, the surgery entails removal of the cartilage in the SI joints followed by an implant of plates or screws to hold the bones together. The technique may even employ the use of bone grafts to promote fusion. Ultimately, the surgery is designed to eliminate SI joint motion with the overall goal to relieve pain. Several implants have received 501(k) approval from the Food and Drug Administration (FDA) and are detailed in table 1. Minimally invasive (MIS) SI joint fusions have not previously been reviewed by the Medical Technology and Assessment Committee (MTAC) and are currently being reviewed due to increased requests for coverage.
Articles: The literature search revealed just under 200 articles. No randomized control trials (RCTs) comparing MIS SI joint fusion with non-surgical treatment for the treatment of chronic low back pain due to sacroiliac joint dysfunction were identified. The only comparison studies were cohorts investigating MIS SI joint fusion versus open surgical techniques or SI joint denervation and were not selected because they did not include a nonsurgical group. Currently, there are numerous trials registered with the NIHCT set to compare MIS SI joint fusion with conservative management. The majority of the literature base was small and retrospective. The best available publications were two prospective cohorts with no comparison groups and a retrospective medical chart review of 18 patients who underwent MIS SI joint fusion surgery. The following publications were selected for critical appraisal: Wise, CL and Dall, B. Minimally invasive sacroiliac arthrodesis outcomes of a new technique. *J Spinal Disord Tech* 2008;**21**(8):579-584. **[Evidence Table 1]**. Cumming, J and Capobianco, RA. Minimally invasive sacroiliac joint fusion: one-year outcomes in 18 patients. *Annals of Surgical Innovation and Research* 2013;**7**(1):12-18. **[Evidence Table 2]**. Duhon BS, Cher DJ, Wine KD, et al. Safety and 6-month effectiveness of minimally invasive sacroiliac joint fusion: a prospective study. *Medical Devices: Evidence and Research* 2013;**6:**219-229. **[Evidence Table 3]**

Minimally invasive sacroiliac joint fusion, with or without bone grafts and other metal implant devices and does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Sacroiliac Fusion (SI Fusion) for Sacroiliac Joint Dysfunction
04/08/2019: MTAC REVIEW
Evidence Conclusion:

- Moderate quality evidence from two open-label short-term, industry sponsored RCTs with subjective outcomes, suggest that sacroiliac joint fusion using triangular titanium implants may be more effective than conservative measures in reducing pain and improving function at 6 months among selected patients with a confirmed diagnosis of SIJ chronic disabling pain or dysfunction.
- An ideal RCT would be a sham-controlled trial or blinded assessment of the outcomes.
- The SIJ fusion procedure was associated with a low rate of adverse events, but some were severe and required re-operation. Reported adverse events include neuropathic pain, neural impingement, respiratory failure, trochanteric bursitis, iliac bone fracture, wound problems, recurrent SIJ pain, malposition or loosening of the implant, recurrent SIJ pain due to implant malposition, and the need for revision surgeries.
- There is insufficient to determine the net health outcome of the SI fusion procedure.
- There is insufficient evidence from RCTs to determine the long-term comparative efficacy and safety of minimally invasive SIJ fusion versus nonsurgical management of patients with SIJ dysfunction.

Articles: The literature search for studies published after the last MTAC review identified 6 systematic reviews (three with quantitative meta-analyses), two randomized control trials (published in multiple articles) comparing minimally invasive SIJ joint fusion with non-surgical treatment for the treatment of chronic low back pain due to sacroiliac joint dysfunction, one observational study with 4 years follow-up, and a retrospective study with six-years follow-up data. One meta-analysis pooled the results of the two published RCTs together with an observational study to identify the patient characteristics that may predict clinical outcome after surgical or nonsurgical treatment. The two RCT were selected for critical appraisal, and the outcome of the meta-analysis was summarized. See Evidence Table.

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Sacroiliac Joint Fusion (SIJ Fusion) for Sacroiliac Joint Pain/Dysfunction does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Minimally Invasive Sacroiliac Joint Fusion (MIS SIJF) for Sacroiliac Joint Pain/Dysfunction
07/12/2021: MTAC REVIEW
Evidence Conclusion:

- Moderate strength evidence from two open-label, industry sponsored RCTs with subjective outcomes, and high crossover rate after 6 months, suggest that minimally invasive sacroiliac joint fusion using the iFuse TTI system may be more effective (for up to six months) than conservative measures in reducing pain and improving function among selected patients with a confirmed diagnosis of SIJ chronic disabling pain or dysfunction.
- There is insufficient evidence from RCTs with long -term follow-up of patients in their initial randomization group, to determine the long-term comparative efficacy and safety of minimally invasive SIJF versus nonsurgical management of patients with SIJ dysfunction. The crossover of participants from the conservative treatment arm to the SIJF limits the long-term comparative assessment.
- Low-to moderate strength evidence from industry sponsored observational studies suggest that the benefits observed with SIJF using iFuse implanted via the lateral transiliac approach may be sustained for the 24 months follow-up duration.
- There is insufficient evidence to determine the safety and efficacy of the SIJF to patients with other sources of back pain who were excluded from the trials. Also, it is unclear if the procedure may be safe and effective in patients with other chronic disease and comorbidities e.g., osteoporosis, diabetes. cardiovascular diseases and others.
- The publishes studies indicate that SIJF procedure was associated with a low rate of adverse events, but some were severe and required re-operation. Reported adverse events include neuropathic pain, neural impingement, respiratory failure, trochanteric bursitis, iliac bone fracture, wound problems, recurrent SIJ pain, malposition or loosening of the implant, recurrent SIJ pain due to implant malposition, and the need for revision surgeries.
- The comparative studies of minimally invasive procedures evaluated lateral transiliac SIJF using iFuse triangular titanium implants, and the result may not be generalized to other devices or implantation approaches used for SIJF.

Articles: The literature search for studies published after the last MTAC review did not identify any more recent meta-analyses or RCTs on the effectiveness and safety of SIJF compared to nonsurgical therapies. The search however, revealed a report on the two-year follow-up of the iMIA randomized controlled trial reviewed earlier (Dengler, et al, 2019); one observational study assessing the long-term outcomes for patients enrolled in the INSITE randomized controlled trial and the SIFI single-arm prospective multicenter study (LOIS study, Whang et al, 2019); a small observational single-arm study assessing the safety and effectiveness of SIJF using a 3D-printed TTI (Patel et al 2020); a systematic review on the safety profile on minimally invasive SIJF (Shamrock, et al, 2019) a cost utility analysis of MIS SIJF from a National Health Service (NHS) England perspective; and a protocol for a meta-analysis on SIJF versus conservative management for low back pain attributed to the SIJ (Chen et al 2020). See evidence tables.

The two long-term observational follow-up of patients participating in the iMIA and INSITE studies were selected for critical appraisal; and the results of the systematic review on the safety of the procedure was summarized.

Minimally Invasive Sacroiliac Joint Fusion (MIS SIJF) for Sacroiliac Joint Pain/Dysfunction
does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® Codes	Description
27280	Arthrodesis, sacroiliac joint, open, includes obtaining bone graft, including instrumentation, when performed
0775T	Arthrodesis, sacroiliac joint, percutaneous, with image guidance, includes placement of intra-articular implant(s) (eg, bone allograft[s], synthetic device[s])
27279	Arthrodesis, sacroiliac joint, percutaneous or minimally invasive (indirect visualization), with image guidance, includes obtaining bone graft when performed, and placement of transfixing device

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***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed	Date Last Revised
08/27/2014	09/02/2014[MPC], 11/03/2015 [MPC], 09/06/2016[MPC], 07/11/2017[MPC], 05/01/2018[MPC], 05/05/2020[MPC], 05/04/2021[MPC], 05/03/2022[MPC], 05/02/2023[MPC]	04/27/2023

[MPC] Medical Policy Committee

Revision History	Description
06/23/2016	Added NCD/LCD Medical Director review language
09/08/2015	Revised LCD L35008
09/06/2016	Added GH policy for Medicare members and new criteria for non-Medicare members
05/07/2019	MPC approved to adopt policy of non-coverage for SIJ Fusion for Sacroiliac Joint Pain/Dysfunction
05/05/2020	Added Medicare LCD L36000 and LCA A57596 for percutaneous/minimally invasive SIJ fusion Added clarification that policy addresses open and percutaneous/minimally invasive SIJ fusion. Added CPT code 27280.
05/21/2020	Removed Medicare LCD L36000 and LCA A57596 for percutaneous/minimally invasive SIJ fusion as it is from Wisconsin Physicians Service instead of Noridian
09/07/2021	MPC approved to adopt MTAC's recommendation of non-coverage, maintaining a non-coverage policy for Minimally Invasive Sacroiliac Joint Fusion (SIJF). Added MTAC's review from 7/12/2021.
01/10/2023	MPC approved to adopt revised changes to the SI Joint Fusion criteria to allow coverage in certain situations. Requires 60-day notice; effective June 01, 2023.
03/06/2023	Updated applicable CPT code 0775T effective 1/1/23.
04/27/2023	Clarified indications for Medicare due to new LCD not covering RFA ablation of SI Joint.

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Clinical Review Criteria
Subcutaneous Implantable Cardioverter Defibrillator (SICD)

- Substernal Implantable Cardioverter Defibrillator

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	Medicare Claims Processing Manual, Change Request 11605 – Transmittal 4513, section 19: Extravascular Implantable Cardioverter Defibrillator (EV ICD) **Covered if performed as part of an approved Investigational Device Exemption (IDE) study*
National Coverage Determinations (NCD)	Implantable Automatic Defibrillators (20.4)
Local Coverage Determinations (LCD)	None
Local Coverage Article	None

For Non-Medicare Members

The use of the SICD may be considered medically necessary for all appropriate pacemaker patients who meet the following criteria:

A. Have a contraindication to a transvenous ICD due to at least **ONE of the following**:
   1. Lack of adequate vascular access; or
   2. The need to preserve existing vascular access due to chronic dialysis; or
   3. Repeat transvenous ICD placement not indicated due to complications with previous transvenous ICD placement; or
   4. Congenital heart disease; or
   5. Increased risk for bacteremia

The use of the SICD is considered investigational when the above criteria are not met.
The use of a substernal ICD (CPT Codes 0571T-0580T, 0614T) is considered investigational.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Cardiovascular disease is the most common cause of death in the Western world, and sudden cardiac death (SCD) accounts for approximately 60% of all cardiovascular mortality. SCD is responsible for ~300,000 annual deaths in the United States; with ventricular fibrillation (VF) accounting for up to one-third of cases (Zipes 1998, Estes 2011, Majithia 2014, Rhyner 2014).

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The implantable cardioverter defibrillator (ICD) was developed and introduced to clinical practice around the 1980s to address this issue of fatal SCD from ventricular tachyarrhythmia. The ICD continuously monitors the heart, identifies malignant ventricular tachyarrhythmia, and delivers an electric counter shock to restore normal rhythm. The first defibrillator received FDA approval in 1985 to be used in patients who had survived cardiac arrests. In 2002, the FDA expanded its use to patients with a history of a heart attack and depressed heart function. ICDs are widely used and studies have shown significant mortality benefit in selected patients at increased risk of SCD. However, the use of ICDs may at times be complicated with the implantation procedure, programing, device malfunction, and lead performance deterioration by time. Traditionally, the ICD is implanted transvenously by creating a pocket in the subclavicular areas and gaining vascular access to reach the heart. This approach has its drawbacks and is associated with short- and long-term adverse events. Reported complications associated with ICD systems include lead dislodgement, lead fracture, conductor coil breaks, pneumothorax, cardiac perforation, pericardial effusion, cardiac tamponade, and systemic infection. Lead malfunction occurs in up to 40% of the transvenous leads at 8 years after implantation. Lead failure either generates inappropriate shocks or impedes appropriate therapy. Extraction of the lead is recommended in cases of lead fracture, malfunction, or other mechanical problems that prevent safe and effective ICD shock therapies. This extraction is complex and can be associated with significant risks including death (Olde Nordkamp 2012, Weiss 2013, Aziz 2014, Chang 2014Majithia 2014).

The complications associated with the intracardiac leads of the implantable cardioverter defibrillators have led to the development of a totally subcutaneous ICD (S-ICD) with the intention to provide the same protection, but with less procedural and device-related risks. The S-ICD system senses, detects, and treats malignant ventricular tachycardia (VT)/ventricular fibrillation (VF) without requiring vascular access or fluoroscopy. The S-ICD system (model SQ-RX 1010, Cameron Health, Inc., San Clemente, CA) includes a dedicated external programmer, a subcutaneous pulse generator enclosed in a titanium case, and a single subcutaneous electrode containing both sensing and defibrillating components. The lead-electrode is composed of proximal and distal sensing electrodes separated by a shocking coil. The pulse generator is implanted in a subcutaneous pocket created over the fifth intercostal space between the mid and anterior axillary lines. The single lead is tunneled from the xiphoid process to the pocket and to the sternal manubrium joint. Fixation is achieved with the addition of a suture sleeve at the level of the xiphoid and a single suture at the superior parasternal portion of the lead. Implantation of the device relies entirely on anatomic landmarks and does not require fluoroscopy (although some investigators advocate brief screening to verify the final position). The currently used pulse generator weighs 145 g, has a volume of 69 ml, and an estimated 5-year battery life. The greatest advantage of S-ICD is that the lead does not pass through the central veins in the chest, nor is it attached to the tissue within the heart chambers. However, the pulse generator of the S-ICD is approximately twice the volume and weight of the currently used transvenous ICD, which may prevent its use in children, and increase the risk of erosion, discomfort, and infection. In addition, the weight of the device may cause its dislodgement and changes in the shock configuration (Olde Nordkamp 2012, Weiss 2013, Aziz 2014, Chang 2014, Grace 2014, Majithia 2014).

The S-ICD system detects changes in the ventricular rate by using subsurface electrocardiography through a primary, secondary, or alternate vector. The device is programmed to select the vector that best avoids double QRS counting or T-wave oversensing events that could lead to misinterpretation of the rhythm and delivery of inappropriate shock. The heart rate is measured as the average of 4 consecutive sensed intervals. VF is diagnosed when 18 of 24 consecutive sensed events exceed the shock zone limit. Once the system detects a malignant arrhythmia, it delivers up to 80 J shock to terminate the arrhythmia and will automatically reverse polarity if the initial shock fails to terminate the arrhythmia. The mean defibrillation threshold is significantly higher than with transvenous devices, and some investigators suggest that high-energy shocks may be harmful to the myocardium (Aziz 2014, Majithia 2014, Nair 2014).

Unlike the conventional ICD devices, S-ICD is unable to provide long-term bradycardia pacing or antitachycardia pacing due to the absence of an endocardial lead. It is thus not suitable for patients with an indication for antibradycardia pacing or cardiac resynchronization therapy, or for those with a history of repetitive monomorphic ventricular tachycardia that would benefit from antitachycardia pacing. S-ICD may not be used concurrently with unipolar pacemaker as that would interfere with the S-ICD arrhythmia detection. This absence of bradycardia pacing in the S-ICD might lead to more bradycardia related events as syncope or even death. The device may be potentially useful for patients who are not eligible for transvenous ICDs, or are at high risk of complications e.g. subjects with congenital heart disease, complicated vascular anatomy, at high risk of infection, or in patients in whom vascular access is limited or needs to be conserved e.g. for renal dialysis or long-term intravenous drug therapy (Akerstrom 2013, Olde Nordkamp 2012, Chang 2014, Majithia 204).

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S-ICD received US FDA approval in September 2012, “To provide defibrillation therapy for the treatment of life-threatening ventricular tachyarrhythmia in patients who do not have sympathetic bradycardia, incessant (continual) ventricular tachycardia, or spontaneous frequently recurring ventricular tachycardia that is reliably terminated with anti-tachycardia Pacing”. The FDA required that a post-approval registry be created to track outcomes of patients and devices for at least 60 months after implantation.

S-ICD has not been previously reviewed by MTAC; it is being reviewed based on a request for the Clinical Review Unit for coverage decision.

Medical Technology Assessment Committee (MTAC)

Subcutaneous Implantable Cardioverter Defibrillator

10/20/2014: MTAC REVIEW

Evidence Conclusion: The results of the published observational studies suggest that S-ICD may be accurate in detecting and reversing induced ventricular arrhythmias, however, the incidence of inappropriate therapy was as high as 13.1% (in a mean duration of 11 months in Weiss et al 2013). Inappropriate shock therapy may decrease the quality of life and increase the mortality risk.

The published studies evaluated the accuracy, efficacy and safety of S-ICD in reversing induced rather than spontaneous arrhythmias. The arrhythmia is not always predictable and as seen in one study (Kobe 2013) the S-ICD system had to be changed to transvenous ICD in a patient who needed antitachycardia pacing (ATP) therapy. A group of investigators (Gold and colleague 2012) noted that though there is no reason to suspect that electograms may differ between induced and spontaneous rhythms of similar rates and regularity, this possibility of this difference cannot be excluded. *Conclusion:* The results of the published literature indicate that: There is some evidence that S-ICD may be accurate in detecting and reversing induced ventricular arrhythmias. There is insufficient evidence to date, to determine the efficacy or effectiveness to S-ICD in terminating spontaneous VT/VF episodes. S-ICD may lead to inappropriate shock therapy in up to 13.1% of cases. There is insufficient evidence to determine the long-term safety of the S-ICD system. There is insufficient evidence to determine that S-ICD is safer or more effective than conventional transvenous ICD. No randomized controlled trial that compared the two devices head to head was published to date. There is insufficient evidence to determine that the use of S-ICD prevents or reduces sudden death from ventricular arrhythmias.

Articles: The literature search revealed over 300 citations on subcutaneous implantable cardioverter defibrillator. The majority were reviews or opinion pieces. No published RCTs that compared the safety and efficacy of the S-ICD head to head with the conventional transvenous ICD or other therapeutic interventions were identified; only the published rationale and design of the ongoing PRAETORIAN trial that is comparing the subcutaneous to the transvenous implantable defibrillators. There were a number of published observational studies including those that led to the European approval as well as the pivotal study (Weiss et al, 2013) leading to the US Food and Drug Administration approval. The search also identified a paper documenting the early results from the EFFORTLESS S-ICD Registry that was created to document the clinical, system, and patient-related outcome data from patients implanted with S-ICD in multiple centers in Europe and New Zealand. The pivotal prospective study (Weiss et al, 2013) and a study with a comparison group (Kobe 2013) were selected for critical appraisal: Weiss R, Knight BP, Gold MR, et al. Safety and efficacy of a totally subcutaneous implantable-cardioverter defibrillator. Circulation. 2013; 128(9):944-953. See Evidence Table. Köbe J, Reinke F, Meyer C, et al. Implantation and follow-up of totally subcutaneous versus conventional implantable cardioverter-defibrillators: a multicenter case-control study. Heart Rhythm. 2013;10 (1):29-36. See Evidence Table.

The use of Subcutaneous Implantable Cardioverter Defibrillator does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Subcutaneous ICD (SICD)

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
33270	Insertion or replacement of permanent subcutaneous implantable defibrillator system, with subcutaneous electrode, including defibrillation threshold evaluation, induction of arrhythmia, evaluation of sensing for arrhythmia termination, and programming or reprogramming of sensing or therapeutic parameters, when performed

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33271	Insertion of subcutaneous implantable defibrillator electrode
33272	Removal of subcutaneous implantable defibrillator electrode
33273	Repositioning of previously implanted subcutaneous implantable defibrillator electrode
93260	Programming device evaluation (in person) with iterative adjustment of the implantable device to test the function of the device and select optimal permanent programmed values with analysis, review and report by a physician or other qualified health care professional; implantable subcutaneous lead defibrillator system
93261	Interrogation device evaluation (in person) with analysis, review and report by a physician or other qualified health care professional, includes connection, recording and disconnection per patient encounter; implantable subcutaneous lead defibrillator system
93644	Electrophysiologic evaluation of subcutaneous implantable defibrillator (includes defibrillation threshold evaluation, induction of arrhythmia, evaluation of sensing for arrhythmia termination, and programming or reprogramming of sensing or therapeutic parameters)

Substernal ICD

Medicare - Considered medically necessary when performed as part of an approved Investigative Device Exemption (IDE) study:
Non-Medicare – Considered not medically necessary - experimental, investigational or unproven:

CPT® or HCPC Codes	Description
0571T	Insertion or replacement of implantable cardioverter-defibrillator system with substernal electrode(s), including all imaging guidance and electrophysiological evaluation (includes defibrillation threshold evaluation, induction of arrhythmia, evaluation of sensing for arrhythmia termination, and programming or reprogramming of sensing or therapeutic parameters), when performed
0572T	Insertion of substernal implantable defibrillator electrode
0573T	Removal of substernal implantable defibrillator electrode
0574T	Repositioning of previously implanted substernal implantable defibrillator-pacing electrode
0575T	Programming device evaluation (in person) of implantable cardioverter-defibrillator system with substernal electrode, with iterative adjustment of the implantable device to test the function of the device and select optimal permanent programmed values with analysis, review and report by a physician or other qualified health care professional
0576T	Interrogation device evaluation (in person) of implantable cardioverter-defibrillator system with substernal electrode, with analysis, review and report by a physician or other qualified health care professional, includes connection, recording and disconnection per patient encounter
0577T	Electrophysiologic evaluation of implantable cardioverter-defibrillator system with substernal electrode (includes defibrillation threshold evaluation, induction of arrhythmia, evaluation of sensing for arrhythmia termination, and programming or reprogramming of sensing or therapeutic parameters
0578T	Interrogation device evaluation(s) (remote), up to 90 days, substernal lead implantable cardioverter-defibrillator system with interim analysis, review(s) and report(s) by a physician or other qualified health care professional
0579T	Interrogation device evaluation(s) (remote), up to 90 days, substernal lead implantable cardioverter-defibrillator system, remote data acquisition(s), receipt of transmissions and technician review, technical support and distribution of results
0580T	Removal of substernal implantable defibrillator pulse generator only
0614T	Removal and replacement of substernal implantable defibrillator pulse generator

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed	Date Last Revised
10/23/2014	11/04/2014 MPC, 09/01/2015MPC, 07/05/2016MPC, 05/02/2017MPC, 03/06/2018MPC, 03/05/2019MPC, 03/03/2020MPC, 03/02/2021MPC, 03/01/2022MPC , 03/07/2023MPC	03/01/2022

MPC Medical Policy Committee

Revision History	Description
07/18/2016	Added NCD 20.4
09/08/2015	Revised LCD L35008
11/07/2017	MPC approved to adopt criteria for SICD
03/01/2022	Added Medicare links and codes related to substernal ICD, noted that substernal ICD is considered investigational for non-Medicare.

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KAISER PERMANENTE®

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Clinical Review Criteria
Signal-Averaged Electrocardiography (SAECG)

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Kaiser Permanente Clinical Review Criteria are developed to assist in administering plan benefits. These criteria neither offer medical advice nor guarantee coverage. Kaiser Permanente reserves the exclusive right to modify, revoke, suspend or change any or all of these Clinical Review Criteria, at Kaiser Permanente's sole discretion, at any time, with or without notice. **Member contracts differ in health plan benefits. Always consult the patient's Evidence of Coverage or call Kaiser Permanente Member Services at 1-888-901-4636 (TTY 711), Monday through Friday, 8 a.m. to 5 p.m. to determine coverage for a specific medical service.**

Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article (LCA)	None
Kaiser Permanente Medical Policy	Due to the absence of an active NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Clinical Review Criteria, **"*Signal-Averaged Electrocardiography (SAECG)*"** for medical necessity determinations. Use the Non-Medicare criteria below.

For Non-Medicare Members

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

If requesting review for this service, please send the following documentation:

- Last 6 months of clinical notes from requesting provider &/or specialist

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Signal-averaged electrocardiography (SAECG) is a technique involving computerized analysis of small segments of a standard ECG to detect abnormalities that would be otherwise obscured by "background" skeletal muscle activity.

Sudden cardiac death (SCD) is a major health problem worldwide. It has been estimated that between 184,000 and 462,000 Americans die suddenly each year from sustained ventricular tachycardia or ventricular fibrillation. The majority have coronary artery disease and left ventricular dysfunction. Multiple large clinical trials have shown that prophylactic implantable cardioverter defibrillator (ICD) can prevent or abort these arrhythmic events and reduce mortality. It is thus critically important to identify those patients at risk to prevent potentially lethal arrhythmias (Cain 1996, Iravanian 2005, Goldberger 2008, Pandey 2010, Stein 2008).

Several invasive and noninvasive approaches or tests have been studied to stratify the patient with risk of ventricular arrhythmia and sudden death. Noninvasive methods include measurement of QRS duration on the 12-

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lead ECG, measurement of heart rate variability (HRV) and baroreflex sensitivity, detection of non-sustained ventricular tachycardia; signal averaged electrocardiography (SAECG), and several others (Stein 2008).

SAECG was introduced in the 1970s primarily for the detection of patients at high risk of sudden cardiac death after myocardial infarction. It is based on the idea that most life-threatening ventricular arrhythmias are reentrant in nature among patients with structural heart disease. The arrhythmias require an area of slow conduction to allow their perpetuation. These areas of delayed conduction within the ventricular myocardium (ventricular late potentials) can often be demonstrated by invasive electrophysiological studies performed in sinus rhythm. SAECG seeks to detect the occurrence of late activation within the myocardium noninvasively via surface ECG electrodes. It involves computerized analysis of segments of a standard surface ECG to compare and average consecutive QRS complexes (usually around 300) and produce a filtered QRS complex that provides information on the presence of ventricular late potentials (Chandrasekaran 1999, Stein 2008, Liew 2010).

Medical Technology Assessment Committee (MTAC)

Signal-Averaged Electrocardiography (SAECG)

12/19/2011: MTAC REVIEW

Evidence Conclusion: The literature search did not identify any randomized controlled trials that examined the effect of stratifying patients at risk of sudden death based on SAECG, or its effect on improving health outcomes. The results of the published studies showed that the sensitivity of SAECG to predict arrhythmic events ranged from 15% to 75%. It had very low positive predictive value which indicates that it is not a useful when used alone to identify high risk patients. However, SAECG had a high negative predictive value, which may indicate that it could potentially be useful in identifying low-risk patients. Bailey and colleagues (2001) conducted a meta-analysis to examine the utility of various tests for risk stratification. The analysis included 44 studies that evaluated the accuracy of signal-averaged electrocardiography, heart rate variability, severe ventricular arrhythmia on ambulatory electrocardiography, left ventricular ejection fraction, and electrophysiological studies in predicting risk major arrhythmic events (MAE) after a myocardial infarction (MI). There were variations between the studies in patient characteristics, cutoff points for the tests, and reporting of cause of cardiac death. In addition, the authors of the meta-analysis did not evaluate the quality of the studies, test for homogeneity or publication bias. Overall the analysis shows that the sensitivity of all tests ranged from 42.8% to 62.4% and the specificity ranged from 77.4% to 85.8%. The pooled sensitivity of SAECG was 62.4% (95% CI; 56.4-67.9%) (ranging from 35%-94% in 22 studies involving 9,883 patients), and the pooled specificity was 77.4% (95% CI; 73.6-80.8%, range 62-95.5%). The technology had a low positive predictive value ranging from 8-29%, but a high negative predictive value (81-99%) suggesting that it may have the potential of avoiding unnecessary implantation of a cardioverter-defibrillator (ICD). 3-stage stratification yielded a low-risk group (80.0% with a two-year MAE risk of 2.9%), a high-risk group (11.8% with a 41.4% risk) and an unstratified group (8.2% with an 8.9% risk equivalent to a 2-year incidence of 7.9%). The authors concluded that sensitivities and specificities for the 5 tests were relatively similar and no one test was satisfactory alone for predicting risk. Combinations of tests in stages allowed the authors to stratify 92% of patients as either high-risk or low-risk. They noted that these data suggest that a large prospective study to develop a robust prediction model is feasible and desirable. The CARISMA study (Huikuri 2009) also evaluated the ability of several invasive and noninvasive risk markers to predict arrhythmias after an acute myocardial infarction, with the potential to be treated with an ICD. 5,869 consecutive patients from 10 European centers were screened 2-7 days after experiencing an acute myocardial infarction (AMI), but only 312 met the inclusion criteria and were included in the study. Risk stratification was performed 6 weeks after the AMI using echocardiography, Holter monitoring, microvolt T-wave alterans, SAECG, standard 12-lead ECG, and electrophysiological studies. The primary endpoint was ECG-documented fatal or near-fatal cardiac arrhythmia (ventricular fibrillation or symptomatic sustained ventricular tachycardia). The arrhythmic events were documented with implantable ECG loop recorder. Patients were followed up for 2 years during which 25 (8%) experienced a fatal or non-fatal tachyarrhythmias. The strongest predictor for these events was heart rate variability ($p<0.001$) as measured by Holter monitor. This was followed by induction of sustained monomorphic ventricular tachycardia during programmed electrical stimulation ($P=0.003$). QRS duration measured from SAECG had a lower predictive value especially after adjustments were made for clinical variables. An assessment made for AHRQ in 1998 also found that SAECG had variable sensitivity and specificity, poor positive predictive value, but relatively high negative predictive value (NPV) for post MI fatal arrhythmic events. The high NPV was attributed to the low incidence of fatal arrhythmic events post MI, due to the increase use of antithrombotic therapy. The 2006 American College of Cardiology, American Heart Association and European Society of Cardiology guidelines (Zippes 2006) for management of patients with ventricular arrhythmias and prevention of

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sudden death, list SAECG with a Class IIb recommendation (Class IIb noted as usefulness/efficacy is less well established by evidence/opinion). The report notes that the presence of an abnormal SAECG was shown to increase the risk of arrhythmic events by 6- to 8-fold in a post-MI setting. However, the restoration of patency to the infarct-related coronary artery with fibrinolysis or angioplasty and the widespread use of surgical revascularization have modified the arrhythmogenic substrate, leading to a noticeable reduction in the predictive power of this tool. The report indicated that SAECG in isolation is no longer useful for the identification of post-MI patients at risk of ventricular arrhythmias. A number of health plans consider signal-averaged electrocardiography investigational and not medically necessary for all indications including risk stratification for arrhythmias after a myocardial infarction. Conclusion: In evaluating any method for risk stratification it is important to demonstrate that the test or marker can be used to select patients for a therapy or intervention that will improve outcome. Signal-averaged electrocardiography (SAECG) has been proposed as a noninvasive method for arrhythmia risk stratification. However, there is insufficient published evidence to its efficacy in establishing the risk of ventricular arrhythmias and sudden death. There is also insufficient evidence to determine clinical utility of SAECG testing in selecting patients for receiving pharmacological therapy, ICD implantation or other treatments.

Articles: The literature search did not identify any large prospective or randomized trials that examined the benefit of using SAECG for selecting patients for electro physiologic studies, or its clinical utility for selecting patients for prophylactic therapies and/or interventions and improving health outcomes. There was a large number of earlier studies conducted in the 1990s that examined the accuracy of SAECG and various other variables in predicting the risk of major arrhythmic events after a myocardial infarction, and a meta-analysis (Bailey 2001) that pooled the results of these studies published before 2001.The search also identified a more recent study (CARISMA study) that evaluated the ability of several invasive and noninvasive risk markers to predict arrhythmias that can potentially be treated with an ICD, and another study that compared the ability off SAECG and ejection fraction for predicting future cardiovascular events including life threatening arrhythmias in different cardiac diseases. The meta-analysis and CARISMA study were selected for critical appraisal: Bailey JJ, Berson AS, Handelsman H. Utility of current risk stratification test for predicting major arrhythmic events after myocardial infarction. *J Am Coll Cardiol* 2001; 38:1902-1911. See Evidence Table Huikuri HV, Raatikainen MJ, Moerch-Joergensen R, et al. Prediction of fatal or near-fatal cardiac arrhythmia events in patients with depressed left ventricular function after an acute myocardial infarction. *Eur Heart J.* 2009; 30:689-698. See Evidence Table

The use of SAECG does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Considered Not Medically Necessary:

CPT® Codes	Description
93278	Signal-averaged electrocardiography (SAECG), with or without ECG

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check.**

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Date Created	Date Reviewed	Date Last Revised
01/03/2012	01/03/2012[MDCRPC], 11/06/2012[MDCRPC], 09/03/2013[MPC], 07/01/2014[MPC], 05/05/2015[MPC], 03/01/2016[MPC], 01/03/2017[MPC], 11/07/2017[MPC], 09/04/2018[MPC], 09/03/2019[MPC], 09/01/2020[MPC], 09/07/2021[MPC], 09/06/2022[MPC], 09/05/2023[MPC], 03/12/2024[MPC]	09/01/2020

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

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Revision History	Description
09/01/2020	Added KPWA Medical Policy statement under Medicare section

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KAISER PERMANENTE®

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Clinical Review Criteria

Sinus Surgeries

- Functional Endoscopic Sinus Surgery (FESS)
- Sinuplasty

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article (LCA)	None
Kaiser Permanente Medical Policy	Due to the absence of an active NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Clinical Review Criteria, ***"Sinus Surgeries"*** for medical necessity determinations. Refer to the Non-Medicare criteria below.

For Non-Medicare Members

Kaiser Permanente will not separately reimburse for the use of robotic surgical systems, including but not limited to the CPT/HCPCS codes listed in this document.

Please refer to Kaiser Permanente payment policy for reimbursement clarifications.

Service	Criteria
Functional Endoscopic Sinus Surgery (FESS)	Kaiser Permanente has elected to use the Functional Endoscopic Sinus Surgery (FESS) (A-0185) MCG* Care Guideline for medical necessity determinations. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under *Quick Access*.
Sinuplasty	Kaiser Permanente has elected to use the Sinuplasty (A-0478) MCG* Care Guideline for medical necessity determinations. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under *Quick Access*.

***MCG manuals are proprietary and cannot be published and/or distributed**. However, on an individual member basis, Kaiser Permanente can share a copy of the specific criteria document used to make a utilization management decision. If one of your patients is being reviewed using these criteria, you may request a copy of the criteria by calling the Kaiser Permanente Clinical Review staff at 1-800-289-1363 or access the MCG Guideline Index using the link provided above.

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For covered criteria:

If requesting this service (*or these services*), please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist

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Background

FESS is a minimally invasive technique in which sinus air cells and sinus ostia are opened using a rigid fiberoptic endoscope. Three factors are crucial in the normal physiologic functioning of the sinuses: a patent ostiomeatal complex, normal mucociliary transport, and normal quantity and quality of secretions. Disruption of at least one of these factors can predispose a patient to inflammation and infection of the sinuses. FESS attempts to address the patency issue in patients with medically refractory chronic rhinosinusitis.

Sinuplasty, also referred to as balloon sinuplasty or balloon ostial dilation, treats ostial narrowing of the paranasal sinuses through the use of a balloon device to enlarge or open the outflow tracts of the maxillary, frontal, or sphenoid sinuses without disrupting the epithelial mucosa. Under direct vision or fluoroscopy, a catheter is inserted into the narrowed ostium and a balloon is inflated under pressure to enlarge the opening by stretching the mucous membrane and creating a small bony fracture. Sinuplasty may be performed in the office or operating room setting, using local or general anesthesia, depending on patient tolerance.

Applicable Codes

Functional Endoscopic Sinus Surgery (FESS)—

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPCS Codes	Description
31237	Nasal/sinus endoscopy, surgical; with biopsy, polypectomy or debridement (separate procedure)
31239	Nasal/sinus endoscopy, surgical; with dacryocystorhinostomy
31240	Nasal/sinus endoscopy, surgical; with concha bullosa resection
31253	Nasal/sinus endoscopy, surgical with ethmoidectomy; total (anterior and posterior), including frontal sinus exploration, with removal of tissue from frontal sinus, when performed
31254	Nasal/sinus endoscopy, surgical with ethmoidectomy; partial (anterior)
31255	Nasal/sinus endoscopy, surgical with ethmoidectomy; total (anterior and posterior)
31256	Nasal/sinus endoscopy, surgical, with maxillary antrostomy;
31257	Nasal/sinus endoscopy, surgical with ethmoidectomy; total (anterior and posterior), including sphenoidotomy
31259	Nasal/sinus endoscopy, surgical with ethmoidectomy; total (anterior and posterior), including sphenoidotomy, with removal of tissue from the sphenoid sinus
31267	Nasal/sinus endoscopy, surgical, with maxillary antrostomy; with removal of tissue from maxillary sinus
31276	Nasal/sinus endoscopy, surgical, with frontal sinus exploration, including removal of tissue from frontal sinus, when performed
31287	Nasal/sinus endoscopy, surgical, with sphenoidotomy;
31288	Nasal/sinus endoscopy, surgical, with sphenoidotomy; with removal of tissue from the sphenoid sinus

Sinuplasty—

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPCS Codes	Description

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31295	Nasal/sinus endoscopy, surgical, with dilation (eg, balloon dilation); maxillary sinus ostium, transnasal or via canine fossa
31296	Nasal/sinus endoscopy, surgical, with dilation (eg, balloon dilation); frontal sinus ostium
31297	Nasal/sinus endoscopy, surgical, with dilation (eg, balloon dilation); sphenoid sinus ostium
31298	Nasal/sinus endoscopy, surgical, with dilation (eg, balloon dilation); frontal and sphenoid sinus ostia

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed	Date Last Revised
09/05/2023	09/05/2023[MPC],	09/05/2023

[MPC] Medical Policy Committee

Revision History	Description
09/05/2023	MPC approved to adopt new criteria Functional Endoscopic Sinus Surgery (FESS), MCG A-0185 and Sinuplasty, MCG A-0478. Requires 60-day notice, effective February 1, 2024.

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KAISER PERMANENTE®

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Clinical Review Criteria
Wireless Motility Capsule

- SmartPill for the Evaluation of Gastrointestinal Motility Disorders

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article	None
Kaiser Permanente Medical Policy	Due to the absence of an active NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Clinical Review Criteria, "***Wireless Motility Capsule***" for medical necessity determinations. Use the Non-Medicare criteria below.

For Non-Medicare Members

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Gastrointestinal (GI) symptoms including abdominal pain, bloating, vomiting, diarrhea, and constipation, are common in the general population and may lead to patient distress, impairment in functioning, and loss of productivity. Many of these symptoms may be linked to motility disorders, which may affect any region of the GI tract and include gastroparesis, intestinal pseudo-obstruction, and slow transit constipation. Gastroparesis is a chronic disorder characterized by delayed gastric emptying in the absence of mechanical obstruction. It is manifested by upper GI symptoms including nausea, vomiting, early satiety, and objective evidence of delayed gastric emptying. Patients with slow transit constipation commonly present with lower GI symptoms such as abdominal pain, infrequent hard stools, and evidence of delayed colonic transit on objective testing. Sometimes it is hard to differentiate between upper and lower GI involvement and some patients may experience overlapping symptoms due to the involvement of multiple regions of the GI tract. In addition, signs of gastroparesis and chronic constipation are often confused with symptoms from conditions such as irritable bowel syndrome (IBS) and functional dyspepsia. It is thus important to localize the transit abnormalities to a specific GI lesion to accurately diagnose the disorder and guide the appropriate management (Williams 2011, Arora 2015, Gronlund 2017).

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Date Sent: 3/29/24
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Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

Motility disorders are hard to diagnose and cannot be measured by routine imaging or endoscopic examinations. A clinical diagnosis is based on physiological tests most of which have some inconsistency in performance, making it hard to interpret the results, and may require using more than one test to make a diagnosis. Experts in the field indicate that currently, there are no gold standards or true motility measures to validate methods used for the assessment of gut motility, and that no current standardized tool can concurrently assess transit time and distinguish between motility abnormalities in the various parts of the GI tract (Stein 2013, Gronlund, 2017).

Commonly used methods for evaluating patients with suspected gastroparesis include gastric emptying scintigraphy, antroduodenal manometry, upper GI barium series, and gastric emptying breath testing utilizing a stable carbon isotope. Scintigraphy is often considered the reference standard for measuring gastric emptying time despite its limitations. It involves exposure to radiation, and lacks standardization between centers as regards meal composition, monitoring times, reported endpoints, and normal values. It also takes long time periods of imaging and may require multiple visits to the investigating facility (Kuo 2008, Stein 2013, Wang 2015, Saad 2016).

The main diagnostic methods used for the evaluation of possible slow-transit constipation include radiopaque marker (ROM) examination, small bowel and colonic scintigraphy, colonic and anorectal manometry, and lactulose breath testing. ROM is widely used, and may be considered a reference standard, but has its drawbacks including radiation exposure, inability to access regional gut transit, and the lack of standardized protocol for the test and its interpretation. In addition, some protocols require multiple visits, which may affect compliance (Rao 2009, Sarosiek 2010, Tran 2012, Stein 2013, Saad 2016)

A wireless motility/pH gastrointestinal monitoring system was developed in 2003, as a radiation-free noninvasive alternative to traditional nuclear and radiological measurements used for the evaluation of GI motility disorder. The system provides a method of measuring regional and whole gut transit time in a single standardized ambulatory test. It consists of a wireless motility capsule (WMC, SmartPill), a SmartPill Data Receiver, a Docking Station, and a system computer loaded with SmartPill Software. WMC is a data recording device 26.8mm in length and 11.7mm in diameter (about the size of a large vitamin pill). It consists of a rigid polyurethane shell containing a battery that lasts for a minimum of 120 hours, sensors for pH, temperature, and pressure; and a transmitter. WMC is a single use, orally ingestible, non-digestible capsule that provides real-time measurement of the temperature, pressure, and pH of its immediate surrounding. It can measure gastric emptying time (GET), small bowel transit time (SBTT), colonic transit time (CTT), and whole gut transit time (WGTT), but does not provide information on segmental colonic transit times, i.e. it is unable to show where the motility disturbance originates in the colon. It is to be noted that WMC measures the emptying of a non-digestible solid, unlike the gastric emptying scintigraphy and breath testing that measure gastric emptying of digestible solids. WMC may not correspond to physiological emptying of food; it does not empty with the meal but is generally cleared from the stomach by powerful inter-digestive antral contractions (phase III MMC [migrating motor complex] contractions) that occur after the meal has been emptied to clear the stomach of indigestible material. Thus, as some investigators indicate, the passage of WMC into the duodenum correlates only modestly with the gastric emptying of nutrients (Kuo 2011, Saad 2011, 2016, Tran 2012, Shin 2013, Gronlund 2017, Keller 2018).

A WMC study can be performed in a physician's office after the patient undergoes an overnight fast and discontinues medication that may potentially affect gastric pH and GI motility. The WMC is swallowed with 50ml water immediately following a standardized meal (egg sandwich [255 kcal, 2% fat, 1g fiber], or a nutritionally equivalent Smart Bar [260 kcal, 2% fat, 2g fiber]). Patient are given a data receiver and a diary for recording bowel movements, food intake, sleep, and GI symptoms. They can leave the clinical setting after the absence of any complications from ingesting the capsule is confirmed. The patients are not permitted to eat for 6 hours after which, they are instructed to consume the regular meals for the testing period of 3-5 days; to avoid vigorous exercise; refrain from alcohol, smoking, and the use of GI medications that could affect motility. The capsule travels through the gastrointestinal tract, collecting, recording, and transmitting data to the SmartPill Data Receiver worn on a patient's belt or around the neck. It is then excreted naturally from the body within a day or two. The data recorder is returned to the physician’s office and the information downloaded via a docking station for analysis (Rao 2009, Saad 2011).

The SmartPill GI Monitoring System (WMC SmartPill®, SmartPill Corporation, Buffalo, NY, USA; now Medtronic, Minneapolis, MN, USA), was cleared by the Food and Drug Administration (FDA) in July 2006, for the evaluation of delayed gastric emptying in the absence of mechanical obstruction. In 2009, the FDA expanded the use of the SmartPill to determine colonic transit time for the evaluation of chronic constipation and to differentiate between slow or versus normal transit constipation.

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The WMC testing is not approved for use in the pediatric population and is not indicated for the diagnosis of IBS or functional dyspepsia. It is contraindicated in patients with suspected or known swallowing disorders; strictures, fistulas, or physiological/mechanical GI obstruction; GI surgery within the past 3 months; severe dysphagia to food or pills; Crohn's disease or diverticulitis; implanted or portable electro-mechanical medical device; or a history of gastric bezoar (a ball of swallowed foreign material most often composed of hair or fiber). WMC is also contraindicated in patients with a cardiac pacemaker or defibrillator due to concerns related to the capsule's radio transmission of data to the receiver (Farmer 2013, Saad 2016).

Reported adverse events and /or equipment failure associated with WMC testing, include inability of the patient to swallow the capsule, equipment failure of the capsule to record or transmit data, failure of the receiver to record and download data, and software malfunction necessitating repeat testing. The most severe, but rare adverse event reported was the capsule retention in the stomach, small intestine or colon, which required operative removal of the device in a small number of patients. Other reported side effects include abdominal pain, dysphagia, nausea, and diarrhea (Saad 2016).

Medical Technology Assessment Committee (MTAC)

Wireless Motility Capsule (WMC; SmartPill) for the Evaluation of Gastrointestinal Motility Disorders

01/14/2019: MTAC REVIEW

Evidence Conclusion:

Diagnostic accuracy of wireless motility capsule (WMC)

- It is difficult to estimate the accuracy of a test when there is no standardized gold standard to compare it with. The reference standards commonly used in practice and in the literature, are mainly gastric scintigraphy for gastroparesis and radiopaque markers (ROM) for colonic transit disorders. These may be considered reference tests, but according to the experts on the field, none is a perfect test. In addition, the tests are not usually conducted according to a standardized technique protocol as regards meal composition, monitoring times, and interpretation. Moreover, WMC and the reference tests were not always performed simultaneously (in some cases conventional tests were performed months earlier) which would not provide accurate comparison as patients with dysmotility may have major day-to-day variability on repeat transit testing. The upper limits for small and large bowel transit times measured by WMC differed between some studies. WMC measures the emptying of a non-digestible solid, unlike the gastric emptying scintigraphy and breath testing that measure gastric emptying of digestible solids. WMC does not empty with the meal but is generally cleared from the stomach powerful inter-digestive antral contractions that occur after the meal has been emptied to clear the stomach of indigestible material.
- The published literature shows wide variations in the calculated accuracy of the wireless motility capsule for the diagnosis of GI dysmotility. The sensitivity of WMC ranged from 59% to 86%, and its specificity ranged from 64% to 81% for gastroparesis when compared with gastric scintigraphy; the overall concordance between the tests ranged from 35% to 81%.
- When compared with radiopaque markers (ROM) for the detection of slow-transit constipation, WMC had a sensitivity of 43-87% and specificity of 67-98%. The concordance ranged between 64% and 87%.
- WMC was found to be less accurate than barium testing of small bowel dysmotility disorders.
- The analysis of the results from one study (Wang, 2015) suggests that regional GI transit time and pH values measured by the WMC may be affected by the testing protocol, gender, age, and country where the test is performed. The authors thus concluded that standardization of the test is essential for cross referencing in clinical practice and research; and presented normative values for regional transit times for reference in clinical practice.
- The results were based on the analyses of prospectively or retrospectively collected data from records of patients referred to tertiary centers specializing in managing severe dysmotility disorders. Retrospective studies have their limitations and are subject to bias and confounding. Patients referred for further investigations in tertiary centers tend to have more severe symptoms, are refractory to therapy and/or have failed several conventional tests. This would affect the accuracy and predictive value of the test and limit generalization of the results.

Safety of WMC

The published studies do not provide sufficient data to determine the safety of WMC.

Clinical utility of WMC

- The literature search did not identify any randomized controlled trials the examined the clinical utility of using WMC in patients with GI motility disorders, i.e. it impacts on managing the patients and improving their health outcomes. All published studies were secondary analyses of prospectively or retrospectively collected patient data obtained from chart reviews or electronic health records.

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- The published secondary analyses of data provide weak evidence suggesting WMC may provide more diagnostic information compared to conventional methods used for evaluating gastrointestinal motility disorders, and the modification of the management plans.
- There is insufficient evidence to determine that the use of WMC improves the health outcomes of patients with gastrointestinal motility disorders.

Articles: The literature search identified an earlier comprehensive AHRQ systematic review (Stein et al, 2013) on the comparative effectiveness of wireless motility capsule and other diagnostic technologies used for evaluating gastroparesis and constipation. The search for studies published after the AHRQ literature review identified over 50 publications; the majority of which were review articles or studies unrelated to the current review. Related articles included two recent observational studies on the diagnostic performance of WMC in patients with suspected gastroparesis, a study that examined the influence of several variables on the outcomes of the WMC testing, two studies on the use of WMC in the assessment of GI dysmotility in patients with diabetes mellitus, and few retrospective studies on the clinical utility of WMC in patients with GI dysmotility. The results of the AHRQ systematic review on the comparative accuracy of WMC vs. alternative tests used for the diagnosis GI dysmotility, as well as the recent validation studies, the study on the variables affecting the outcome of the test, and selected studies evaluating the clinical utility of WMC and using gastric scintigraphy and ROM as reference standards for evaluating the accuracy of WMC for upper and lower GI dysmotility respectively were reviewed and summarized.

The use of Wireless Motility Capsule (WMC; SmartPill) for the Evaluation of Gastrointestinal Motility Disorders does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Considered Not Medically Necessary

CPT® or HCPC Codes	Description
91112	Gastrointestinal transit and pressure measurement, stomach through colon, wireless capsule, with interpretation and report

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Date Created	Date Reviewed	Date Last Revised
02/05/2019	02/05/2019[MPC], 01/07/2020[MPC], 01/05/2021[MPC], 01/04/2022[MPC], 01/10/2023[MPC], 03/12/2024[MPC]	

[MPC] Medical Policy Committee

Revision History	Description
02/05/2019	MPC approved to adopt criteria of non-coverage; added 01/2019 MTAC review

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KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Inpatient Skilled Nursing Facility

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Criteria

For Medicare Members

On initial review, Kaiser Permanente will use the Recovery Facility Care guidelines (MCG*) for inpatient skilled nursing facility, but if criteria are not met, then the Medicare Benefit Policy Manual (chapter 8, section 30) for inpatient skilled nursing facility coverage must be used. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.

For Non-Medicare Members

To meet Skilled Nursing facility coverage eligibility requirements, **ALL of the following** 3 factors must be met:

Admission:

A. Must meet **One** or more of the following to qualify for admission to Skilled Nursing Service, Skilled Rehab Service or both:
   1. **Requires Skilled Nursing** of RN, LPN, PT, OT, or SLP: Inherent complexity of service is such that it can be performed safely and/or effectively only by, or under, general supervision of licensed professionals and cannot be provided by non-skilled personnel. Requires skilled services on a daily basis. Patients functional or medical complexity are such that outcome would be compromised with less than daily skilled services. Multiple skilled nursing services are required daily 7d/wk. **Skilled Nursing Services** must meet **ONE or more** of the following:
      a. Injections: IV, IM, SQ (new &/or complex needs, not typically for insulin)
      b. Intravenous: fluids, meds, or line flushes
      c. Nebulizers: oxygen eval saturations when unstable, complex
      d. Enteral feedings new or enteral pt with recent change in medical condition requiring monitoring
      e. Care of new colostomy or teaching ostomy care associated with complication
      f. Frequent suctioning, trach, &/or vent needs
      g. Frequent irrigation, replacement of urinary catheters; care of new/complex suprapubic catheter
      h. Treatment Stage III/IV pressure ulcers; widespread skin disorder or complex wounds requiring RN/LPN wound treatment
      i. Nursing evaluation of unstable & complex medical condition, e.g. recovery from septicemia, coma, severe respiratory disease, uncontrolled pain
      j. Nursing rehab teaching, e.g. bowel & bladder training, adaptive aspects of care.
   2. **Skilled Rehab Services:** Requires rehab teaching, training, or monitoring. Complexity and sophistication of treatment is such that the specialized skills of a therapist are needed. Pt is significantly below baseline level of function and is able to learn and retain new information and skills. **Note:** Rehab services are not required for deconditioning/ temporary reduction in function which could reasonably be expected to spontaneously improve as pt gradually resumes activities. Repetitious exercises to improve gait or maintain strength and endurance and assistive walking are appropriately provided by supportive personnel and do not meet skilled rehab criteria.
      Must meet **ALL of the following** below for **Skilled Rehab Services**:
      a. Requires establishment and ongoing assessment of a complex rehab treatment plan such as gait training in patients with neurological, muscular or skeletal abnormality, use of new assistive device, compensatory strategies, cg training, monitoring of activity tolerance with vital signs or O2 checks.

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   b. Patient requires more than minimal or light physical assist for basic ADLs and mobility (based on evidence that patients needing only minimal assist do comparably well with Home Health therapy and do not need daily rehab)
   c. Does not require one or two more hospital days to arrange home care plan. If pt requires only one or two more hospital days to arrange home care plan, then would not require inpt SNF daily rehab or nursing.
3. Patients receiving **elective total joint replacements** often need additional caregiving assistance that can be provided by non-professional staff and intermittent therapy services (not daily). In the event a total joint replacement patient is referred to SNF for daily therapy**, you must** check functional mobility levels; patients requiring minimal assistance or less (<25% assist) generally do not require daily therapy by a licensed therapist. Some patients have post-operative pain or nausea which may impede progress initially. For those patients, an additional day or two in the hospital may avoid a SNF stay. Elective Total Joint patients must meet **one** of the following:
   a. Patient requires moderate or greater level of assistance with overall mobility. (This does not mean that there is just one area where patient needs moderate assistance. i.e.: min A with t/f and gait, but Mod A with supine<>sit would not indicate a daily need.)
   b. Patient is functioning at minimal assist with mobility- review with NHS/ CRUS MD to determine if patient has need for daily therapy at this high functional level.

B. **Requires inpatient SNF level of care** - Complexity and frequency of needs for skilled services require inpt setting; requires multiple skilled treatments daily (can be combination of nursing & rehab) or need for daily skilled services exceeds care available at lesser levels such as home with Home Health.
C. **SNF inpatient services are reasonable and medically necessary** (i.e. consistent with the nature and severity of the individual's illness or injury, the individual's particular medical needs, and accepted standards of medical practice. The services must also be reasonable in terms of duration and quantity.)

For continued stay and discharge
Kaiser Permanente has elected to use MCG* Recovery Facility Care Guidelines for inpatient skilled nursing facility coverage medical necessity determinations.

***MCG are proprietary and cannot be published and/or distributed**. However, on an individual member basis, Kaiser Permanente can share a copy of the specific criteria document used to make a utilization management decision. If one of your patients is being reviewed by our Nursing Home Services department, you may request a copy of the criteria that is being used to make the coverage determination. Call Nursing Home Services for more information regarding the case under review.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Skilled nursing facility services are frequently required to transition patients from the hospital setting to home. At times these services must be delivered in a skilled nursing facility because of patient care needs and clinical condition. When the member has coverage for this care the skilled nursing facility admission criteria must be met for eligibility. Members who require this level of care but do not have coverage must pay for the service themselves. Because the majority of members requiring this service have Medicare coverage, Medicare criteria were used as a guide in the development of the Kaiser Permanente criteria.

Evidence and Source Documents

Medicare criteria

Applicable Codes

POS 26

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Date Created	Date Reviewed	Date Last Revised
08/11/1998	07/13/2009 MDCRPC, 07/06/2010MDCRPC, 05/03/2011MDCRPC, 03/06/2012MDCRPC, 01/08/2013MDCRPC, 11/05/2013MPC, 09/02/2014MPC, 02/03/2015MPC, 07/07/2015MPC, 05/03/2016MPC, 03/07/2017MPC, 01/09/2018MPC, 12/04/2018MPC, 12/03/2019MPC, 12/01/2020MPC,12/07/2021MPC,12/06/2022MPC, 12/09/2023MPC	02/03/2015

MDCRPC Medical Director Clinical Review and Policy Committee

MPC Medical Policy Committee

Revision History	Description

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KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
SpaceOAR (Spacing Organs at Risk)

- Rectal Protection during Prostate Cancer

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Criteria

For Medicare Members

No review required.

For Non-Medicare Members

No review required.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Prostate cancer is the most common cancer (excluding skin cancer) and the third leading cause of cancer death in men in the United States (American cancer Society Cancer facts and figures 2017). Treatment options for prostate cancer include active surveillance and watchful waiting, radical prostatectomy, radiation therapy, hormone therapy, chemotherapy, immunotherapy and other treatment modalities depending on the stage of the disease, patient age, health condition, and personal preference.

External beam radiation therapy (EBRT) remains one of the primary treatment modalities for patients with localized prostate cancer. Studies show that it is highly effective in patients with a localized disease, and that a dose escalation improves biochemical control in intermediate risk patients. However, dose escalation can also increase the risk of urinary and bowel toxicity (Pinkawa 2011, Uhl 2013, Chung 2016).

Advances in in radiotherapy treatment techniques including image-guided radiation therapy (IGRT) and intensity modulated radiation therapy (IMRT) that limit the margins and conform the high dose radiation volume, have allowed increasing the radiation dose to ≥78Gy while maintaining an acceptable toxicity profile. However, as the prostate is directly adjacent to the rectum, the anterior rectal wall cannot be completely spared from the high dose region regardless of the treatment technique. The rectum is the most radiation sensitive organ within the pelvic tissue and is the primary organ at risk (OAR) with external beam radiation therapy. Studies showed that rectal toxicity is associated with both the total radiation dose to a specific volume and the volume inside a specific isodose, and that Grade ≥2 rectal toxicity is significantly associated with the volume of rectum receiving >70Gy (V70) (Noyes 2012, Pinkawa 2013, Song 2013, Wolf 2015, Chung 2016, Hamstra 2017).

Researchers have been evaluating methods to create more space between the prostate and rectum to allow for prostate dose escalation while reducing anterior rectal wall radiation exposure. One of the promoted approaches involves the placement of a temporary injectable spacer to push the rectum away from the prostate before treatment planning and maintain the space throughout the treatment period. Different injectable agents including

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human derived products (e.g. hyaluronic acid and collagen), synthetic polyethylene-glycol (PEG) hydrogel, and implantable absorbable balloons have been evaluated as spacing materials (Song 2013, Mariados 2015).

SpaceOAR (Spacing **O**rgans **A**t **R**isk), Augmenix, Inc., Waltham MA, USA, is an absorbable polyethylene glycol (PEG) hydrogel that expands the perirectal space as an injectable liquid and then solidifies into a soft absorbable spacer between the prostate and rectum. It consists of two liquid hydrogel precursors, that after hydro dissection with a saline solution, are injected using a small needle under transrectal ultrasound (TRUS) guidance through the perineum to the perirectal space (between the Dennonvilliers' Fascia and the frontal rectal wall). There, the liquid hydrogel polymerizes (solidifies) within seconds and creates a physical barrier between the prostate and rectum. The additional space created by the spacer has a volume of about 10-15 ml. The solidified hydrogel is compression resistant and is maintained for approximately three months. It should be absorbed in approximately six months and the degradation products cleared via renal filtration (Pinkawa 2011, Rucinski 2015, Wolf 2015).

Potential complications that may be associated with the use of the SpaceOAR system include, but are not limited to pain and discomfort associated with SpaceOAR or hydrogel injection; needle penetration and/or injection of the hydrogel into the bladder, prostate, rectal wall, rectum, or urethra; infection or local tissue inflammatory reactions; urine retention, bleeding, rectal mucosal damage, ulcers, necrosis, constipation; rectal urgency; injection of air, fluid or SpaceOAR hydrogel intravascularly; device functional failure or its inability to maintain the space stability during the course of radiation therapy; prolonged or delayed procedure; and incomplete absorption of the hydrogel (FDA decision summary, FDA website, accessed May 2017).

Medical Technology Assessment Committee (MTAC)

SpaceOAR

06/21/2017: MTAC REVIEW

Evidence Conclusion: The SpaceOAR pivotal trial (See Evidence Table 1) is a multicenter single-blinded phase III trial that evaluated the safety and effectiveness of SpaceOAR among 222 patients undergoing prostate image guided intensity modulated radiation therapy (IG-IMRT).The study included men with clinical stage T1 or T2 prostate cancer, Gleason score ≤7, and PSA concentration ≤20 ng/ml. Patients with prostate volume>80cm^3, extracapsular extension of the disease, >50% positive biopsy cores as well as those with prior prostate surgery or radiation therapy were excluded from the study. After undergoing initial treatment planning, and implantation of fiducial markers, the study participants were randomized in a 2:1 to receive spacer injection or no injection (control). Patients, but not the providers were blinded to their treatment allocation. Planning scans were then performed followed by image guided intensity modulated radiation therapy (79.2Gy in 1.8-Gy fractions). The primary effectiveness endpoint was the proportion of patients achieving >25% rectal volume receiving at least 70Gy (rV70) due to spacer placement, and the safety endpoint was the proportion of spacer and control patients with ≥grade 1 rectal toxicity or procedural adverse event (AEs) in 6 months. The results showed a significant reduction in the mean rectal V70 (>70Gy) in the post vs. pre- treatment plan. Overall 97.3% of spacer patients experienced ≥25% reduction in rectal volume receiving at least 70Gy (rV70).

Mean ± SD rectal dose volume at baseline and post- spacer dose plans

parameter	rV50	rV60	rV70	rV80
% before spacer	25.7 ± 11.1	18.4 ± 7.7	12.4 ± 5.4*	4.6 ± 3.1
% after spacer	12.2 ± 8.7	6.8 ± 5.5	3.3 ± 3.2**	0.6 ± 0.9
% absolute reduction	13.442	11.563	9.078	3.933
% relative reduction	52.3	62.9	73.3	86.3
P value	<0.0001	<0.0001	<0.0001	<0.0001

As regards the primary safety endpoint, the results showed no significant differences in the rates of ≥grade 1 rectal or procedural adverse event (AEs) in 6 months between spacer and control groups (34.2% and 31.5% respectively (p =0.7). 10% of the patients in the spacer group experienced mild transient procedural perineal discomfort and other symptoms.

Acute and late (up to 15 months) rectal toxicity

Rectal toxicity	Spacer (n=148)	Control (n= 73)	P value
Acute toxicity: from procedure through 3-months visit, n (%)			
Grade 0	108 (73.0%)	49 (68.0%)	0.525
Grade 1	34 (23.0%)	20 (27.8%)	
Grade >2	6 (4.1%)	3 (4.2%)	
Late toxicity Between the 3rd and 15th month visits			

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Grade 0	145 (98.0%)	66 (93.0%)	0.044
Grade 1	3 (2.0%)	4 (5.6%)	
Grade >2	0 (0.0%)	1 (1.4%)	

The results show that the rate of rectal toxicity in the control group was low, which as the authors indicated was very low compared to earlier studies, and attributed that to several potential factors including the use of different toxicity scales, uniform use of both IMRT and IGRT, small PTV (planning target volume) margin, MRI planning, and strict dosimetric constraints with centralized pretreatment review of the plans. The extended follow-up reported by Hamstra and colleagues (2017), suggest that the benefit observed with the hydrogel spacer at 15 months was maintained at a median of 37 months of follow-up. However, this extended follow-up was optional and the long-term data were available for 66% of the patients at 30 months, and 17.5% at 40 months. The trial was randomized and controlled. However, it had its limitations. The providers were not blinded to the treatment allocation; the study had strict inclusion/exclusion criteria, which may limit generalization of its results, and the follow-p duration was insufficient to determine the long-term safety of the technology. The extended 3 years follow-up was voluntary and only 66% were followed up for 30 months, and 17.5% at 40 months, In addition the study was performed under an investigational setting, was sponsored by the manufactures, and the principal investigators had financial ties with the industry. Pinkawa and colleagues, 2017 compared the numbers of interventions resulting from bowel problems during the first 2 years after RT to assess the benefit of the using hydrogel spacer before prostate cancer radiotherapy (RT) according to patient's perspective. The study included 167 consecutive prostate cancer patients treated with radiotherapy (RT) in the years 2010 to 2013. 101 patients received 76-80Gy with hydrogel, and 66 were treated with up to 76Gy without hydrogel. All patients were surveyed prospectively before RT, at the last day of RT, and at a median of 2 and 17 months after RT using a validated questionnaire (Expanded Prostate Cancer Index Composite). The outcome was the difference between using and not using hydrogel on the rate of interventions resulting from bowel problems during the first 2 years after radiotherapy. The results show that treatment for bowel symptoms was performed less frequently with a using a spacer (0 with spacer vs. 11 % with no spacer; $p < 0.01$). Similarly there were less endoscopic examinations in patients receiving a spacer versus those who did not receive one (3 vs. 19 % respectively; $p < 0.01$). Mean bowel function scores did not change for patients with a spacer in contrast to patients without a spacer (mean decrease of 5 points) >1 year after RT in comparison to baseline. None of the spacer parents vs. 12% of those with no spacer reported a new moderate/big problem with passing stools ($p < 0.01$). The authors concluded that spacer injection is associated with a significant benefit for patients after prostate cancer RT. However, the study was only observational and patients were not randomized to the treatment groups.

Conclusion:

- There is insufficient published evidence to recommend for or against the use of SpaceOAR in prostate cancer patients treated with external beam radiotherapy.
- The only published RCT trial to date, had its limitations and does not provide sufficient evidence to determine the long-term safety and efficacy of the hydrogel spacer, or to determine its effect on the net health outcome outside the investigational setting.

Articles: The literature search for published studies on the efficacy and safety of injecting a temporary hydrogel spacer between the rectum and prostate in patients undergoing extremal beam radiotherapy revealed one randomized controlled trial (pivotal trial), a retrospective comparative study, observational studies with no controls, as well as a number of phase I/II studies investigating the feasibility, efficacy, safety, and/or dosimetric benefits of the spacers. The literature search also identified a small nonrandomized observational study that compared SpaceOAR to a saline inflated balloon (ProSpace) in terms of spacer volume, stability and radiation dose reduction to the anterior rectal wall. The pivotal RCT was selected for critical appraisal. Hamstra DA, Mariados N, Sylvester J, et al. Continued Benefit to Rectal Separation for Prostate Radiation Therapy: Final Results of a Phase III Trial. *Int J Radiat Oncol Biol Phys*. 2017 Apr 1; 97(5):976-985. Mariados N, Sylvester J, Shah D, et al. Hydrogel Spacer Prospective Multicenter Randomized Controlled Pivotal Trial: Dosimetric and Clinical Effects of Perirectal Spacer Application in Men Undergoing Prostate Image Guided Intensity Modulated Radiation Therapy. *Int J Radiat Oncol Biol Phy.* 2015; 92:971-977

The use of SpaceOAR (Spacing Organs at Risk) Hydrogel for Rectal Protection during Prostate Cancer Radiotherapy does meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

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Applicable Codes

Medical Necessity Review not required:

CPT® Codes	Description
55874	Transperineal placement of biodegradable material, peri-prostatic, single or multiple injection(s), including image guidance, when performed

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Date Created	Date Reviewed	Date Last Revised
08/01/2017	08/01/2017[MPC], 07/10/2018[MPC], 07/09/2019[MPC], 07/07/2020[MPC], 07/06/2021[MPC], 07/05/2022[MPC], 07/11/2023[MPC]	07/07/2020

[MPC] Medical Policy Committee

Revision History	Description
01/08/2018	Medicare - No review required
07/07/2020	Removed deleted CPT code 0438T

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Date Sent: 3/29/24
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Clinical Review Criteria

Single Photon Emission Computed Tomography (SPECT)

- Evaluation of Origin of Behavior Problems
- DaT-SPECT (Dopamine Transporter-Single Photon Emission Computed Tomography)
- Imaging with (123I)Ioflupane, DaTscan, or (123I)FP-CIT

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Single Photon Emission Computed Tomography (SPECT) (220.12). *Medical necessity review no longer required
Local Coverage Determinations (LCD)	None
Local Coverage Article	None

For Non-Medicare Members

Service	Criteria
Evaluation of Origin of Behavior Problems	There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies
DaT-Spect for evaluation of movement disorders (e.g., Parkinson's, essential tremor, etc.)	There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.
SPECT	No review required for other indications.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Single Photon Emission Computed Tomography (SPECT) is a nuclear medicine technique that can be used to image almost any organ system. SPECT imaging is performed by acquiring multiple images (aka projections) with a gamma camera. A topographic reconstruction algorithm is then applied to the multiple two-dimensional projections, resulting in a three-dimensional dataset. To acquire the images, the gamma camera is rotated around the patient. The camera typically moves 3-6o each time until a 360 rotation is achieved. Each image takes approximately 15-20 seconds, for a total scanning time of approximately 15-20 minutes.

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Brain imaging with SPECT is generally performed with the radiopharmaceutical hexamethylpropylene amine oxime (99mTC-HMPAO). 99mTC emits gamma rays that are detectable by a gamma camera. When attached to HMPAO, it can be taken up by brain tissue at a rate proportional to brain metabolism. Brain blood flow is highly correlated to local brain metabolism and energy use. Areas of the brain that are undergoing increased neuronal activity consume greater amounts of oxygen and energy and are perfused more, and areas of the brain that area less functionally active are perfused less. The SPECT image thus indirectly reflects cerebral metabolism. Patients undergoing brain SPECT are exposed to approximately 2-8 mSv of radioactivity, a level comparable to a CT scan. 99mTC-HMPAO SPECT brain scanning provides similar information about local brain function to FDG PET scans and functional MRI. Although PET has a higher resolution, the SPECT equipment is less expensive and may be more widely available. While MRI and PET are limited to hospitals due to their cost, SPECT equipment can be installed in physicians' offices (Overmeyer & Taylor, 2001).

A report contracted by the American Psychiatric Association (APA) in 2005 concluded that SPECT is useful for research on psychiatric disorders, and for diagnosing cerebral trauma, seizure disorders and brain tumors for which there are detectible patterns of perfusion abnormalities. However, the authors found insufficient evidence to support the use of SPECT for the diagnosis and treatment of psychiatric disorders in the pediatric population. The APA report stated that there is a lack of evidence linking a particular structural or functional brain abnormality to a single psychiatric disorder. In addition, the authors cautioned that the long-terms effects of using the radioactive nucleotides associated with SPECT imaging in children and adolescents are not known.

A group of SPECT practitioners have criticized the APA report as being flawed and misleading (Wu et al, unpublished manuscript). They counter the APA claim that SPECT cannot yet diagnose psychiatric illness with the statement that clinicians do not rely on SPECT to make psychiatric diagnoses. Instead, SPECT practitioners use brain imaging as another source of data, along with clinical presentation, to help them make informed decisions about diagnosis. They also state that it is unfair to single out the possible danger associated with radioactive nucleotides used with SPECT imaging since children are treated with other nuclear medicine procedures such as studies for cardiovascular, cerebrovascular and orthopedic disease. They report that the average radiation exposure for one SPECT scan is similar to the exposure from a bone scan, brain CT scan or abdominal x-ray.

Medical Technology Assessment Committee (MTAC)

Single Photon Emission Computed Tomography

10/02/2006: MTAC REVIEW

Evidence Conclusion: In order to demonstrate that SPECT brain imaging is able to accurately diagnose behavior problems, there needs to be sufficient evidence that particular SPECT findings correlate with specific behavioral conditions, and that SPECT is sensitive and specific at diagnosing these conditions compared to a gold standard diagnostic tool. Most of the published studies on the first topic, SPECT findings associated with a clinical behavior problem are too small to produce reliable estimates. The largest study was by Amen and colleagues (1997). They compared SPECT scans of children with and without ADHD both at rest and while performing an intellectual stress task. The study found significantly decreased prefrontal activity during the intellectual stress activity in the ADHD group, but not the non-ADHD group. The Amen study is inconclusive due to the small sample size and lack of adjustment for confounding variables. Moreover, since only 65% of the participants with ADHD had decreased prefrontal activity during intellectual stress, it is not clear how the SPECT information would be used to help diagnose ADHD. In addition, Dr. Amen has a private clinic that performs SPECT which may bias the study's methods and conclusions. Gustafsson and colleagues performed a variety of tests on 28 children with ADHD, including brain SPECT and EEG. The investigators did not find a significant association between EEG and SPECT findings. They found several statistically significant correlations between regional cerebral blood flow detected by SPECT and several instruments, particularly the number of Minor Physical Abnormalities (MPA). The vast majority of statistical comparisons were not statistically significant, and since such a large number of comparisons were performed at $p<0.05$, some significant findings would be expected by chance alone. No empirical evidence was identified on the effectiveness of brain SPECT at assisting practitioners in making a clinical diagnosis, e.g. of ADHD. Such a study would compare the diagnosis made by practitioners with and without information from SPECT, with the diagnosis confirmed by a qualified objective third party. In addition, there was no empirical evidence on the long-term safety of SPECT brain imaging in children. In conclusion, there is insufficient evidence in the published literature on the ability of SPECT brain imaging to diagnose behavior problems or assist clinicians in making a diagnosis, and insufficient evidence on the safety of brain SPECT in the pediatric population.

Articles: Objective 1a: The ideal study design is a comparison of brain function or structure as assessed by SPECT among individuals with and without behavioral problems. Methodological features include sufficient

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sample size, appropriate selection of controls, matching or controlling for confounding variables, objective confirmation of diagnosis and appropriate statistical analysis. Several studies were identified that compared brain activity using SPECT among children with ADHD and healthy controls. The studies were generally limited by small sample sizes. Most included 20 or fewer children with ADHD and 7 or fewer controls. The largest study (n=54 ADHD, n=18 non-ADHD) was conducted by a prominent SPECT practitioner (Dr. Amen)—this study was critically appraised. Objective 1b: The ideal study of diagnostic accuracy would report the sensitivity and specificity of SPECT imaging and include an independent blinded comparison to a "gold standard" diagnosis. No studies that met the above criteria were identified. Only one study compared SPECT findings to another imaging technique, EEG (Gustafasson et al., 2000) and this study was critically appraised
Objective 2: A strong study would compare the accuracy of the diagnosis made with and without information from SPECT imaging, with the diagnosis confirmed by an objective expert such as experienced psychiatrist blinded to diagnosis. No relevant studies were identified. Objective 3: No studies were identified on the long-term safety of SPECT brain imaging in children. *The studies that were critically appraised were:*
Amen DG, Carmichael BD. High-resolution brain SPECT imaging in ADHD. Ann Clin Psychiatry 1997; 9: 81-86. See Evidence Table**.** Gustafsson P, Thernlund G, Ryding E et al. Associations between cerebral blood flow measured by single photon emission computed tomography (SPECT), electro-encephalogram (EEG), behavior symptoms, cognition and neurological soft signs in children with attention-deficit hyperactivity disorder (ADHD). Acta Pediatr 2000; 89: 830-835. See Evidence Table.

The use of Single Photon Emission Computed Tomography in the evaluation of origin of behavior problems does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

DaT-SPECT

Movement disorders are neurological conditions that affect the speed, fluency, quality, and ease of movement. They include a wide range of disorders including, but not limited to, Parkinsonian syndromes (PS) and essential tremor (ET). ET, the most common movement disorder, typically involves involuntary shaking movement with no cause. PS, on the other hand, is a group of neurodegenerative disorders that have similar features and symptoms, of which, the most frequent form is idiopathic Parkinson's disease (PD) accounting for 80% of all PS. Although ET and PS have different underlying etiologies, they present with similar clinical features, especially in the early stages of disease progression, thus complicating diagnostic differentiation. Accurate diagnosis of patients with suspected PS is critical for patient management because the disease course, therapy and prognosis greatly differ from non-degenerative diseases (Dauer and Przedborski 2003; de Lau and Breteler 2006).

Currently, the gold standard for the diagnosis of PS is post-mortem neuropathological examination. In practice, however, diagnosis is based on the presence of two or more classical motor features including bradykinesia, rigidity, tremor, and postural instability which can be atypical or mild in the early stages of the disease. Long-term clinical follow-up and good response to dopaminergic drugs have also been used to support clinical diagnosis (de la Fuente-Fernández 2012). Pathologic studies have shown that the lack of an objective diagnostic tool has resulted in an error rate of 10-30% (Rajput, Rozdilsky et al. 1991). Misdiagnosis can lead to unnecessary disability if effective treatment options are not initiated, and inappropriate therapies may unnecessarily expose patients to the potential side effects thus warranting an early and accurate diagnostic tool to ensure appropriate management.

DaTscan™ is a recent advance in imaging technology that supports the clinician in the differential diagnosis of PS and ET. While there is limited knowledge on the etiology of ET, the main pathological hallmark of PS is the loss of dopaminergic neurons in the substantia nigra, leading to striatal dopamine depletion (Dauer and Przedborski 2003). The DaTscan™ technology is able to determine the location and measure the amount of dopamine transporter (DaT) in the brain. More specifically, through small amounts of a contrast agent called (^{123}I)ioflupane and using a single photon emission computerized tomography (SPECT) scanner, DaTscan™ is able to demonstrate reduced striatal uptake of DaT where PS is present and, in contrast, normal striatal uptake in patients with ET. The results of DaTscan™ are not intended to differentiate between different PS disorders, but instead, should be used when diagnosis is inconclusive to rule out other movement disorders with similar presenting symptoms.

In January 2011, the U.S. Food and Drug Administration (FDA) approved the DaTscan™ for striatal dopamine transporter (DaT) visualization using SPECT brain imaging to assist in the evaluation of adult patients presenting with symptoms or signs suggestive of dopaminergic neurodegeneration. In these patients, DaTscan may be used to help differentiate ET from tremor due to PS and is intended for use as an adjunct to other diagnostic evaluations.

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Medical Technology Assessment Committee (MTAC)

DaT-SPECT

02/10/2014: MTAC REVIEW

Evidence Conclusion: Marshall and colleagues conducted a prospective, longitudinal study. Among 102 patients with an early Parkinsonian syndrome with or without tremor (possible and probable) vs. a combination of patients with non-PD tremor (essential or dystonic tremor) and healthy volunteers. Clinical and DaTscan assessments were made at baseline, 18 months, and 36-month follow-up. The primary endpoint was the baseline DaTscan image assessment by three independent blinded readers as normal or abnormal. The standard of truth was the clinical diagnosis established by two independent movement disorder specialists in consensus, based on the assessment of patient's clinical examination videos at 36 months of follow-up. The standard of truth was used to judge whether or not a subject had a striatal dopaminergic deficit (Marshall, Reininger et al. 2009). Ultimately, the study concluded that in the 99 patients who completed all three assessments, on-site clinical diagnosis over-diagnosed degenerative parkinsonism at baseline (sensitivity was 93% and specificity was 46%) compared with the standard of truth clinical diagnosis (sensitivity 78% and specificity 97%). See Evidence Table. Vlaar and colleague's meta-analysis included eight studies that specifically assessed the diagnostic differentiation between PD and ET and concluded that SPECT with presynaptic tracers may accurately differentiate between patients with PD and ET with a reported sensitivity ranging from 88-100% and specificity of 80%-100%. Two of the included studies compared the diagnostic accuracy of the treating physician with the SPECT in its capacity to delineate PD from ET. Initial clinical diagnosis in these trials reached a sensitivity of respectively 76% and 87% and a specificity of 50% and 80%. More often than not, the included studies compared DaTscan diagnoses with clinical diagnoses, and it is not known how often the clinical diagnosis was wrong. Ideally, a study would follow patients until death to confirm diagnosis with autopsy (Vlaar, van Kroonenburgh et al. 2007). See Evidence Table *Risks of Diagnostic Test:* The Marshall et al. study, recorded adverse events (AE) at each follow-up visit. During the 36-month period, a total of 4 subjects died and 32 subjects (18%) experienced 71 nonfatal serious AEs, none of which were deemed to be related to the DaTscan. Only 24 (6.0%) AEs, reported by 13 subjects were considered to be related to the DaTscan. The most common AEs were headache (3%), nausea (2%), injection site hematoma (1%), dizziness (1%) and dysgeusia (1%) (Marshall, Reininger et al. 2009). Kupsch and colleagues also collected information on AE in their study which only resulted in two patients with AE that were considered related to the DaTscan. Both of the events, sleep disorder and headache, occurred following administration and prior to imaging and required no treatment (Kupsch, Bajaj et al. 2012). *Impact on Diagnosis and Patient Management:* In practice, clinical diagnosis is sufficient and accurate for many patients with advanced and typical manifestations of PD. There is a subset of patients, however, with suspected PS, particularly those with early-stage disease or atypical signs and symptoms, who theoretically may benefit from further diagnostic evaluation. The recently published, and rigorous evaluation of the impact of diagnostic test on clinical outcomes is a randomized, prospective, multicenter, global (US and Europe), controlled clinical trial conducted by Kupsch and colleagues in 2012. The study sought to demonstrate the impact of (^{123}I) Ioflupane on clinical management, diagnosis and confidence of diagnosis during a one-year follow-up in 273 patients with clinically uncertain PS of whom 138 were randomized to (^{123}I) Ioflupane and 135 randomized to no imaging. Significantly more patients in the (^{123}I) Ioflupane imaging group had at least one change in their actual clinical management after 12 weeks ($p=0.002$) and after 1 year ($p<0.001$) compared with patients in the control group. In addition, significantly more (^{123}I)ioflupane patients had changes in diagnosis and an increased confidence diagnosis at 4 weeks, 12 weeks and 1 year (all $p<0.001$) compared with control patients (Kupsch, Bajaj et al. 2012). See Evidence Table. Although the literature reports good accuracy with minimal safety concerns, the studies should be interpreted with caution. It is important to remember that throughout the literature, there was no autopsy confirmation of diagnosis, and thus no confirmed "gold standard". The interpretation of the imaging data is controversial due to inter-reader reliability and the target populations are poorly defined with many studies using clearly defined later-stage patients that are obviously not representative of the FDA indication. Even with the use of the DaTscan, the diagnosis of PS remains a clinical judgment based on imaging technology. Finally, it should be noted that the majority of the literature has received some sort of industry sponsoring. Conclusion*:* The evidence supports high sensitivity and specificity, but the lack of a gold standard limits the value of these numbers. There is evidence to indicate that the use of DaTscan™ can sometimes result in changes in diagnosis and treatment, however, there is no evidence to support that these changes result in improved health outcomes.

Articles: The literature search for studies on the accuracy of DaTscan in patients with suspected PS revealed almost 200 articles that assessed the DaTscan in a variety of differential diagnostic situations. This search was further narrowed down to include studies that specifically addressed diagnostic differentiation between PS and ET. For the most part, the literature was comprised of studies that were small with limited methodology due to a lack of gold standard for diagnosis.

The following articles were selected for critical appraisal:

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Marshall VL, Reininger CB, Marquardt M et al. Parkinson's Disease is overdiagnosed clinically at baseline in diagnostically uncertain cases: A 3-year European multicenter study with repeat [^{123}I]-FP-CIT SPECT. *Movement Disorders*. 2009;24(4):500-508. See Evidence Table. Vlaar AM, van Kroonenburgh MJ, Kessles AG, et al. Meta-analysis of the literature on diagnostic accuracy of SPECT in parkinsonian syndromes. BMC Neurol 2007; 7:27. See Evidence Table. Kupsch AR, Bajaj N, Weiland F, et al. Impact of DaTscan SPECT imaging on clinical management, diagnosis, confidence of diagnosis, quality of life, health resource use and safety in patients with clinically uncertain parkinsonian syndromes: a prospective 1-year follow-up of an open-label controlled study. *J Neurol Neurosurg Psychiatry*. 2012; 83:620-628. See Evidence Table.

The use of DaT-SPECT does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Evaluation of Origin of Behavior Problems –
Considered Not Medically Necessary:

CPT® or HCPC Codes	Description
	With ADHD dx F90.0-F90.9
78803	Radiopharmaceutical localization of tumor, inflammatory process or distribution of radiopharmaceutical agent(s) (includes vascular flow and blood pool imaging, when performed); tomographic (SPECT), single area (eg, head, neck, chest, pelvis) or acquisition, single day imaging
78830	Radiopharmaceutical localization of tumor, inflammatory process or distribution of radiopharmaceutical agent(s) (includes vascular flow and blood pool imaging, when performed); tomographic (SPECT) with concurrently acquired computed tomography (CT) transmission scan for anatomical review, localization and determination/detection of pathology, single area (eg, head, neck, chest, pelvis) or acquisition, single day imaging

DaT-SPECT-
Medicare – Medical Necessity review not required
Non-Medicare - Considered Not Medically Necessary

CPT® Codes	Description
78803	Radiopharmaceutical localization of tumor, inflammatory process or distribution of radiopharmaceutical agent(s) (includes vascular flow and blood pool imaging, when performed); tomographic (SPECT), single area (eg, head, neck, chest, pelvis) or acquisition, single day imaging
A9584	Iodine I-123 Ioflupane, diagnostic, per study dose, up to 5 mCi
ICD-10 Codes	**Description**
G20	Parkinson's disease
G25.0	Essential tremor
G40	Epilepsy and recurrent seizures

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
10/26/2006	04/04/2011 MDCRPC, 02/07/2012 MDCRPC, 12/04/2012 MDCRPC, 10/01/2013 MPC, 08/05/2014 MPC, 06/02/2015MPC, 04/05/2016MPC, 02/07/2017MPC, 12/05/2017MPC, 11/06/2018MPC, 11/05/2019MPC, 11/03/2020MPC, 11/02/2021MPC, 11/01/2022MPC	05/25/2023

MDCRPC Medical Director Clinical Review and Policy Committee

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MPC Medical Policy Committee

Revision History	Description
05/25/2023	Merged DaT-Spect criteria with SPECT criteria set.

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Clinical Review Criteria
Speech Generating Devices

- Augmented and Alternative Communication Devices or Communicators

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Speech Generating Device (50.1)
Local Coverage Determinations (LCD)	Speech Generating Device (L33739)
Local Coverage Article	None

For Non-Medicare Members

Kaiser Permanente has elected to use the Augmentative Communication Devices, Electronic (KP-0516) MCG* for medical necessity determinations. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.

MCG* are proprietary and cannot be published and/or distributed. However, on an individual member basis, Kaiser Permanente can share a copy of the specific criteria document used to make a utilization management decision. If one of your patients is being reviewed using these criteria, you may request a copy of the criteria by calling the Kaiser Permanente Clinical Review staff at 1-800-289-1363 or access the MCG Guideline Index using the link provided above.

If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider and/or specialist (neurology)
- Speech therapy notes

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Augmentative and alternative communication (AAC) is an area of clinical practice that attempts to temporarily or to permanently compensate for the impairment and disability patterns of children with severe oral and written expressive communication disorders. Interventions that use AAC should incorporate the individual's full communication abilities e.g. any existing speech or vocalization, gestures, manual signs, communication boards, and speech output communication devices. Abilities may change over time and the AAC may need to be modified as a child grows and develops.

AAC has four components: symbols, aids, techniques, and strategies. Aids are the physical objects or devices used to transmit or receive messages. These include books, communication boards, charts, mechanical or electronic devices, and computers. The AAC devices have variable capabilities, durability, and cost. The delivery of AAC services to children with severe spoken language disorders requires the collaboration and competence of

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families, professionals, and paraprofessionals. Effective, co-coordinated multidisciplinary and an integrated service is crucial in achieving optimal outcome for the children.

The role an AAC system plays in a particular child's life varies with the type and severity of the language disorder. Children with congenital language disorders who may benefit from AAC include those with cerebral palsy, dual sensory impairments, developmental apraxia, oro-motor dyspraxia, language learning disabilities, mental retardation, autism, and pervasive developmental disorders. Acquired language disorders include: traumatic brain injury, aphasia, spinal cord injuries, and other physical disabilities. Not all these indications are covered by health insurance companies.

Medical Technology Assessment Committee (MTAC)

Augmentative Communication Devices

02/13/2002: MTAC REVIEW

Evidence Conclusion: The study reviewed had several limitations; it had a small sample size, lacked a control group, used only subjective measures, and was subject to selection and observation biases. In conclusion the literature available does not provide enough evidence to determine the effect of the augmentative communication devices on the communication skills of children with speech impairments.

Articles: The search yielded 43 articles. Most were reviews, tutorials, notes, and discussions. The search did not reveal any randomized controlled trials, or meta-analyses, only four case reports and two studies that only measured young patients' or parents' satisfactions and /or utilization of the communication systems. The study with the larger sample size was selected for critical appraisal. *An evidence table was created for the following study:* Ko MLB, et al. Outcome of recommendations for augmentative communication in children. *Child Care, Health and Development* 1998; 24(3): 195-205. See Evidence Table.

The use of augmentative communication devices on the communication skills of children with speech impairments not voted using the *Kaiser Permanente Medical Technology Assessment Criteria*.

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
E1902	Communication board, nonelectronic augmentative or alternative communication device
E2500	Speech generating device, digitized speech, using prerecorded messages, less than or equal to eight minutes recording time
E2502	Speech generating device, digitized speech, using prerecorded messages, greater than eight minutes but less than or equal to 20 minutes recording time
E2504	Speech generating device, digitized speech, using prerecorded messages, greater than 20 minutes but less than or equal to 40 minutes recording time
E2506	Speech generating device, digitized speech, using prerecorded messages, greater than 40 minutes recording time
E2508	Speech generating device, synthesized speech, requiring message formulation by spelling and access by physical contact with the device
E2510	Speech generating device, synthesized speech, permitting multiple methods of message formulation and multiple methods of device access
E2511	Speech generating software program, for personal computer or personal digital assistant
E2512	Accessory for speech generating device, mounting system
E2599	Accessory for speech generating device, not otherwise classified

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Creation Date	Review Date	Date Last Revised
06/18/2001	03/02/2010[MDCRPC], 02/10/2011[MDCRPC], 12/06/2011[MDCRPC], 10/02/2012[MDCRPC] ,08/06/2013[MPC],11/05/2013[MPC], 09/02/2014[MPC], 07/07/2015[MPC], 05/03/2016[MPC], 03/07/2017[MPC], 01/09/2018[MPC], 12/04/2018[MPC], 12/03/2019[MPC], 12/01/2020[MPC],12/07/2021[MPC],12/06/2022[MPC], 12/09/2023[MPC], 02/13/2024[MPC]	08/31/2015

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
08/31/2015	Added Update to Pub. 100-03 NCD Manual
02/26/2024	Removed CPT 92609 from criteria page as this code is for the service and not the device.

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Clinical Review Criteria
Sphenopalatine Ganglion (SPG) Block

- Allevio SPG Nerve Block Catheter
- SphenoCath
- TX360

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article (LCA)	Billing Medicare for the SphenoCath® and Other Similar Devices (A55585)
Kaiser Permanente Medical Policy	Due to the absence of an active NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Clinical Review Criteria, ***Sphenocath Ganglion Block,*** for medical necessity determinations. Use the Non-Medicare criteria below.

For Non-Medicare Members

No review required at this time.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Sphenopalatine ganglion (SPG):

Robbins et al., 2016: The SPG is a triangular ganglion situated in the pterygopalatine fossa (PPF) on the medial wall. It is suspended by two branches of the maxillary nerve. The SPG received 3 inputs from the sensory, sympathetic, & parasympathetic fibers which innervate the face and head. The parasympathetic fibers originate from the superior salivatory nucleus (SSN) in the brainstem. The SSN stimulates the SPG whose activation results in pain/headache through several mechanisms (production of vasoactive peptides, neurogenic inflammation, vasodilation). SPG activation is therefore responsible for the clinical symptoms seen in migraine headaches, cluster headaches, trigeminal-mediated headaches and other headaches. Treatments that block SPG may alleviate headaches.

SPG block:

There are three methods to complete SPG block: transnasal, transoral, and transcutaneous blocks (Alexander et al., 2020). Some of these approaches utilized intranasal devices. Intranasal devices use catheter to perform

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sphenopalatine ganglion blockade. There are several devices including Sphenocath, Allevio SPG nerve block catheters, and Tx360 nasal applicator. Sphenocath is the focus of the current review.

Sphenocath:
Sphenocath is composed of an external sheath in which there is a catheter with a preformed angle (http://sphenocath.com/). The device is introduced in the nasal cavity and inserted in the superior part of the middle nasal turbinate while the patient is in supine position with extension of the cervical spine. The procedure can be performed under fluoroscopy to locate the tip of the sheath. The anesthetic agent, 1-2 ml of 2% lidocaine is then administered by the catheter. After the procedure, the patient remains in supine position for 10 minutes (Robins et al., 2016). Sphenocath may prevent nasal mucosal irritation due to its flexibility and physical integrity (http://sphenocath.com/).
There are several indications for the procedure. However, the review focuses on the efficacy and safety of the procedure on migraine and trigeminal neuralgia. Contraindications consist of allergy to lidocaine, stenosis of nasal canal, inability to thread the catheter, and severe cardiac arrhythmia (Forrest et al., 2018).

Migraine:
Migraine is an attack of intermittent headache lasting four to 72 hours with or without aura. Fifteen percent (15%) of US population has migraine. Patients with migraine experience pain with visual disturbances (flashes, sparks, luminous hallucinations), photophobia, aura. Migraine can be precipitated by emotions and is associated with nausea and vomiting. Several medications including triptans, nonsteroidal anti-inflammatory drugs (NSAIDs), opiate-based analgesics, and ergotamine tartrate are available for the management of acute episodic and chronic migraine (Mwanburi et al., 2018).

Trigeminal neuralgia:
Trigeminal neuralgia (TN) is a severe, shock-like, paroxysmal pain in the face along the divisions of the trigeminal nerve. It can be precipitated by touching the face. Its management consists of sodium channel blockers and neurosurgical intervention (second line treatment) (Maarbjerg et al., 2017).

Medical Technology Assessment Committee (MTAC)

Sphenopalatine ganglion block using Sphenocath device for migraine and trigeminal neuralgia

Date: 01/11/2021

Evidence Conclusion:

- No studies comparing Sphenocath device to other methods performing SPG block were identified. The studies reviewed were of very low quality.

- There is insufficient evidence to determine the efficacy and safety of sphenopalatine ganglion block using Sphenocath device in patients with migraine.

- There is insufficient evidence to determine the efficacy and safety of SPG block using Sphenocath device in patients with trigeminal neuralgia.

Articles:
PubMed was searched through December 3, 2020 with the search terms ((migraine) AND (sphenopalatine ganglion block OR sphenopalatine block OR SPG OR sphenopalatine ganglion)) AND (Sphenocath) with variations. The search was limited to English language publications and human populations. The reference lists of relevant studies were reviewed to identify additional publications. RCTs, meta-analysis of RCTs, observational studies were included in the search. Regarding trigeminal neuralgia, search terms included: sphenopalatine ganglion block AND trigeminal neuralgia. Four studies were reviewed. Clinicaltrial.gov was also searched and found one study with no results (NCT03666663). See Evidence Table**.**

The use of Sphenopalatine ganglion block using Sphenocath device for migraine and trigeminal neuralgia does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Medicare and Non-Medicare: No review required – *may be submitted with the following code(s)*

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CPT® or HCPC Codes	Description
64999	Unlisted procedure, nervous system

Non-Medicare: No review required

CPT® or HCPC Codes	Description
64505	Injection, anesthetic agent; sphenopalatine ganglion

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed	Date Last Revised
03/02/2021	03/02/2021[MPC], 03/01/2022[MPC], 03/07/2023[MPC]	

[MPC] Medical Policy Committee

Revision History	Description
03/02/2021	MPC approved to adopt coverage Sphenopalatine Ganglion (SPG) Block

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KAISER PERMANENTE®

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Clinical Review Criteria
Spinal Cord Stimulator for Pain

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Electrical Nerve Stimulators (160.7) Assessing Patient's Suitability for Electrical Nerve Stimulation Therapy (160.7.1)
Local Coverage Determinations (LCD)	Spinal Cord Stimulators for Chronic Pain (L36204)
Local Coverage Articles (LCA)	Spinal Cord Stimulators for Chronic Pain (A57792)

For Non-Medicare Members

Dorsal column (spinal cord) neurostimulation is the surgical implantation of neurostimulator electrodes within the dura mater (endodural) or the percutaneous insertion of electrodes in the epidural space.

A. Kaiser Permanente covers a ***short-term*** trial of a dorsal column spinal cord stimulator (SCS) as medically necessary for the treatment of chronic, intractable pain secondary to **ONE of the following** indications:
   1. Failed Back Syndrome (FBS) with intractable neuropathic leg pain, (FBS or post-laminectomy syndrome is a condition characterized by chronic pain following back surgeries.) **OR**
   2. Complex Regional Pain Syndrome (CRPS)/Reflex Sympathetic Dystrophy (RSD) when **ALL of the following** criteria are met:
      a. Failure of at least six consecutive months of physician-supervised conservative medical management (e.g., pharmacotherapy, physical therapy, cognitive therapy, and activity lifestyle modification)
      b. Surgical intervention is not indicated
      c. An evaluation by a mental health provider (e.g., a face-to-face assessment with or without psychological questionnaires and/or psychological testing) reveals no evidence of an inadequately
      d. Controlled mental health problem (e.g., alcohol or drug dependence, depression, psychosis) that would negatively impact the success of a SCS or contraindicate its placement

B. Kaiser Permanente covers ***permanent*** implantation of a dorsal column spinal cord stimulator (SCS) as medically necessary for the treatment of chronic, intractable pain secondary to **ONE of the following** indications:
   1. Beneficial clinical response from a temporarily implanted electrode has been demonstrated prior to consideration of permanent implantation (Member experienced significant pain reduction (70% or more) with a 3- to 7-day trial)
   2. Covered for the **ONE of the following** indications:
      a. Failed Back Syndrome (FBS) with intractable neuropathic leg pain (FBS or post-laminectomy syndrome is a condition characterized by chronic pain following back surgeries.) **OR**
      b. Complex Regional Pain Syndrome (CRPS)/Reflex Sympathetic Dystrophy (RSD) when **ALL of the following** criteria are met:
         - Failure of at least six consecutive months of physician-supervised conservative medical management (e.g., pharmacotherapy, physical therapy, cognitive therapy, activity lifestyle modification

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- Surgical intervention is not indicated
- An evaluation by a mental health provider (e.g., a face-to-face assessment with or without psychological questionnaires and/or psychological testing) reveals no evidence of an inadequately controlled mental health problem (e.g., alcohol or drug dependence, depression, psychosis) that would negatively impact the success of a SCS or contraindicate its placement

If requesting these services, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist
- Last 6 months of radiology notes if applicable

High Cervical Epidural Neurostimulation (Spinal Cord Stimulator) for Migraine/Cluster Headaches
There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies or provides better long-term outcomes than current standard services/therapies.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Spinal cord stimulation (SCS) involves insertion of a stimulator electrode into the spinal cord that is connected to a power source. Patients are routinely screened for their likelihood of being a good SCS candidate by temporary placement of a percutaneous epidural electrode. Patients who respond well during the trial period (generally defined as 50% pain relief) can undergo permanent electrode placement. Both temporary and permanent devices are manufactured by Medtronic, Inc.

The most common application of SCS in the United States is chronic low back pain; SCS has also been used for plexus lesions, peripheral nerve injury, reflex sympathetic dystrophy, post amputation pain syndromes, spinal cord injury, post cordotomy dysesthesia, peripheral vascular disease and angina pectoris (North, 1995).

MTAC has previously reviewed SCS. The initial review of SCS in April 2000 evaluated the use of SCS to treat intractable pain and was not limited to a particular disease or condition. At that time, the evidence consisted of case series and a small RCT with threats to validity on SCS for failed back pain syndrome (North, 1995). The item failed MTAC evaluation criteria. Conclusions about the North RCT in this review were: “Preliminary results of this RCT show that more patients assigned to reoperation choose to crossover to SCS than patients assigned to SCS opt for re-operation. It is not known from this study whether actual pain relief is greater for SCS than re-operation.”

In October 2000, a second review was conducted due to the publication of a RCT on the effect of SCS on functional status and pain in patients with chronic reflex sympathetic dystrophy (Kemler, 2000). Again, SCS failed MTAC evaluation criteria. Conclusions about the Kemler study in the MTAC report were: “In the intention to treat analysis, this new RCT did not find a difference in functional status improvement between the two groups. There was significantly greater improvement in the SCS group in two outcome measures (pain score as measured by a visual-analogue scale, global perceived effect of intervention), but not in health-related quality of life. A substantial proportion of patients experienced complications. The study had several limitations, which include:

- The choice of physical therapy as the comparison intervention. All patients in the study had already failed 6 months of physical therapy. This may have biased the study towards finding improved outcomes with the SCS intervention, which had not yet been attempted with these patients.
- Potential bias towards more positive responses on self-report measures among patients who received the SCS intervention (a new and more intensive intervention, patients were not blinded).
- The difference in scores between groups on the pain measure, although statistically significant, has unclear clinical significance.
- The analysis that compared patients who actually received SCS to those assigned to physical therapy is subject to selection and observation biases. The analysis is biased towards finding a positive outcome in the SCS group since only patients shown to benefit from SCS during the test period were included and the comparison group included patients previously found to receive no sustained benefit from physical therapy.

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Due to the above factors, the new evidence is not sufficient to permit conclusions about the effects of spinal cord stimulation on health outcomes for patients with reflex sympathetic dystrophy."

The current review attempted to identify any recent literature on the use of SCS for intractable pain; the review was not limited to any specific condition.

Medical Technology Assessment Committee (MTAC)

High Cervical Epidural Neurostimulation (Spinal Cord Stimulator) for Migraine/Cluster Headaches

BACKGROUND

Implanted electrical stimulation devices have been used for the management of chronic intractable pain since the late 1960s. One of the most commonly used devices is the spinal cord stimulation (SCS) system. This consists of a lead tipped with 4-16 electrodes and a small implantable device. The latter may be battery operated or powered by an externally worn power source. Electrical current from the lead generates parasthesia that can be adjusted in intensity and location to achieve the optimum pain relief (North 2003, 2005, Buchser 2006). Candidates for this therapy include patients with intractable chronic pain of the body and limbs, continued pain after back surgery, reflex sympathetic dystrophy, and complex regional pain syndrome. SCS has been used for decades to treat neurogenic pain. It is now being evaluated for the use in patients with migraines and cluster headaches. Patients with pacemakers, implantable cardioverter defibrillators, untreated drug addicts, and pregnant women are not candidates for the therapy (Arcidicono 2006). It is also contraindicated for patients with chronic anticoagulation, severe distortion or disease of the spinal column, or infection at the insertion site. Patient cooperation is essential for the successful use of SCS therapy. It should not be used by patients who cannot operate the device e.g. those with cognitive, psychiatric, or psychomotor disorders (North 2003, North 2005, and Arcidicono 2006). Spinal cord stimulation was approved by the FDA for the treatment of chronic intractable pain in the trunk and limbs, but it has not been approved for the use in migraines and cluster headaches. This technology has been reviewed previously for the use in back pain, leg pain, refractory angina, and critical leg ischemia

04/19/2010: MTAC REVIEW

High Cervical Epidural Neurostimulation (Spinal Cord Stimulator) for Migraine/Cluster Headaches

Evidence Conclusion: Currently, there is insufficient evidence to evaluate this technology as the literature only consists of case reports and case series with less than twenty-five participants. Two randomized controlled trials, the Precision Implantable Stimulator for Migraine (PRISM) and the Occipital Nerve Stimulator for the Treatment of Intractable Chronic Migraine (ONSTIM), have recently been completed and results are pending.

Articles: Currently, there is insufficient evidence to evaluate this technology as the literature only consists of case reports and case series with less than twenty-five participants. Two randomized controlled trials, the Precision Implantable Stimulator for Migraine (PRISM) and the Occipital Nerve Stimulator for the Treatment of Intractable Chronic Migraine (ONSTIM), have recently been completed and results are pending.

The use of High cervical epidural neurostimulation (Spinal Cord Stimulator) for the treatment of migraine/cluster headaches does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Spinal Cord Stimulators in the Treatment of Intractable Pain

04/12/2000: MTAC REVIEW

Evidence Conclusion: There is weak evidence from the case series studies that about half of patients with back or extremity pain who tolerate SCS for a year have a successful outcome one-year post-implantation. The Broggi et al. study provides weak evidence that long term success rates (i.e. 5 years) are low. Conclusions about efficacy cannot be drawn from the RCT because of the small sample size, high refusal rate and poor outcome measurement. Complications from SCS are mainly minor, but these often require reoperation. There is insufficient evidence to draw conclusions about the efficacy of SCS for peripheral vascular diseases, peripheral neuropathy, multiple sclerosis and reflex sympathetic dystrophy.

Articles: Articles were selected based on study type; there was one randomized controlled trial (RCT), there were no cohort studies or meta-analyses. The remaining empirical studies were case series. Most addressed one clinical area (predominantly failed back surgery syndrome) and several addressed intractable pains in multiple clinical areas. There was one small case series each on peripheral vascular disease (n=10), reflex sympathetic dystrophy (n=12) and peripheral neuropathy (n=10). Articles on critical limb ischemia, angina pectoris and spinal cord injury were not considered for this review (these conditions were not specified in the MTAC request).

Evidence tables were created for the three largest case series studies and one RTC. These examined:

Burchiel, KJ, Anderson, VC, Brown, FD, Fessler, RG, Friedman, WA, Pelofsky, S, Weiner, RL, Oakley, J, Shatin, D. Prospective, multicenter study of spinal cord stimulation for relief of chronic back and extremity pain. Spine 1996; 21: 2786-2794. See Evidence Table**.** Failed back surgery syndrome (De la Porte, C, Van de Kelft, E.

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Spinal cord stimulation in failed back surgery syndrome. Pain 1993; 52: 55-61); See Evidence Table**.** Multiple conditions (Broggi, G, Serville, D, Dones, I, Carbone, G. Italian multicentric study on pain treatment with epidural spinal cord stimulation. Stereotact Funct Neurosurg 1994; 62: 273-278). See Evidence Table**.** (North, RB, Kidd, DH, Piantadosi, S. Spinal cord stimulation versus reoperation for failed back surgery syndrome: A prospective, randomized study design. Acta Neurchir 1995; 64: 106-108). See Evidence Table**.** Kemler MA, Barendse GAM, Kleef VM, deVet HCW, Rijks CPM, Furnee CA, Van Den Wildenberg, NEJM. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. N Engl J Med 2000; 343: 618-24. See Evidence Table.

The use of Spinal Cord Stimulators in the treatment of intractable pain does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

10/11/2000: MTAC REVIEW
Spinal Cord Stimulators in the Treatment of Intractable Pain
Evidence Conclusion: In the intention to treat analysis, this new RCT did not find a difference in functional status improvement between the two groups. There was significantly greater improvement in the SCS group in two outcome measures (pain score as measured by a visual-analogue scale, global perceived effect of intervention), but not in health-related quality of life. A substantial proportion of patients experienced complications.
The study had several limitations, which include: The choice of physical therapy as the comparison intervention. All patients in the study had already failed 6 months of physical therapy. This may have biased the study towards finding improved outcomes with the SCS intervention, which had not yet been attempted with these patients. Potential bias towards more positive responses on self-report measures among patients who received the SCS intervention (a new and more intensive intervention, patients were not blinded). The difference in scores between groups on the pain measure, although statistically significant, has unclear clinical significance. The analysis that compared patients who actually received SCS to those assigned to physical therapy is subject to selection and observation biases. The analysis is biased towards finding a positive outcome in the SCS group since only patients shown to benefit from SCS during the test period were included and the comparison group included patients previously found to receive no sustained benefit from physical therapy. Due to the above factors the new evidence is not sufficient to permit conclusions about the effects of spinal cord stimulation on health outcomes for patients with reflex sympathetic dystrophy
Articles: The search yielded 184 articles. Many of these were reviews or opinion pieces, were on related procedures or evaluated SCS for indications other than pain relief. There were 4 new RCT publications, but none of these was a new study comparing SCS to an alternative intervention. The new articles consisted of an additional publication on the Kemler 2000 data previously reviewed by MTAC, two studies that compared different SCS techniques (two types of electrodes in North, 2002 and two ways to adjust stimulation in North, 2003), and one study that compared two types of drugs given to patients who had SCS implanted (Harke, 2001). No new large case series or cohort studies were identified. There was no new evidence to critically appraise.

The use of Spinal Cord Stimulators in the treatment of intractable pain does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

12/04/2006: MTAC REVIEW
Spinal Cord Stimulators in the Treatment of Intractable Pain
Evidence Conclusion: *Spinal cords stimulation (SCS) in complex regional pain syndrome (CRPS) and refractory neuropathic back and leg pain/failed back surgery syndrome (FBSS)* Kemler et al, studied the effect of SCS plus physical therapy versus physical therapy alone, in the treatment of 54 patients with resistant chronic reflex sympathetic dystrophy. The trial was randomized and controlled, and the patients were followed up for 24 months. However, the patients and providers were not blinded, and the primary outcomes were mainly self-reported and subject to bias. There was no comparison arm with a sham treatment to exclude the placebo effect and reduce bias. The SCS therapy was compared to physical therapy, which is not the ideal control as the study participants were those who did not have a sustained response to standard treatment including physical therapy. The results of the trial show that patients randomized to receive SCS plus PT (ITT analysis) or those who actually received a permanent SCS implant plus PT had statistically greater improvement in the two self-reported outcome measures (pain score as measured by a visual-analogue scale, global perceived effect of intervention). No statistical difference between two groups in the functional status was observed. There was s significant improvement in the QoL among patients who actually received the SCS implant plus PT vs. PT alone. The SCS therapy was associated with side effects among all patients who received it, and 38% needed a reoperation related to the implant. North and colleagues' (2005) RCT evaluated the use of spinal cord stimulation versus reoperation for the treatment of patients with failed back surgery syndrome (FBSS). The investigators included 50 patients with pain refractory to conservative treatment, with concordant neurological, tension, and/or mechanical signs and imaging

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findings of neural compression. The follow-up duration was 2 years, and the study outcomes were the frequency of crossover to alternative procedure, pain control and patient satisfaction. The results show that significantly more patients in the SCS group achieved ≥50% pain relief compared with those who underwent reoperation (37.5 % vs. 12 %, p= 0.02). They also required significantly less opioid analgesics. The rate of cross over to the other treatment was significantly less among those randomized to spinal cord stimulation. The trial had several exclusion criteria, which may limit generalization of the results. *Spinal cord stimulation for the management of refractory angina pectoris:* The published studies on the use of SCS for the treatment of refractory angina were all conducted in Europe. In the ESBY trial, 104 patients at high risk for coronary artery bypass surgery were randomized to SCS or CABG. The follow-up duration was 4.8 years, and the primary outcome was the effect of treatment on angina. The trial was randomized, controlled, and had clinically important outcomes. However, due to the nature of the intervention it was unblinded, it was relatively small, and may have had insufficient power to detect statistically significant differences between the two intervention groups. No comparison was made to a sham treatment, thus the placebo effect of the SCS cannot be ruled out. The results of the study show that there was a significant improvement in the quality of life in the two treatment groups when compared to baseline. The differences in the observed improvement in quality of life and survival were not significant between the two interventions. The study was not designed as equivalence study, and the absence of significant difference does not necessarily indicate that the two treatments were comparable or equivalent. The SPiRiT trial compared the effects of SCS versus percutaneous myocardial laser revascularization, on treadmill exercise time, among patients with refractory angina pectoris. The trial was randomized and controlled. However, it was unblinded, with an intermediate primary outcome, and short follow-up duration. Its results show that that there were no significant differences between the two treatment groups in the exercise tolerance at 3 and 12 moths (primary outcome). Also, no significant differences were observed in the 2 or more points improvements on the Canadian Cardiovascular Society angina class, or quality of life. Patients in the SCS group had a significantly higher event rate mainly angina or system related. A placebo effect may contribute to the improvement in anginal symptoms after SCS. The only sham controlled RCT conducted was a very small trial (n=25) that implanted the SCS in all patients but was left it inactivated for 6 weeks in the control group. The study was too small, had only 6 weeks of follow-up, and other limitations. *Spinal cord stimulation for the management of critical leg ischemia (CLI)* The published studies on the use of SCS for the treatment of critical leg ischemia were also conducted in European countries. The three meta-analyses published by Ubbink and colleagues (2004, 2005, and 2006) pooled data from 5 RCTs and one nonrandomized controlled trial. The sample sizes in these trials varied from 37 to 120 with a total of 444 participants. All suffered from inoperable CLI with ischemic rest pain or ulcers < 3cm in diameter. In these trials, the patients received standard control treatment with or without SCS, and the primary outcome was limb salvage (no amputation of foot or higher within 12 months). The meta-analysis had valid methodology. The trials included were small but were judged by the authors to have good quality. The results of the analysis indicate that highly selected patients with inoperable critical limb ischemia had better outcomes with the SCS therapy compared to those who were treated conservatively. They experienced significantly less amputation rates in 12 months (NNT to salvage a limb was 9) and showed significant clinical improvement (NNT to improve the condition from critical leg ischemia to claudications =3). The procedure was not associated with a difference in mortality or QoL vs. conservative treatment. *Conclusion:* There is insufficient evidence to determine the long-term benefits and safety of SCS therapy among patients with refractory neuropathic back and leg pain, failed back surgery, and chronic reflex sympathetic dystrophy. There is insufficient published evidence to determine the long-term efficacy and safety of SCS in treating patients with chronic refractory angina. There is fair evidence from a meta-analysis of small trials that the addition of SCS to the standard conservative therapy for patients with chronic critical leg ischemia may improve the clinical condition of the leg and lead to less amputation rates.

Articles: The search yielded 199 articles. Many were reviews or opinion pieces, or small case series with no control or comparison groups. *Spinal cords stimulation (SCS) in complex regional pain syndrome (CRPS) and refractory neuropathic back and leg pain/failed back surgery syndrome (FBSS)* The search revealed 2 systematic reviews (Taylor 2004, and Taylor 2006) of studies that used spinal cords stimulation in complex regional pain syndrome (CRPS) and refractory neuropathic back, and leg pain/failed back surgery syndrome (FBSS). It also revealed a RCT on SCS for chronic pain (North 2005), and a more recent publication with a longer-term follow-up for a RCT (Kemler 2000) that was previously reviewed f or MTAC in 2000. Several small case series with no comparison or control groups were also identified. The 2 systematic reviews were conducted by the same principal author and had several limitations. The results of the included RCTs were presented individually without pooling of data, and the results of case series were pooled. The quality of the included case series was poor as judged by the authors; they were heterogeneous, and subject to bias. Due to these as well as other limitations, the meta-analyses ware not presented in evidence tables. Evidence tables were constructed for the North et al RCT, and the more recent publication of Kemler and colleagues' RCT with the 2-year follow-up data. *Spinal cord stimulation for the management of refractory angina pectoris:* The literature search revealed three RCTs and several case series. One RCT compared SCS with coronary artery bypass grafting (ESBY trial), another

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compared it with percutaneous myocardial laser revascularization (SPiRiT), and in the third trial (Hautvast 1998) all patients received the SCS implant, but the stimulator was inactivated in the control group for the 6 weeks of study. This last trial was not critically appraised due to its small sample size (n=25), short follow-up duration as well as other limitations in the trial. The ESBY and SPiRiT trials were critically appraised. *Spinal cord stimulation for the management of critical leg ischemia:* The literature search revealed 5 randomized controlled trials, and one non- randomized comparative study on the use of SCS for the treatment of critical leg ischemia. It also revealed three systematic reviews; all conducted by the same principal authors. These analyses pooled the results of the published RCTs. All three were critically appraised and presented in one evidence table. *The following articles were critically appraised:* Kemler MA, deVet HCW, Barendse GAM, et al. the effect of spinal cord stimulation in patients with chronic reflex sympathetic dystrophy: two years' follow-up of the randomized controlled trial. Ann Neurol 2004; 55:13-18. See Evidence Table. North RB, Kidd DH, Farrokhi F, et al. Spinal cord stimulation versus repeated lumbosacral spine surgery for chronic pain: A randomized controlled trial. Neurosurg 2005; 56:98-107. See Evidence Table. Ekre O, Eliason T, Norsell H, et al. Long-term effects of spinal cord stimulation and coronary artery bypass grafting on quality of life and survival in the ESBY study. *Eur Heart J* 2002; 23:1938-1945. See Evidence Table. McNab D, Khan SN, Sharples LD, et al. An open label, single –center, randomized trial of spinal cord stimulation vs. percutaneous myocardial laser revascularization in patients with refractory angina pectoris: The SPiRiT trial. *Eur Heart J* 2006;27:1048-1053 See Evidence Table. Ubbink D T, Vermeulen H. Spinal cord stimulation for critical leg ischemia: A review of effectiveness and optimal patient selection. *J Pain Symptom Manage.* 2006;31: S30-S35. See Evidence Table. Ubbink DT, Vermeulen H. Spinal cord stimulation for non-reconstructable chronic critical leg ischemia. *The Cochrane Database of systematic reviews* 2005 Issue 3. Art No.:CD00401 DOI:10.1002/14651858.CD004001. pub2. See Evidence Table. Ubbink D T, Vermeulen H, Spincemaille GH, et al. Systematic review and meta-analysis of controlled trials assessing spinal cord stimulation for inoperable critical leg ischemia. *Br J Surg.*2004; 91:948-955. See Evidence Table.

The use of Spinal Cord Stimulators in the treatment of intractable pain, angina or leg ischemia does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® Codes	Description
63650	Percutaneous implantation of neurostimulator electrode array, epidural
63655	Laminectomy for implantation of neurostimulator electrodes, plate/paddle, epidural
63685	Insertion or replacement of spinal neurostimulator pulse generator or receiver, direct or inductive coupling
63688	Revision or removal of implanted spinal neurostimulator pulse generator or receiver
HCPC Codes	**Description**
L8679	Implantable neurostimulator, pulse generator, any type

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed	Date Last Revised
04/27/2001	06/01/2010[MDCRPC], 04/05/2011[MDCRPC], 02/07/2012[MDCRPC], 12/04/2012[MDCRPC], 10/01/2013[MPC], 12/02/2014[MPC], 10/06/2015[MPC], 08/02/2016[MPC], 06/06/2017[MPC], 04/03/2018[MPC], 04/02/2019[MPC], 04/07/2020[MPC], 04/06/2021[MPC], 04/05/2022[MPC], 04/04/2023[MPC]	04/02/2019

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

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Revision History	Description
09/28/2017	Added definition of FBS
04/02/2019	MPC approved to increase pain reduction rate from 50% to 70%

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Clinical Review Criteria
Spinal Fusion

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Criteria

All radiology studies (X-ray, MRI, etc.) must be submitted in a written form: films must be read by a Radiologist.

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article (LCA)	Spinal Fusion Services: Documentation Requirements (A53975) See also the following Medicare Technology Center article - Spinal Fusion for the Treatment of Low Back Pain Secondary to Lumbar Degenerative Disc Disease
Kaiser Permanente Medical Policy	Due to the absence of an active NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Clinical Review Criteria, "***Spinal Fusion***," for medical necessity determinations. Use the Non-Medicare criteria below.

For Non-Medicare Members

LUMBAR SPINE

**All radiology studies (X-ray, MRI, etc.) must be submitted in a written form: films must be read by a Radiologist.*

NOTE: Any operative candidate should be nicotine-free for at least 6 weeks prior to elective surgery. For persons with recent nicotine use (unless there is evidence of cord compression, or other indications for urgent intervention, noted below), documentation of nicotine cessation should include a lab report (not surgeon summary) showing blood or urine nicotine level of 0, drawn within 6 weeks prior to surgery)

NOTE: BMI > 40 is a relative contraindication to fusion in patients without progressive neurologic deficit or cord compression

Spinal Fusion may be indicated for **ONE or more** of the following:

1) Spinal fracture (acute) repair indicated by **ONE or more** of the following:
   - Spinal instability due to trauma
   - Neural compression due to trauma
2) Lumbar spinal stenosis with spondylolisthesis due to degenerative disease or congenital spondylolysis. Treatment indicated by **ALL of the following:**

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- Imaging findings of lumbar spondylolisthesis defined as ≥ 4 mm forward shift in the sagittal plane (viewed from the side) on standing flexion/extension plain x-rays **OR** Grade I or greater on the Myerding grading system (see table below)
- Clinically important findings of spinal stenosis indicated by **ONE or more** of the following:
  i. Progressive or severe symptoms of neurogenic claudication* (see below) or radicular pain/ suspected radiculopathy** (see below) with ALL of the following documented in notes:
    - Significant functional impairment
    - Central, lateral recess or foraminal stenosis demonstrated on imaging (e.g., MRI, CT myelography)
    - Failure of at least 3 months of conservative therapy*** (see below)
  ii. Severe or rapidly progressive symptoms of motor loss, neurogenic claudication, or cauda equina syndrome

The Myerding grading system measures the percentage of vertebral slip forward over the body beneath:

Grade	Percentage
grade 1	25 % of vertebral body has slipped forward
grade 2	25 % to 49 % of vertebral body has slipped forward
grade 3	50 % to 74 % of vertebral body has slipped forward
grade 4	75 % to 99 % of vertebral body has slipped forward
grade 5	Vertebral body has completely fallen off (i.e., spondyloptosis)

3) Severe degenerative scoliosis treatment with progression of deformity to greater than 30 degrees (and 40 degrees for adolescents) and having failed 3 months of conservative treatment*** (see below) and with **ONE of the following:**
   i. Persistent significant radicular pain** (see below) or weakness unresponsive to non-operative therapy
   ii. Persistent neurogenic claudication unresponsive to non-operative therapy) * (see below)
4) Spinal instability due to prior surgery for neural decompression including laminectomy (must meet criteria of imaging findings of lumbar spondylolisthesis defined as > or equal to 4 mm shift in the sagittal plane (viewed from the side) on flexion/extension plain x-rays; dislocation, infection, abscess, or tumor.
5) Anticipated spinal instability (patient has not had prior fusion) due to **ONE or more of the following**:
   - Planned extensive surgery for dislocation, infection, abscess, or tumor
   - Current plan for revision of prior decompressive surgery with anticipated instability due to wide resection needed
6) Revision fusion surgery (with history of previous fusion surgery) due to **ONE of the following:**
   - For adjacent segment disease as indicated by **ALL of the following**:
     i. Radiographic evidence of adjacent segment disease (e.g., significant neural compression that correlates with symptoms
     ii. Persistent disabling symptoms (low back pain, radiculopathy** (see below), neurogenic claudication* (see below)
     iii. Failure of 3 months of conservative therapy*** (see below)
7) Documented pseudoarthrosis (nonunion of prior fusion) **when ALL of the following** are met:
   - Radiological studies showing **ONE of the following**:
     - lucency surrounding the hardware
     - fracture of the hardware
     - absence of bridging bony arthrodesis on CT imaging 12 months or more post-operative
   - Previous fusion at least 12 months ago
   - Persistent daily axial back pain with or without neurogenic claudication* (see below) or radicular** (see below) pain
   - Significant functional impairment inability to perform activities of daily living, school, and work
   - Failure of 3 months of conservative therapy*** (see below)
8) Recurrent disc herniation in the setting of previous surgical microdiscectomy at the same level when **ALL of the following are met**:
   i. Previous disc surgery greater than 6 months ago
   ii. Recurrent neurogenic claudication* (see below) or radicular pain** (see below) unresponsive to 3 months of conservative therapy*** (see below)

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iii. Neural element compression (central, lateral recess or foraminal stenosis) documented by recent imaging consistent with signs and symptoms

The following are **NOT** considered medically necessary:

a. A lumbar fusion for a spinal deformity not meeting one of above criteria performed primarily for low back pain.
b. A lumbar fusion performed for any condition not listed above, including non-radicular pain with common degenerative changes (degenerative disc disease, facet joint arthrosis, etc.) or post-laminectomy low back pain.

* Neurogenic claudication defined as: bilateral or unilateral leg pain upon standing and walking that is temporarily relieved by forward flexion or sitting or lying down. The pain of lumbar stenosis is caused by relative ischemia of the lumbar nerve roots when in an upright position.

** Radicular pain/suspected radiculopathy defined as:

- Leg pain is > or equal to back pain present in *nerve root distribution* (e.g., L5, S1, etc.) **PLUS, ONE or MORE**:
  - Positive supine straight leg raising test - radicular leg pain reproduced when the leg is extended >30°(e.g., if patient reported pain down the posterior thigh and lateral calf, expectation is a positive SLR test would reproduce that pain and not cause nonspecific pain like calf tightness or low back pain) OR
  - Motor weakness or sensory loss in a radicular distribution (must be in a specific radicular distribution) OR
  - EMG/NCS confirms acute radiculopathy consistent with the patient's symptoms

***Conservative treatment defined as: Patients must have three months of non-operative treatment as demonstrated by a trial of one or more of the following medications:

A. Non-steroidal anti-inflammatory drugs (oral or topical)
B. Acetaminophen
C. Epidural steroid injection of corticosteroids as appropriate
   AND
D. A trial of **All** of the following physical measures:
   i. Supervised Physical therapy, attendance at >75% of sessions, minimum of 3 visits
      - At least half of PT must be in person (not virtual)
   ii. Flexibility and muscle strengthening exercises
   iii. Reasonable restriction of activities
   iv. If conservative therapy is not appropriate, the medical record must clearly document why such an approach is not reasonable.

Allograft and autograft use in spinal fusion is covered if the requested procedure meets the criteria above for a spinal fusion procedure, **with the exception of InFUSE™ Bone Graft** (see separate criteria here).

Minimally Invasive Lumbar Decompression
There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

Axial Lumbar Interbody Fusion System
There is insufficient evidence in the published medical literature to show that this procedure is as safe as standard procedures and/or provides better long-term outcomes than current standard procedure.

If requesting these services, please send the following documentation to support medical necessity:

- Specific procedure(s) requested with related procedure/diagnosis codes and identification of the disc levels for surgery
- Clinical notes to include:
  - History and Physical
    - Duration/character/location/radiation of pain
    - Activity of daily living (ADL) limitations
    - Physical examination
  - Evidence/support of specific prior conservative treatment measure(s) attempted

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- Imaging reports pertinent to performed procedure, including x-ray report of flexion-extension films that demonstrate the presence of lumbar spine instability

**All radiology studies (X-ray, MRI, etc.) must be submitted in a written form: films must be read by a Radiologist.*

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Chronic lower back pain is a major health problem and cause of disability in Western countries. The cause of the persistent pain is not well understood for the majority of patients. It generally occurs without specific damage or signs that can be revealed by imaging or other neurophysiological techniques. It is believed that the pain starts as acute pain of muscle and connective tissue and persists among approximately one third of the patients (Rittweger 2002). Mechanical low back pain may have various causes including degenerative disc disease, degenerative spondylosis, disc herniation, facet arthropathy, and others. Patients with low back pain may also experience reduced lumbar flexibility, reduced flexion-relaxation and static balance. The pain is aggravated by sitting, standing and lifting, which increase axial loading on the spine. Walking may relieve some of the pain, but patients experience more relief by lying down as it unloads the spine and reduces intradiscal pressure (Gose 1998).

Conservative medical care for chronic back pain includes bed rest, steroid injection, anti-inflammatory drugs, muscle relaxants, conventional physiotherapy, exercises, stretching, manipulative techniques, ultrasound treatments, electric stimulation techniques and others. These measures ease the pain for some patients but are ineffective, intolerable, or unsuitable for others. Patients not responding to conservative therapy may be offered conventional or percutaneous surgical procedures such as disc space decompression, epidural blocks, and spinal instrumentation. These interventions play an important role in treating patients with low back pain due to herniated disc and degenerative disc problems. However, surgery may not relieve all the pain, and could permanently disrupt the biomechanical and physiological function of the disc. Moreover, not all patients are candidates for surgery.

In patients with non-radicular low back pain, common degenerative spinal changes, and persistent and disabling symptoms, it is recommended that clinicians discuss risks and benefits of surgery as an option (weak recommendation, moderate-quality evidence). The net benefit of lumbar fusion was moderate compared to standard nonsurgical therapy; however, there was no difference between lumbar fusion and intensive rehabilitation.

Medical Technology Assessment Committee (MTAC)

Allogenic Bone for Spinal Fusions- Allograft Bone

BACKGROUND

Arthrodesis of the spine has been performed for decades for various spinal conditions such as fractures, congenital or developmental deformities, arthritis, degenerative disease, disc lesions, tuberculosis and other infections. With the overall intent to prevent movement in painful bones by permanently joining two or more vertebrae, bone grafting is an integral part of the fusion process. The choice of bone graft is dependent on various factors including patient specific disease, type and location of fusion, the number of levels involved, patient and surgeon preference, as well as, surgeon experience. Non-fusion risks should also be taken into consideration such as patient age, gender, tobacco use and the patient's health status (Deyo 2004).

Historically, autograft bone harvested from the iliac crest of the patient who is undergoing the procedure has been the gold standard. This type of graft requires an additional incision during operation, lengthening surgery and causing morbidity associated with harvesting the tissue. It is further limited by, inconsistent size, quantity, and quality of tissue. One alternative to autograft is allogeneic bone graft, or allograft bone, which is harvested from cadaver bone. Allograft bone is typically acquired through a bone bank and can be procured in greater quantities than autograft (Ehrler and Vaccaro 2000).

Currently, there are three types of allograft, fresh frozen bone allograft, freeze dried bone allograft and demineralized freeze-dried bone allograft. Allograft bone is available in different shapes and sizes to fit into the

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area of the spine where it is needed. Allograft materials are difficult to standardize because of the heterogeneity of the donor tissue. In addition, allografts can be prepared in a number of different ways with the characteristics of a particular allograft affected by its method of preparation. Regulations for allograft bone procurement, as well as screening and testing procedures are extensive and enforced by both the American Association of Tissue Banks and the U.S. Food and Drug Administration (FDA).

While allogeneic bone avoids the common complication of donor site morbidity that occurs with autogenic bone grafting the obvious disadvantage is potential disease transfer. Contaminants and pathologies that may be transferred include viral and bacterial infections, malignancy, systemic disorders or toxins. The allograft bone used in spinal fusion procedures is provided by tissue banks (bone banks) which are regulated by the FDA. With that said, a retrospective review done by Mroz and colleagues in 2009, examined the safety of allograft bone through data from the FDA, recalls of musculoskeletal allografts data from the Center for Disease Control (CDC), and literature reviews. The review identified 59,476 recalls between 1994 and 2007 citing improper donor evaluation, contamination and infection as the main reasons for recall (Mroz, Joyce et al. 2009). In addition, there have been several reported cases of HIV transmission (Asselmeier, Caspari et al. 1993).

03/04/2014: MTAC REVIEW
Allograft Bone
Evidence Conclusion: *Efficacy* - A meta-analysis of autograft versus allograft in anterior cervical discectomy and fusion (ACDF) was conducted in 2000 by Floyd and Ohnmeiss and concluded that it was not possible to ascertain whether autograft is clinically superior to allograft. When the data from all four studies were pooled, a significantly higher rate of union and a lower incidence of collapse was found with autograft for both one- and two-level fusions. Patient satisfaction and clinical outcomes were not adequately addressed in all of the studies and although autograft has a higher fusion rate than allograft, the clinical results did not rely solely on radiographic results (Floyd and Ohnmeiss 2000). [Evidence Table Allograft bone1] In a comparison of allograft versus autograft in multilevel ACDF with instrumentation, Samartzis et al reported fusion rates of 94.3% and 100% for allograft and autograft, respectively. In this study, nonunion occurred in patients with allograft but this difference was not statistically significant. Excellent and good clinical outcomes were noted in 88.8% of patients. These results should be interpreted with caution as the study was retrospective in nature and only included 80 non-blinded patients. With that said, the authors mention that meticulous surgical technique and patient selection were more important than graft type for successful outcome (Samartzis, Shen et al. 2003). [Evidence Table Allograft bone2] Samartzis and colleagues completed an additional and similar study in 2005 which demonstrated a fusion rate of 100% and 90.3% for allograft and autograft, respectively, in one-level ACDF. Clinical outcomes in relation to graft-type were also analyzed with no statistical differences detected (P>0.05). The study took place at a single institution and was retrospective in nature including only 66 non-blinded participants. (Samartzis, Shen et al. 2005). [Evidence Table Allograft bone3] In a prospective randomized study, Gibson and colleagues reported similar clinical results in 69 patients who received either fresh-frozen allograft or autograft during instrumented posterolateral lumbar fusion. The groups were very similar before operation in terms of back pain and leg pain scores, but the allograft group showed a slightly higher overall pain score, which was statistically significant. After one year, however, the scores from the questionnaire were significantly different in that the group that had received allograft bone seemed to have done better in terms of back pain than those who had received the autograft bone (Gibson, McLeod et al. 2002). [Evidence Table Allograft bone4]
Safety - Both the Gibson et al., and the 2005 Samartzis et al. studies reported no complications associated with allograft bone use, however, it is unclear how systematic they were in collecting this information (Gibson, McLeod et al. 2002; Samartzis, Shen et al. 2005). None of the other studies reported on the safety or adverse events of allogeneic bone grafts when used in spinal fusions. While it appears that allografts have comparable fusion rates with autografts, proper evaluation of the efficacy and safety is difficult to make as the risk of bias throughout the studies was high, especially concerning small population sizes and retrospective, non-randomized or non-blinded studies. Patient risk factors, including body mass index, smoking, age and sex also contribute to the diversity of the study groups. As mentioned previously, surgical technique may have as much influence on fusion as the choice of graft and the contributions of factors such as nutrition, sex, age, bone metabolic factors, and smoking on the success of autograft versus allograft. These variations of standard procedures make it difficult to define the true effectiveness of grafts. Moreover, the absence of standardized fusion criteria and inconsistent outcome reporting creates heterogeneity of studies making it difficult to compare and contrast autograft and allograft across studies. Beyond the question of efficacy, the potential risk of disease transmission is the large concern which, on the whole, did not seem to be adequately addressed by the literature. The use of allograft bone in spinal fusion surgery warrants further clinical studies.
Conclusions:
- There is low quality evidence to support the effectiveness of allogeneic bone grafts for ACDL.

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- There is insufficient evidence to determine the effectiveness of allogeneic bone grafts in lumbar surgery.
- There is insufficient evidence to determine the safety of allogeneic bone grafts in both cervical and lumbar spinal fusions.

Articles: The literature search revealed just over 100 studies many of which were case reports examining the performance of allograft for spinal fusion, but very few have been prospectively designed and well conducted. Selection of articles relied on the comparison of allograft to autograft. Studies that combined allograft bone with other materials and studies that compared allograft bone to other spinal fusion techniques were excluded. The following publications were selected for critical appraisal: Floyd, T and Ohnmeiss, D. A meta-analysis of autograft versus allograft in anterior cervical fusion. European Spine Journal 2000; 9:398-403. [Evidence Table Allograft bone1] Samartzis D, Shen FH, Matthews DK, Yoon T, et al. Comparison of allograft to autograft in multilevel anterior cervical discectomy and fusion with rigid plate fixation. The Spine Journal 2003; 3:451-459. [Evidence Table Allograft bone2] Samartzis D, Shen FH, Goldberg EJ, An HS. Is autograft the gold standard in achieving radiographic fusion in one-level anterior cervical discectomy and fusion in one-level anterior cervical discectomy and fusion with rigid anterior plate fixation? 2005;30(15):1756-1761. [Evidence Table Allograft bone3] Gibson S, McLeod I, Wardlaw D, Urbaniak S. Allograft versus autograft in instrumented posterolateral lumbar spinal fusion. Spine 2002;27(15):1599-1603. [Evidence Table Allograft bone4]

The use of allograft bone for spinal fusion does meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Spinal Fusion

09/2011: MTAC REVIEW

Evidence Conclusion: The 2009 APS guideline recommends that clinicians discuss risks and benefits of surgery as an option for patients with non-radicular low back pain, common degenerative spinal changes, and persistent and disabling symptoms; however, they also note that there was no difference between lumbar fusion and intensive rehabilitation (weak recommendation, moderate-quality evidence). The 2009 NICE guideline also recommends considering a referral for an opinion on spinal fusion for patients who have completed an optimal package of care, including a combined physical and psychological treatment program and still have severe non-specific low back pain for which they would consider surgery.

Articles: The literature search did not reveal any new studies that addressed the safety or effectiveness of lumbar fusion for the treatment of chronic low back pain. NICE 2009 Consider referral for an opinion on spinal fusion for people who: Have completed an optimal package of care, including a combined physical and psychological treatment program AND Still have severe non-specific low back pain for which they would consider surgery. American Pain Society (Chou) 2009 In patients with non-radicular low back pain, common degenerative spinal changes, and persistent and disabling symptoms, it is recommended that clinicians discuss risks and benefits of surgery as an option (weak recommendation, moderate-quality evidence). The net benefit of lumbar fusion was moderate compared to standard nonsurgical therapy; however, there was no difference between lumbar fusion and intensive rehabilitation. The literature search revealed several studies published after the 2009 guidelines that addressed the safety or effectiveness of lumbar (spinal) fusion compared to non-surgical interventions for the treatment of chronic low back pain; however, none of these were selected for review because of severe methodological limitations (small sample size, power was not assessed, high level of crossover, etc.). PubMed was searched from July 2008 (NICE literature search date) or November 2006 (APS/ACP literature search date) through July 2011 with the search terms acupuncture, back pain, spinal manipulation, meditation, massage, mindfulness-based stress reduction, multidisciplinary rehabilitation, physical therapy, sacroiliac joint injections, corticosteroid injections, epidural steroid injections, spinal injections, spinal fusion, and surgery with variations. Searches were limited to English-language studies of human subjects. Only randomized controlled trials (RCTs), meta-analyses, and clinical trials were included in the review. Reference lists and the related articles function in PubMed were used to identify additional publications. Studies were excluded if they had severe methodological limitations (e.g. small sample size, power and/or ITT analysis were not performed, etc.) or if pain or functional disability was not a primary or secondary outcome.

Reviewed by the content of care committee and not MTAC.

AxiaLIF

12/16/2013: MTAC REVIEW

Evidence Conclusion: *Efficacy* The literature search revealed five case series that report on outcomes associated with AxiaLIF. The largest, published in 2011, was a retrospective analysis of 156 patients from 4 clinical sites in the US. Ultimately, the mean pain and ODI scores improved by approximately 63% and 54% respectively ($P<0.001$) and the overall radiographic fusion rate at 2 years was 94%. The study did not report any adverse events. The patient population was reported to be homogenous, however, the variable nature and

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progression of the disease compromises the reliability of this claim. Limitations of this study include the retrospective analysis, industry funding as well as selection bias. Outcome measures were not all objective and relied on patient reporting. Only half of the patients were accounted for in the preoperative and postoperative ODI outcome (Tobler, Gerszten et al. 2011). Several smaller case series were also identified and are summarized in a table 1. Ultimately, all of the studies report similar results and conclusions but are subject to the bias of any retrospective series. Further limitations include a lack of control subjects, potential for selection bias as only one of the studies enrolled consecutive patients and unclear study objectives. All studies, with the exception of the publication by Patil and colleagues, received industry funding from TranS1 (Patil, Lindley et al. 2010; Gerszten, Tobler et al. 2012; Marchi, Oliveira et al. 2012). *Safety* Two publications addressed the safety of AxiaLIF with conflicting results. The first study was a 5-year surveillance study of 9,152 patients (Gundanna, Miller et al. 2011) and the second, a retrospective review of 68 patient records (Lindley, McCullough et al. 2011). Gundanna and colleagues reported minimal complications (1.3%) in their study while Lindley et al. reported high complication rates (23.5%). The observed adverse events across both the studies included pseudoarthrosis, superficial infection, sacral fracture, pelvic hematoma, failure of wound closure, and rectal perforation. Although both studies were designed to be systematic in their investigation, neither study had a control group for comparison and the results are dependent on either spontaneous reporting or the accuracy of medical records. In addition, both of the studies are subject to a variety of bias due to patient selection and industry funding.
Conclusion: There is insufficient evidence to determine the efficacy of AxiaLIF compared to standard fusion procedures. There is insufficient evidence to establish whether the AxiaLIF is as safe as standard fusion procedures.
Articles: Currently, there are no randomized control trials that compare the AxiaLIF with other approaches to lumbosacral interbody fusion. The literature related to the safety and efficacy is primarily comprised of case series.
The following studies were selected for review: Tobler WD, Gerszten PC, Bradley WD, Raley TJ, Nasca RJ and Block JE. Minimally invasive axial presacral L5-S1 interbody fusion. *Spine* 2011;**36**(20): E1296-E1301. See Evidence Table. Gerszten PC, Tobler W, et al. Axial presacral lumbar interbody fusion and percutaneous posterior fixation for stabilization of lumbosacral isthmic spondylolisthesis. *Journal of Spinal Disorders & Techniques* 2012;**25**(2):E36-E40.See Evidence Table. Marchi L, Oliveira L, et al. Results and complications after 2-level axial lumbar interbody fusion with a minimum 2-year follow up. *Journal of Neurosurgery: Spine* 2012;**17**(3):197-192. See Evidence Table. Patil S, Lindley E, et al. Clinical and radiological outcomes of axial lumbar interbody fusion. *Orthopedics* 2010;**33**(12). See Evidence Table Aryan H, Newman C, et al. Percutaneous axial lumbar interbody fusion (AxiaLIF) of the L5-S1 segment: initial clinical and radiographic experience. *Minimally Invasive Neurosurgery* 2008; 51:225-230. See Evidence Table.

The use of AxiaLIF does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Lumbar Spine –
Non-Medicare: Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® Codes	Description
22533	Arthrodesis, lateral extracavitary technique, including minimal discectomy to prepare interspace (other than for decompression); lumbar
22534	Arthrodesis, lateral extracavitary technique, including minimal discectomy to prepare interspace (other than for decompression); thoracic or lumbar, each additional vertebral segment (List separately in addition to code for primary procedure)
22558	Arthrodesis, anterior interbody technique, including minimal discectomy to prepare interspace (other than for decompression); lumbar
22585	Arthrodesis, anterior interbody technique, including minimal discectomy to prepare interspace (other than for decompression); each additional interspace (List separately in addition to code for primary procedure)
22612	Arthrodesis, posterior or posterolateral technique, single level; lumbar (with lateral transverse technique, when performed)
22614	Arthrodesis, posterior or posterolateral technique, single level; each additional vertebral segment (List separately in addition to code for primary procedure)

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22630	Arthrodesis, posterior interbody technique, including laminectomy and/or discectomy to prepare interspace (other than for decompression), single interspace; lumbar
22632	Arthrodesis, posterior interbody technique, including laminectomy and/or discectomy to prepare interspace (other than for decompression), single interspace; each additional interspace (List separately in addition to code for primary procedure)
22633	Arthrodesis, combined posterior or posterolateral technique with posterior interbody technique including laminectomy and/or discectomy sufficient to prepare interspace (other than for decompression), single interspace and segment; lumbar
22634	Arthrodesis, combined posterior or posterolateral technique with posterior interbody technique including laminectomy and/or discectomy sufficient to prepare interspace (other than for decompression), single interspace and segment; each additional interspace and segment (List separately in addition to code for primary procedure)
22800	Arthrodesis, posterior, for spinal deformity, with or without cast; up to 6 vertebral segments
22802	Arthrodesis, posterior, for spinal deformity, with or without cast; 7 to 12 vertebral segments
22804	Arthrodesis, posterior, for spinal deformity, with or without cast; 13 or more vertebral segments
22808	Arthrodesis, anterior, for spinal deformity, with or without cast; 2 to 3 vertebral segments
22810	Arthrodesis, anterior, for spinal deformity, with or without cast; 4 to 7 vertebral segments
22812	Arthrodesis, anterior, for spinal deformity, with or without cast; 8 or more vertebral segments
22840	Posterior non-segmental instrumentation (eg, Harrington rod technique, pedicle fixation across 1 interspace, atlantoaxial transarticular screw fixation, sublaminar wiring at C1, facet screw fixation) (List separately in addition to code for primary procedure)
22841	Internal spinal fixation by wiring of spinous processes (List separately in addition to code for primary procedure)
22842	Posterior segmental instrumentation (eg, pedicle fixation, dual rods with multiple hooks and sublaminar wires); 3 to 6 vertebral segments (List separately in addition to code for primary procedure)
22845	Anterior instrumentation; 2 to 3 vertebral segments (List separately in addition to code for primary procedure)
22846	Anterior instrumentation; 4 to 7 vertebral segments (List separately in addition to code for primary procedure)
22848	Pelvic fixation (attachment of caudal end of instrumentation to pelvic bony structures) other than sacrum (List separately in addition to code for primary procedure)
22849	Reinsertion of spinal fixation device
22853	Insertion of interbody biomechanical device(s) (eg, synthetic cage, mesh) with integral anterior instrumentation for device anchoring (eg, screws, flanges), when performed, to intervertebral disc space in conjunction with interbody arthrodesis, each interspace (List separately in addition to code for primary procedure)
22854	Insertion of intervertebral biomechanical device(s) (eg, synthetic cage, mesh) with integral anterior instrumentation for device anchoring (eg, screws, flanges), when performed, to vertebral corpectomy(ies) (vertebral body resection, partial or complete) defect, in conjunction with interbody arthrodesis, each contiguous defect (List separately in addition to code for primary procedure)
22859	Insertion of intervertebral biomechanical device(s) (eg, synthetic cage, mesh, methylmethacrylate) to intervertebral disc space or vertebral body defect without interbody arthrodesis, each contiguous defect (List separately in addition to code for primary procedure)
63052	Laminectomy, facetectomy, or foraminotomy (unilateral or bilateral with decompression of spinal cord, cauda equina and/or nerve root[s] [eg, spinal or lateral recess stenosis]), during posterior interbody arthrodesis, lumbar; single vertebral segment (List separately in addition to code for primary procedure)
63053	Laminectomy, facetectomy, or foraminotomy (unilateral or bilateral with decompression of spinal cord, cauda equina and/or nerve root[s] [eg, spinal or lateral recess stenosis]), during posterior interbody arthrodesis, lumbar; each additional segment (List separately in addition to code for primary procedure)
S2348	Decompression procedure, percutaneous, of nucleus pulposus of intervertebral disc, using radiofrequency energy, single or multiple levels, lumbar

Allograft and Autograft (except for InFUSE™ bone graft and other bone graft substitutes and adjuncts HERE)- Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

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CPT® Codes	Description
20930	Allograft, morselized, or placement of osteopromotive material, for spine surgery only (List separately in addition to code for primary procedure)
20931	Allograft, structural, for spine surgery only (List separately in addition to code for primary procedure)
20936	Autograft for spine surgery only (includes harvesting the graft); local (eg, ribs, spinous process, or laminar fragments) obtained from same incision (List separately in addition to code for primary procedure)
20937	Autograft for spine surgery only (includes harvesting the graft); morselized (through separate skin or fascial incision) (List separately in addition to code for primary procedure)
20938	Autograft for spine surgery only (includes harvesting the graft); structural, bicortical or tricortical (through separate skin or fascial incision) (List separately in addition to code for primary procedure)

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed	Date Last Revised
10/04/2011	11/01/2011[MDCRPC], 09/04/2012[MDCRPC], 06/04/2013[MDCRPC], 11/05/2013[MDCRPC], 04/01/2014[MPC], 07/01/2014[MPC], 05/05/2015[MPC], 03/01/2016[MPC], 01/03/2017[MPC], 11/07/2017[MPC], 10/02/2018[MPC], 10/01/2019[MPC], 10/06/2020[MPC], 10/05/2021[MPC], 10/04/2022[MPC], 10/03/2023[MPC]	10/17/2022

[MPC] Medical Policy Committee

Revision History	Description
12/06/2016	Added clarification to indication: Spondylolisthesis for spine fusion (> or equal to 4 mm)
7/26/2017	Removed spinal decompression codes 22867-22870
05/29/2020	Updated links to related criteria; removed minimally invasive sacroiliac joint fusion codes and deleted codes
07/07/2020	MPC approved to adopt updates to the clinical indications for Non-Medicare: spondylolisthesis > or equal to 4mm on flexion/extension x-rays; inclusion of the Myerding scale and detailed documentation requirements. Linked to InFUSE Bone Graft criteria as a non-covered allograft.
06/07/2022	MPC approved to adopt updates to criteria to include indications for smoking-cessation, BMI and Spondylisthesis grading and definitions
10/04/2022	MPC approved to include quantifying number of 3 visits for physical therapy of conservative treatment. 60-day notice required.
10/17/2022	Updated applicable codes.
10/26/2022	Corrected Myerding Grading for spondylolisthesis.

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Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Sports Hernia Surgery
- Athletic Pubalgia Surgery

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article	None
Kaiser Permanente Medical Policy	Due to the absence of a NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Clinical Review Criteria, ***Sports Hernia Surgery*** for medical necessity determinations. Use the Non-Medicare criteria below.

For Non-Medicare Members

Surgical treatment of groin pain in athletes (also known as athletic pubalgia, Gilmore groin, osteitis pubis, pubic inguinal pain syndrome, inguinal disruption, slap shot gut, sportsmen groin, footballers groin injury complex, hockey groin syndrome, athletic hernia, sports hernia, or core muscle injury) is unproven and not medically necessary due to insufficient evidence.

If requesting review for this service, please send the following documentation:

- Last 6 months of clinical notes from requesting provider &/or specialist

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Background

The incidence of groin pain among athletes is estimated to be from 2% to 20%; however, the incidence in the general population is unknown. Groin hernias and hip joint pathologic findings are common and often considered; once ruled out by physical examination with or without imaging, the differential diagnoses and workup of groin pain is confounding to many practitioners. This ambiguous nature of non-hernia, non-hip groin pain is understandable because routine physical examination often only reveals groin tenderness, and imaging may or may not have abnormalities. Most of the literature written about the subject are case series or opinions. Many of these case series only involve professional male athletes, and the reported end points are often: return to sport, time to return to sport, or level of sport. Thus, the level of evidence of the studies is low quality, and the findings may not be applicable to the general population.

In the acute setting, pain is treated with rest (2-8 weeks) and nonsteroidal anti-inflammatory drugs. If pain continues, the mainstay of initial therapy is physical rehabilitation. Nonoperative, exercise-based therapy has

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Date Sent: 3/29/24
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been suggested to be an effective first-line therapy, with treatment success ranging from 40% to 100%. Some report that among individuals with greater than 2 months of pain, resolution is unlikely without surgery. Multiple operative approaches have been used. Although there are numerous single-center case series and several meta-analyses, there are no high-quality trials evaluating operative approaches.

Reference

Zuckerbraun BS, Cyr AR, Mauro CS. Groin Pain Syndrome Known as Sports Hernia: A Review. *JAMA Surg.* 2020;155(4):340–348. doi:10.1001/jamasurg.2019.5863. Retrieved May 19, 2020.

Applicable Codes

Considered Not Medically Necessary - experimental, investigational or unproven:

CPT® Codes	Description
No specific codes	

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed	Date Last Revised
06/02/2020	06/01/2021[MPC], 06/07/2022[MPC] , 06/06/2023[MPC]	06/02/2020

[MPC] Medical Policy Committee

Revision History	Description
06/02/2020	MPC approved to adopt a new policy of non-coverage. Requires 60-day notice, effective 10/1/2020.

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Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Standers

- Adult Standers
- Pediatric Standers

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Durable Medical Equipment Reference List (280.1) *Per NCD - Standing Tables are not covered because they are not primarily medical in nature.*
Local Coverage Determinations (LCD)	None
Local Coverage Article	None

For Non-Medicare

Kaiser Permanente has elected to use the Standing Frame (A-0996) MCG* for medical necessity determinations. This service is not covered per MCG* for medical necessity determinations. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Supported standing programs are routinely used by therapists as part of a postural management approach in children with severe developmental disabilities (e.g. cerebral palsy, spinal cord injuries, meningomyelocele, osteogenesis imperfecta) as they are unable to stand or walk by themselves due to poor motor control. These programs use assistive devices or adaptive equipment, eg. standers or standing frames that provide external adjustable support, to facilitate an upright position. Standers allow weight bearing activities which are believed to increase bone mineral density (BMD), manage contractures, increase muscle strength and postural control, as well as improve visuals and oral motor skills and social communication. These in turn, may prevent or reduce the children's musculoskeletal problems, increase their independence, and enhance their functional abilities (Gudjonsdottir 2002, Caulton 2003).

Medical Technology Assessment Committee (MTAC)

Pediatric Standers

10/16/2012: MTAC REVIEW

Evidence Conclusion: The is insufficient evidence to date to determine the efficacy of standers in reducing risk of fractures among children who are unable to stand independently due to severe developmental disabilities. The published pilot RCT did not study the effect of stander equipment but examined the effect of increasing standing time in children with cerebral palsy who are already involved in a standing program. In addition, it used bone

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mineral density, an intermediate outcome, as the primary end point. A more important clinical outcome would be the effect of the program on reducing the risk of bone fracture. Larger RCTs with long-term follow-up are needed to determine the long-term safety and efficacy of standers on reducing the risk of fractures in children severe developmental disabilities.

Articles: There is very limited published literature on the use of standers for non-ambulant children due to significant developmental disabilities. The search identified a small pilot randomized controlled trial (RCT) that examined the effect of increasing the duration of a standing program on bone mineral density (BMD) in children with cerebral palsy, and another also very small pilot RCT (N=20) that examined the effect of standing on BMD in children with disabling conditions. There was also a number of published small case series with twenty or less participants each that examined the short-term effect of standing frames or prolonged standing on gait, muscle contracture, or BMD in children with cerebral palsy. The following RCT was critically appraised in the 2012 review. Caulton JM, Ward KA, Alsop CW, et al. A randomized controlled trial of standing program on bone mineral density in non-ambulant children with cerebral palsy. Arch Dis Child. 2004;89;131-135. See Evidence Table.

The use of use of standers to reduce fracture risk does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Pediatric Standers

02/11/2013: MTAC REVIEW

Evidence Conclusion*:* There is insufficient evidence to date to determine the efficacy of standers in reducing risk of fractures among children who are unable to stand independently. The published pilot RCT by Caulton and colleagues (2004), did not study the effect of stander equipment, but examined the effect of increasing standing time in children with cerebral palsy who are already involved in a standing program. In addition, it used bone mineral density, an intermediate outcome, as the primary end point. A more important clinical outcome would be the effect of the program on reducing the risk of bone fracture. Ward and colleagues' (2004) RCT included children who were able to stand independently but had limited mobility due to their disability (autism, involuntary movements, limb deformity, and spasticity). 20 children 4-19 years of age were randomized to standing on active (vibrating platform) or placebo devices for 10 minutes/day, 5 days/week for 6 months. The primary outcome was proximal tibial spinal bone mineral density (vTBMD). The compliance rate was only 44%, and the 6 months results showed a net benefit of treatment equal to +15.72 mg/ml (17.7%; p =0.0033) for proximal tibial BMD and + 6.72 mg/ml, (p = 0.14) for the spine, compared with placebo. Larger RCTs with long-term follow-up, and patient oriented outcomes, are needed to determine the long-term safety and efficacy of standers on reducing the risk of fractures in children with developmental disabilities.

Articles: There is very limited published literature on the use of standers for non-ambulant children due to significant developmental disabilities. The search identified a small pilot randomized controlled trial (RCT) that examined the effect of increasing the duration of a standing program on bone mineral density (BMD) in children with cerebral palsy, and another also very small pilot RCT (N=20) that examined the effect of standing on BMD in children with disabling conditions. There was also a number of published small case series with twenty or less participants each that examined the short-term effect of standing frames or prolonged standing on gait, muscle contracture, or BMD in children with cerebral palsy. The following RCT was critically appraised in the 2012 review. Caulton JM, Ward KA, Alsop CW, et al. A randomized controlled trial of standing program on bone mineral density in non-ambulant children with cerebral palsy. *Arch Dis Child.* 2004;89;131-135. See Evidence Table.

The use of standers to improve pulmonary function does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Adult Standers

BACKGROUND

Standing frames also known as standers, standing devices, standing systems, or standing aids, are assistive devices that enable non-ambulatory individuals to achieve and maintain an upright posture. These may be used by patients with mild to severe disabilities such as spinal cord injury, traumatic brain injury, cerebral palsy, muscle dystrophy, or other neuromuscular conditions that do not enable the individual to stand independently. They can be used at home, in the workplace, extended care units, assisted living centers, nursing homes, and rehabilitation facilities. Prolonged standing has been investigated over the years for its possible benefits for patients with spinal cord injuries and other disabilities. It is suggested that standing and weight bearing activities may increase bone mineral density and muscle strength, reduce abnormal muscle tone and spasticity, improve circulation, reduce lower limb swelling, improve bowel and bladder function, prevent pressure sores, as well as other potential benefits. Many of these benefits, however, are not supported by good quality evidence (Eng 2001, Bagley 2004, Bernhardt 2012).

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There are a variety of standing systems. The common types include sit to stand, prone, upright, prone, multi-positioning standers, and standing wheelchairs. Some systems can be changed by the user from a sitting to a standing position; others require the assistance of another person to change its position. Standing systems can generally be divided into three groups: 1. Passive or static standers that remain in one place and cannot be self-propelled, 2. Mobile or dynamic standers that can be propelled by the user if he/she has the ability to do so, and 3. Active standers that can create reciprocal movements of the arms and legs while the patient is standing.

08/17/2015: MTAC REVIEW
Adult Standers
Evidence Conclusion: There is insufficient evidence to date, to determine the efficacy of standing devices on health outcomes of patients with disabilities or health conditions that render them unable to stand independently. The published RCT conducted by Bagley and colleagues (2005) (Evidence table 1) evaluated the effectiveness of the Oswestry Standing Frame for severely disabled stroke patients. The trial included 140 inpatients in a stroke rehabilitation unit. In addition to undergoing the usual stroke care, the patients were randomized in a 1:1 ratio to receive 14 consecutive treatment with the use of Oswestry standing frame, or to receive 14 consecutive treatments but without access to the Oswestry standing frame. The primary outcome of the trial was the change in the Rivermead Mobility Index (RMI) from baseline to 6 weeks post stroke. The results of the trail showed no statistically significant difference between the study groups in any of the primary or secondary outcome measures or for resource savings. Larger RCTs with long-term follow-up and patient-oriented outcomes are needed to determine the long-term safety and efficacy of standing devices or systems among adults with different health conditions and/or disabilities that do not enable them to stand on their own.
Articles: There is very limited published literature on the use of standers for non-ambulatory adults with mild to severe physical disability. The literature search identified one RCT (Bagley et al, 2005) that evaluated the Oswestry standing frame for patients after stroke, and another very small pilot RCT (Allison et al, 2007) that assessed the impact of additional supported standing practice on the functional ability post stroke in 14 patients. The following trial was selected for critical appraisal: Bagley P, Hudson M, Forster A, Smith J, et al. A randomized trial evaluation of the Oswestry Standing Frame for patients after stroke. *Clin Rehabil*. 2005 June; 19(4):354-364.See Evidence Table 1.

The use of Adult Standers does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Applicable Codes

Considered Not Medically Necessary:

CPT® or HCPC Codes	Description
E0637	Combination sit-to-stand frame/table system, any size including pediatric, with seat lift feature, with or without wheels
E0638	Standing frame/table system, one position (e.g., upright, supine or prone stander), any size including pediatric, with or without wheels
E0641	Standing frame/table system, multi-position (e.g., 3-way stander), any size including pediatric, with or without wheels
E0642	Standing frame/table system, mobile (dynamic stander), any size including pediatric

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Date Created	Date Reviewed	Date Last Revised
03/05/2013	03/05/2013[MDCRPC], 01/07/2014 [MPC], 11/04/2014 [MPC], 09/01/2015[MPC], 06/07/2016[MPC], 04/04/2017[MPC], 02/06/2018[MPC], 02/05/2019[MPC], 02/04/2020[MPC], 02/02/2021[MPC], 02/01/2022[MPC], 02/07/2023[MPC], 01/09/2024[MPC]	10/06/2020

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MDCRPC Medical Director Clinical Review and Policy Committee
MPC Medical Policy Committee

Revision History	Description
10/28/2015	Added NCD link
10/06/2020	MPC approved the MCG 24th ed. guideline for Standing Frame: A-0996

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Patient Referral Guidelines
Stem Cell Transplant/Bone Marrow Transplant

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Stem Cell Transplantation Formerly 110.8.1 (110.23)
Local Coverage Determinations (LCD)	None
Local Coverage Article	None
Kaiser Permanente Medical Policy - **Stem Cell Transplant for Orthopedic Conditions**	Due to the absence of an active NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Clinical Review Criteria, "**Stem Cell Transplant for Orthopedic Conditions**," for medical necessity determinations. Use the Non-Medicare criteria below.

For Federal Members:

Please refer to the member contract for specific diagnoses and types of stem cell transplants that are covered.

For all other Non-Medicare Members

Stem Cell Transplant for Orthopedic Conditions	Mesenchymal stem cell therapy is considered **investigational** for all orthopedic applications, including use in repair or regeneration of musculoskeletal tissue or joint.

Stem Cell Storage:
Per Kaiser Permanente policy, stem cell storage is only covered for members who are scheduled to receive a stem cell transplant. Medically indicated storage is reviewed by Clinical Review on a case-by-case basis.

Transplantation may be considered for patients with end-stage or life-threatening disease who have no prospect for prolonged survival, or whose quality of life is severely impaired. The following are current, generally accepted, guidelines for Blood and Marrow Transplantation. It is important to note that these are guidelines and should be applied together with careful clinical judgment.

1. **GENERAL PRINCIPLES**
   a. If clinical parameters of end-stage or life-threatening disease indicate the need for transplantation, then early referral should be made.
   b. Uncontrollable active infection is a contraindication to transplant.
   c. Candidates with a history of substance abuse must be free from alcohol and other substance abuse for six (6) months and have been evaluated by a substance abuse program. Exceptions may be made on a case-by-case basis.
   d. Candidates must have adequate social support systems and display a proven record of adherence to medical treatment.

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e. Patients must be willing and able to travel within short notice to the KP approved transplant Center of Excellence and, if necessary, return for treatment of complications.
f. Patient must have a caregiver or caregivers who are physically and cognitively able to assist the patient with self-care activities and are available to travel within short notice to the KP approved transplant Center of Excellence.
g. The presence of significant irreversible neurologic dysfunction, active psychological and/or psychiatric conditions, and/or other social behaviors that prevent adherence with a complex medical regimen, are considered contraindications for referral for transplant.
    a. Evidence of such non-adherence may be, failure to keep appointments failure to make steady progress in completing pre-transplant evaluation requirements, failure to accurately follow medication regimens or failure to accomplish the activities required for maintenance on the waiting list.
h. Whenever transplant is considered as an option and discussed with the patient and/or family, consultation with Advanced Life Care Planning/Palliative Care resources is strongly recommended.

2. GENERAL CONSIDERATIONS

a. Blood and Marrow Transplantation will be considered for patients with fatal hematologic, malignant, and metabolic conditions for whom other medical therapy is not as likely to be curative, or to prolong disease-free and overall survival, or to prevent progressive disability.
b. Patients are encouraged to participate in clinical studies supported by the National Cancer Institute, Clinical Trials Network (CTN), or other cooperative groups in which National Transplant Services (NTS) transplant centers are participating entities.
c. The indications for cord blood and haploidentical transplant are the same as for allogeneic and matched unrelated donor transplant.
d. The indications for autologous transplant overlap, but are not identical to, those for allogeneic transplant.
e. The decision to recommend blood and marrow transplantation and the choice of stem cell product is complex and dependent upon multiple factors including the disease, stage, response to treatment, remission status, risk factors, performance status and physiological condition of the patient, availability of a donor, availability of other therapies, institutional practices and preferences, etc. It is beyond the scope of these guidelines to outline the specific factors that might be considered in an individual case. It is the role of the transplant physician to carefully evaluate the patient and recommend the appropriate treatment using best available published evidence and consensus guidelines from national professional organizations such as the National Comprehensive Cancer Network (NCCN), American Society of Hematology (ASH), American Society of Clinical Oncology (ASCO), and the American Society of Blood and Marrow Transplantation (ASBMT).

INDICATIONS FOR BLOOD & MARROW TRANSPLANT [1]

GUIDELINES FOR BMT CANNOT LIST EVERY POSSIBLE INDICATION ALTHOUGH THE MAJOR ONES ARE LISTED BELOW. IN THE RARE CASES WHERE THE GUIDELINES DO NOT SPEAK TO A PARTICULAR CONDITION, A CALL TO A NETWORK TRANSPLANT CENTER MAY BE INDICATED.

a. Leukemias, Lymphomas, and other Blood Cancers
    i. Acute myelogenous leukemia (AML)[2]
        1. Intermediate and poor risk cytogenetics in first complete remission (CR)
        2. Poor risk molecular markers in first CR (based on emerging data)
        3. Induction failure
        4. Second or subsequent complete remission (CR2)
        5. Relapsed AML (selected cases; treatment on investigational protocols encouraged)
        6. Secondary AML
    ii. Acute lymphocytic leukemia (ALL)
        1. Immediate or High Risk in first CR (based cytogenetics, WBC count at diagnosis, and/or failure to achieve CR within 4 weeks of initial treatment)
        2. Extra medullary disease
        3. Induction failure
        4. Second or subsequent complete remission
        5. Relapsed ALL (selected cases; treatment on investigational protocols encouraged)
    iii. Chronic myelogenous leukemia (CML)
        1. Chronic phase: only if failure to achieve adequate response and/or development of intolerance to tyrosine kinase inhibitors
        2. Accelerated phase
        3. Blast crisis

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iv. Chronic lymphocytic leukemia (CLL)
1. High risk cytogenetics or molecular markers
2. Resistant to initial therapy
3. Short initial response
4. Fludarabine-resistant
5. Richter's transformation

v. Biphenotypic leukemia

vi. Juvenile myelomonocytic leukemia

vii. Hodgkin's lymphoma
(Note: chemo sensitive disease is required for autologous stem cell transplant)
1. Induction failure
2. Second or subsequent complete or partial remission

viii. Follicular non-Hodgkin's lymphoma
(Note: chemo sensitive disease is required for autologous stem cell transplant)
1. Resistant to initial therapy
2. Initial duration of response <12 months
3. First relapse
4. Transformation to diffuse large B cell lymphoma

ix. Diffuse large cell lymphoma/high grade NHL/T cell lymphoma
(Note: chemo sensitive disease is required for autologous stem cell transplant)
1. Induction failure
2. Second or subsequent complete or partial remission
3. High risk features in first complete remission

x. Mantle cell lymphoma
1. First CR
2. Second or subsequent complete or partial remission

b. Multiple Myeloma and other Plasma Cell Disorders
i. Symptomatic and/or with evidence of end organ damage
1. After initial therapy
2. At first progression
ii. Special Note: Tandem autologous or allogeneic transplant is generally not indicated as front-line therapy.

c. Myelodysplastic Disorders
i. Advanced intermediate or high risk by IPSS
ii. Progressive disease after treatment by hypomethylating agents

d. Myeloproliferative Disease (Neoplasm)
Special note: a heterogenous group of disorders including idiopathic (primary) myeloproliferative neoplasm and other rarer conditions. (Note: CML is covered in 2.1.3 in these guidelines). The complexity of this group of diseases does not lend itself to establishing a uniform set of guidelines. Consultation with a transplant physician is recommended when there is uncertainty regarding best treatment approach.
i. High risk disease (based on age, symptoms, splenomegaly, cell counts, blast percentage, cytogenetics)
ii. Poor response to treatment or progressive disease

e. Severe aplastic anemia and other bone marrow failure states
i. Severe aplastic anemia:
1. In patients >40 years, immunotherapy should be considered first
2. Pediatric patients with HLA matched sibling donor
3. Disease unresponsive to immunosuppressive therapy

ii. Fanconi's anemia

iii. Dyskeratosis congenital with transfusion dependent cytopenias

iv. Schwachmann-Diamond syndrome with cytopenias and/or dysplastic marrow changes

v. Paroxysmal Nocturnal Hemoglobinuria

vi. Constitutional red cell aplasia

vii. Amegakaryocytosis /congenital thrombocytopenia

f. Immune system disorders
i. Severe combined immunodeficiency disease (SCID)

ii. Wiskott-Aldrich syndrome

iii. Chronic-granulomatous disease

iv. Chediak-Higashi syndrome

v. Infantile genetic agranulocytosis – refractory to GCSF

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vi. Severe leukocyte adhesion defect
vii. Other – rare disorders to be considered on a case by case basis

g. Hemoglobinopathies
  i. Thalassemia major
    1. Matched related donor with HLA matched sibling
    2. Matched unrelated donor – select cases
  ii. Sickle cell disease
    1. Recurrent pain crises, acute chest syndrome, high stroke risk, or other life-threatening complications
    2. Appropriate stem cell source at the discretion of the KP physician and COE

h. Metabolic and other non-malignant genetic disorders
  i. Hurler's Syndrome
  ii. Adrenoleukodystrophy
  iii. Mucopolysaccharidosis after consultation with local genetics
  iv. Infantile osteopetrosis
  v. Kostmann's Syndrome

i. Familial erythrophagocytic lymphohistiocytosis and other histiocytic disorders

j. Solid Tumors (autologous)
  i. Neuroblastoma [3] – high risk disease, upfront tandem transplant should be considered unless specified by the COE
  ii. Germ cell neoplasms – chemo sensitive relapse and high-risk disease
  iii. Relapsed Wilm's tumors – high risk, chemo sensitive disease, lung only
  iv. Malignant brain tumors in young children
  v. Ewing's sarcoma – chemo sensitive relapse

k. Systemic Sclerosis (Autologous):
  i. Adults (18-70) and select pediatric patients at discretion of COE
  ii. Referrals should be made to centers with multidisciplinary teams (rheumatology, cardiology, nephrology, and pulmonology) who have inclusion and exclusion criteria based on SCOT trial experience.[4,5]

CONTRAINDICATIONS FOR BLOOD & MARROW TRANSPLANT

a. Myeloablative Conditioning Regimens
  i. Irreversible decreased organ function
  ii. Class III or IV heart failure
  iii. Heart EF <45%
  iv. Lung FEV1 <50% or DLCO <50% predicted
  v. Kidney
    1. Creatinine clearance of <60 ml/min
    2. Except patients with multiple myeloma and primary systemic amyloidosis in which autologous transplants may be performed if <60 ml/min.
    3. For pediatric patients creatinine clearance <60 ml/min/1.73m^2
  vi. Liver bilirubin >3.0, and transaminase >3x upper limit of normal.
  vii. Liver cirrhosis

  *Patients with borderline organ function may still be eligible based on COE standards

b. Non-Myeloablative/Reduced Intensity Conditioning Regimens

  Requirements for heart, lung, kidney, and liver function may be less stringent than myeloablative conditioning regimens.

[i] Organized by disease classification rather than stem cell source.

[ii] Also known as acute myeloblastic leukemia or acute myelogenous leukemia.

[iii] Adamson, Blaney, O'Connor, Hendricks, Devidas & Alonzo (2015). Update for ANBL0532, Phase III Randomized Trial of Single vs. Tandem Myeloablative Consolidation Therapy for High-Risk Neuroblastoma, Children's Oncology Group: The Children's Hospital of Philadelphia.

[iv] Sullivan KM, Goldmuntz EA, Keyes-Elstein L, McSweeney PA, Pinckney A, Welch B, Mayes MD, Nash RA, Crofford LJ, Eggleston B, Castina S, Griffith LM, Goldstein JS, Wallace D, Craciunescu O, Khanna D, Folz RJ, Goldin J, St Clair EW, Seibold JR, Phillips K, Mineishi S, Simms RW, Ballen K, Wener MH, Georges GE, Heimfeld S, Hosing C, Forman S, Kafaja S, Silver RM, Griffing L, Storek J, LeClercq S, Brasington R, Csuka ME, Bredeson C, Keever-Taylor C, Domsic RT, Kahaleh MB, Medsger T, Furst DE; SCOT Study Investigators. Myeloablative Autologous Stem-Cell Transplantation for Severe Scleroderma. N Engl J Med. 2018 Jan 4;378(1):35-47.

[v] City of Hope. Division of Hematology and Hematopoietic Cell Transplantation: POLICY & PROCEDURE HEMATOPOIETIC CELL TRANSPLANT CLINICAL MA

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If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Evidence and Source Documents

Allogeneic Bone Marrow Transplantation (BMT) in Low-Grade Lymphoma (LGL) and Chronic Lymphocytic Leukemia (CLL)
Autologous Stem Cell Transplant (SCT)/Bone Marrow Transplant for Chronic Myeloid Leukemia (CML)
High Dose Chemotherapy with Autologous Stem Cell Rescue for Treating Multiple Sclerosis
High-Dose Chemotherapy with Stem Cell Transplant for Breast Cancer
Multiple Myeloma
Nonablative SCT for Renal Cell Carcinoma and Melanoma
Scleroderma
Stem Cell Transplantation for Amyloidosis
Stem Cell Transplantation for Autoimmune Diseases

Background

A stem cell transplant is the infusion of healthy stem cells into your body. A stem cell transplant may be necessary if the bone marrow stops working and doesn't produce enough healthy stem cells. Stem cell transplantation is necessary following high dose chemotherapy/radiation for several types of cancers. Stem cells are a type of cell that divide and develop into one of the three main types of cells found in the blood; red blood cells, white blood cells, and platelets.

Although the procedure generally is called a stem cell transplant, it's also known as a bone marrow transplant or an umbilical cord blood transplant, depending on the source of the stem cells. Stem cell transplants can use cells from your own body (autologous stem cell transplant) or they can utilize stem cells from donors (allogenic stem cell transplant).

The first step in the process of stem cell transplantation is the collection of stem cells from a patient or a donor. When a patient's own stem cells are used, they are frozen and stored until needed. Stem cells can be collected from a donor when they are needed. The patient then receives high-dose chemotherapy and the stem cells are infused into the patient's bloodstream. The stem cells travel to the bone marrow and begin to produce new blood cells, replacing the normal cells lost during high-dose chemotherapy.

Medical Technology Assessment Committee (MTAC)

Autologous Stem Cell Transplant (SCT)/Bone Marrow Transplant for Chronic Myeloid Leukemia (CML)

BACKGROUND

Chronic myelogenous leukemia (CML) also referred to as chronic myeloid leukemia, chronic myelocytic leukemia, and chronic granulocyte leukemia, is a malignant disease of the hematopoietic stem cells. Most cases occur in adults, with a median age of approximately 50 years. CML has three stages: Chronic phase, accelerated phase, and blast phase, which is always fatal. Transition from one phase to the other occurs gradually over a period of one year or more however it may take place abruptly and is called the blast crisis. The average survival of CML is 42 months, however after the development of the accelerated phase, survival is usually less than a year, and only a few months after blastic transformation.

There are many treatment options available, yet management of CML remains unsatisfactory. Currently accepted therapies for the chronic phase range from relatively non-toxic oral medications, to alpha interferon-based therapy or aggressive high-dose chemotherapy with allogenic stem transplantation. Conventional chemotherapy usually does not produce a lasting complete remission, nor does it prevent or delay transformation of the disease from an indolent chronic phase to an accelerated phase and blast crisis. High dose therapy, at concentrations much higher than conventional therapy, is highly toxic to the bone marrow and may be able to alter the haematopoietic environment to favor regrowth of normal stem cells. The most effective treatment of CML is high dose chemotherapy with allogenic bone marrow transplantation, which may result in long-term disease-free survival in the majority of patients who receive transplants early in the chronic phase (Meloni 2001). Unfortunately, allogenic

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stem cell transplantation is limited by donor availability and toxicity of graft-versus-host disease (GVHD), especially in the elderly. Transplant of stem cells derived from a patient's own marrow or peripheral blood (autologous transplant) avoids the need for an HLA-matched donor, has less complications, and shorter hospital stay than allogenic transplantations. Autologous bone marrow transplantation was started at the University of Colorado in 1977 and has been successful in other hematological malignancies.

10/9/2002: MTAC REVIEW

Autologous Stem Cell Transplant (SCT)/Bone Marrow Transplant for Chronic Myeloid Leukemia (CML)

Evidence Conclusion: The studies reviewed do not provide sufficient evidence to determine the efficacy and outcome of stem cell/ bone marrow transplantation for CML patients. Results of these studies suggest that this treatment modality has a potential to lead to hematologic and cytogenic response, as well as prolonging survival of younger patients in the first chronic stage. However, the reviewed studies are limited by their design, size, length of follow-up, and lack of a control or comparison group. Their results should be interpreted cautiously. Prospective randomized clinical trials with larger patient sizes, and longer follow-up is needed to assess and compare efficacy of autologous transplantation for CML with other approaches.

The search yielded 79 articles. Articles were selected based on study type. The majority were reviews, opinion pieces, editorials, letters, and commentaries. Some used different adjunct therapies for conditioning, treatment or immunotherapy.

Articles: The literature search did not reveal any randomized controlled trials, or meta-analyses. A study that pooled data from 8 marrow transplant center, and four case series with patients who underwent an autograft after intensive chemotherapy, were identified. The studies with the larger size and/ or better methodology were selected for critical appraisal. Khouri IF, Kantarjian HM, Talpaz M, et al. Results of high dose chemotherapy and unpurged autologous stem cell transplantation in 73 patients with chronic myelogenous leukemia. The MD Anderson experience. *Bone marrow transplantation* 1996; 17:1775-779. See Evidence Table McGlave PB, De Fabritis P, Deisseroth A, et al. Autologous transplants chronic myeloid leukemia: results from eight transplant groups. *Lancet* 1994; 34:1486-1488. See Evidence Table Singer IO, Franklin IM, Clark RE, et al. Autologous transplantation in chronic myeloid leukemia using peripheral blood stem cells. *British Journal of Haematology* 1998; 102:1359-1362. See Evidence Table

The use of autologous SCT/BMT in the treatment of CML does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

High Dose Chemotherapy with Autologous Stem Cell Rescue for Treating Multiple Sclerosis

BACKGROUND

Multiple Sclerosis (MS) is a progressive debilitating neurological disorder with a relapsing and remitting course of symptoms including tremor. MS is caused by a progressive and selective destruction of myelin that is thought to occur as a result of an autoimmune reaction. It is typically treated with anti-inflammatory and immunosuppressive agents such as high-dose steroids, cyclophosphamide and as a last resort, beta-interferon. The symptomatic improvement seen following immune suppression led investigators to propose treating MS by destroying the immune system with high dose chemotherapy and then restoring immune function by replacement of the patients own stem cells. Patient's stem cells are mobilized by administering cyclophosphamide and then harvested for later reinfusion. High doses of chemotherapeutic agents are then used to destroy the patient's immune system. The previously harvested stem cells are then re-infused and, in most cases, restore normal immunologic function.

8/11/1999: MTAC REVIEW

High Dose Chemotherapy with Autologous Stem Cell Rescue for Treating Multiple Sclerosis

Evidence Conclusion: Evidence identification was conducted by searching MEDLINE from 1995-1999 using terms multiple sclerosis, hematopoietic stem cell transplant, stem cells, and transplantation. The author of the largest case series was contacted to ascertain if there were any studies published which had not been previously identified.

Articles: The best, published scientific evidence consists of a case series of 15 patients with a history of progressive MS for a median of 6 yrs and severe disability. Most of the patients were observed for only a few months after treatment; only 3 of the 15 patients were followed for a year or more. Six months after treatment, 3 of 13 patients had improved by at least 1.5 points on the Kurtzke Disability Status Scale (0=normal to 10=death from MS) and 1 patient had worsened by 1 point. The mean improvement was less than 1 point at 6 months. Using the Scripps Neurological Rating Scale (0-100) eight of 13 patients improved by 20 points or more at 6 months. The mean improvement was 22.5 points at 6 months. Transplant-related complications included sepsis and anaphylactic shock. This case series does not prove that high dose chemotherapy with stem cell rescue is an effective treatment for MS. Because some patients who carry the diagnosis of progressive MS may experience neurologic improvement without treatment, one cannot be certain that the clinical improvement documented in

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this study was the result of the therapeutic intervention. Fassas A, et al. Peripheral blood stem cell transplantation in the treatment of progressive multiple sclerosis: first results of a pilot study. *Bone Marrow Transplantation* 1997; 20:631-8 See Evidence Table

The use of stem cell transplantation in the treatment of multiple sclerosis does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

High-Dose Chemotherapy with Stem Cell Transplant for Breast Cancer

BACKGROUND

The success of high-dose chemotherapy (HDC) for some hematologic cancers stimulated hope that high doses might also improve survival for patients with metastatic breast cancer. The usual approach for the use of high-dose chemotherapy in breast cancer treatment involves the delivery of maximally tolerable doses of a combination of chemotherapy drugs supported by autologous stem or bone marrow cells. In the last 10 years, dozens of phase I and II studies have been reported. There is agreement that HDC is highly toxic, with treatment-related mortality rates in the range of 5% to 30%. There has been serious disagreement, however, about whether existing evidence establishes that the treatment is effective in improving survival and whether the benefits, if they exist, outweigh the harms. The strongest “evidence” of the efficacy of this treatment came from the work of a South African researcher, Dr. Bezwoda. He recently admitted falsifying data in a randomized controlled trial (RCT) in which he had reported that HDC, done in conjunction with bone marrow transplantation, prolonged the lives of some women with advanced breast cancer. None of the other peer-reviewed RCTs have shown a statistically significant advantage for HDC with stem-cell support over conventional chemotherapy. The current Kaiser Permanente clinical indications include using high-dose chemotherapy for breast cancer treatment. The purpose of this review is to critically appraise the existing literature in order to evaluate the efficacy of this treatment regimen.

6/14/2000: MTAC REVIEW

High-Dose Chemotherapy with Stem Cell Transplant for Breast Cancer

Evidence Conclusion: A critical appraisal of the existing evidence strongly suggests that high-dose chemotherapy with stem or bone marrow cell support is not beneficial in breast cancer treatment. Studies that have shown some benefit, even in a subset of patients, have numerous threats to validity, including selection bias, small sample sizes, and confounding. Furthermore, the procedure is associated with significant morbidity and mortality, a high rate of relapse, and potentially irreversible long-term effects. The available evidence therefore does not permit conclusions about the effectiveness of this treatment. The final results of large, multi-center, randomized trials may help determine the role of HDC in the management of breast cancer.

Articles: Articles were selected based on study type. There were four randomized controlled trials (RCTs) comparing HDC with “standard treatment” as well as several prospective studies, and meta-analyses. Since the results from the randomized trials were essentially similar (except for studies by Dr. Bezwoda), evidence tables were created for one randomized controlled trial and one prospective phase II trial– 1 each with favorable and unfavorable findings (attached). Reviews, editorials, and comments were reviewed, but no evidence tables were created. *The articles (RCT) selected for critical appraisal include* Nieto et al. Phase II trial of high-dose chemotherapy with autologous stem cell transplant for Stage IV Breast Cancer with Minimal Metastatic Disease. Clinical Cancer Research 1999 July; 5:1731-1737. See Evidence Table Staudmauer et al. Conventional-dose chemotherapy compared with high-dose chemotherapy plus autologous hematopoietic stem-cell transplantation for metastatic breast cancer. NEJM 2000; 342:1069-76. See Evidence Table

The use of high-dose chemotherapy followed by stem-cell transplant treatment of breast cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria* (fails criteria 2).

Multiple Myeloma

BACKGROUND

Multiple myeloma (MM) is a plasma cell neoplasm that accounts for almost 10% of hematologic malignancies, and about 1% of all cancer related deaths. There are approximately 50,000 patients with MM in the United States, and it is estimated that there are more than 15,000 new cases per year. The median age at onset is 66 years, and only 2% of patients are younger than 40 years at diagnosis. Their median survival is around 3 years, but some patients can live longer than 10 years (Hari 2006, Terpos 2005, Levy 2005, Rajkumar 2005). High dose chemotherapy (HDT) with autologous stem cell transplant (ASCT) is regarded as the standard of care for newly diagnosed myeloma in patients less than 65 years of age. This can prolong remission duration, progression free survival, and overall survival in a significant proportion of patients. However, the therapy is not curative, and survivors eventually experience relapse or progression of the disease. Only a few patients who undergo the procedure are free of the disease for more than 10 years. Recurrences are primarily due to the failure of

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chemotherapy to eradicate all myeloma cells. Once relapse has occurred, survival is limited despite the use of novel drugs and salvage regimens (Terpos 2005, Hari 2006, Gerull 2005, Bruno 2007). Researchers have found that allogenic hematopoietic cell transplantation, following high dose conditioning may lead to lower relapse rates and longer remissions, and possibly cure of MM. This is presumably due to the graft versus myeloma effects, in addition to the advantage of a tumor-free graft. However, only a small percentage of patients are candidates for allogenic transplants because of age, availability of an HLA-matched sibling donor, and adequate organ function. Conventional allogenic transplantation is also limited by the high transplant-related morbidity and mortality associated with myeloablative conditioning regimens, and graft versus host disease (GVHD). The risk of treatment-related mortality (TRM) could be as high as 30-60% (Bruno 2007, Gerull 2005). Reduced intensity (non-myeloablative) conditioning was thus developed to decrease toxicity and treatment related mortality while maintaining the graft versus tumor effect. However, relapses are frequent when non-myeloablative allogenic transplantation is used in patients with a relapsed or refractory disease (Harousseau 2005). In the past few years, researchers have been studying the efficacy and feasibility of performing non-myeloablative allogenic transplantation after one or two procedures of high dose therapy and ASCT. This concept combines the advantage of cytoreduction achieved with the high-dose autologous transplant with the graft versus myeloma effect of the non-myeloablative allogenic transplant in order to eradicate the minimal residual disease with a goal of long-term disease control, and hopefully cure of MM (Maloney 2003, Hari 2006).

04/10/2002: MTAC REVIEW
Multiple Myeloma
Evidence Conclusion: The case series reviewed do not provide sufficient evidence to determine the efficacy and outcome of mini stem cell transplantation, for multiple myeloma. In addition to the small sample size of the study reviewed, and the relatively short follow-up, case series provide the lowest grade of evidence; they lack a control or comparison group and are prone to selection bias, and confounding.
The search yielded 59 articles. Articles were selected based on study type. Most of the articles were reviews, opinion pieces, editorials, letters, and commentaries. The literature did not reveal any randomized controlled trials, or meta-analyses. There was only one case series on MM patients who had mini-stem transplantation.
Articles: *The following article was critically appraised:* Badros A, et al. High response rate in refractory and poor-risk multiple myeloma after transplantation using a nonmyeloablative conditioning regimen and donor lymphocyte infusions. *Blood* 2001; 97:2574-9. See Evidence Table

The use of mini stem cell transplant in the treatment of multiple myeloma does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

12/05/2005: MTAC REVIEW
Multiple Myeloma
Evidence Conclusion: Gerull and colleagues (2005) reported the outcomes of 52 MM patients who received non-myeloablative allogenic transplantation between September 1999 and June 2003, at the University of Heidelberg, Germany. The ages of the patients ranged from 36 to 68 years, and they were followed up for a median of 567 days, (479 days for survivors). At the time of analysis only 24 patients (46%) were alive. The results show that the estimated overall survival at 18 months was 41%, and the estimate progression free survival also at 18 months was 29.4%. 38% developed GVDH grade II-IV, and 70% developed chronic GVHD. This study only presents an analysis of a retrospective data of a heterogeneous group of patients treated at one center, followed up for a relatively short time, and the treatment was not compared to an alternative therapy or no treatment.
Articles: Compiled data in Djulbegovic's systematic review on 103 patients with MM show complete response rate of 37%, acute GVHD among 59%, and chronic GVHD among 18% of the patients.
Gerull S, Goerner M, Benner A, et al. Long-term outcome of nonmyeloablative allogenic transplantation in patients with high –risk multiple myeloma Bone Marrow Transplant 2005;doi: 10.1038/sj.bmt.1705161 See Evidence Table

The use of non-myeloablative stem cell transplantation (mini-stem cell transplantation) in the treatment of hematologic malignancies, acute myeloid leukemia, myelodysplastic syndrome, multiple myeloma, lymphomas, renal cell carcinoma does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

08/06/2007: MTAC REVIEW
Multiple Myeloma
Evidence Conclusion: To date, there is no high-quality evidence on the safety and efficacy of mini stem cell transplantation with a preceding autologous hematopoietic cell transplantation for the treatment of multiple myeloma. There are no published randomized controlled trials that compare allografting with non-myeloablative
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conditioning following a cytoreductive autograft to double (tandem) autologous stem cell transplantation, or to an alternative therapy. The best published evidence to date consists of one nonrandomized controlled trial (Bruno 2007) and another study that compared two series of patients (Garban 2006). Bruno and colleagues' study (2007) recruited 245 patients < 65 years old with stage II or III multiple myeloma, from five centers in Italy. 199 of the participants had at least one sibling, and only 104 received treatment. The patients were not randomized to the treatment groups. Those with an HLA-identical sibling (n=58, 56%) received a myeloablative autograft followed by a nonmyeloablative allograft transplantation, and patients without an HLA identical sibling (n=46, 44%) received two consecutive myeloablative doses conditioning, each followed by an autologous stem cell transplant. The primary endpoints of the study were overall survival and event-free survival. After a median follow-up of 45 months, the overall survival and event free survival were significantly longer in patients who completed the autograft-allograft treatment versus those who completed the high-dose, double autograft treatment. The results of the study also show that there was no significant difference between the two groups in the treatment related deaths, but the autograft-allograft transplantation was associated with high rates of acute and chronic GVHD (43% and 64% respectively). Thechronic GVHD was extensive among 36% of the patients in that treatment group. Garban and colleagues (2006) compared the results of two multicenter trials (IFM99-03 and IFM99-04). The studies recruited patients <65 years old with newly diagnosed MM, and with two adverse prognostic factors. After 3-4 cycles of induction regimens, the participants received their first ASCT. Then, according to the availability of an HLA-identical sibling, they either received an allograft with a nonmyeloablative conditioning (IFM99-03 trial) or a second allograft with or without anti-IL-6 monoclonal antibody (IFM99-04 trial). After a relatively short follow-up period (median 24 months) the authors compared the outcomes from both studies. The results showed no significant difference between the two strategies in terms of overall survival or event free survival. Patients were not randomized to one of the two transplantation protocols, and the study was not powered to detect any significant difference between these two treatments. The two studies have their limitations, and it is hard to compare their results because different regimens were used for conditioning, and different intensities of immune suppression drugs were used. Moreover, the participants in Garban's study had a high-risk myeloma unlike those in Bruno's study who were at intermediate or good risk. Large randomized controlled trials would provide higher quality evidence the efficacy and safety of allografting with nonmyeloablative conditioning following a cytoreductive autograft, to other alternative therapies e.g. the tandem autograft used in these non-randomized studies.

Articles: The search yielded around 140 articles. Several were not related to the current review, and many others were review articles. There were two nonrandomized studies with comparison groups, and several prospective and retrospective case series. The two trials with comparison groups were selected for critical appraisal.
Bruno B, Rotta M, Patriarca F, et al. A comparison of allografting with autografting for newly diagnosed myeloma. NEJM 2007; 356:1110-1120. See Evidence Table. Garban F, Attal M, Michallet M, et al. Prospective comparison of autologous stem cell transplantation followed by dose-related allograft (IFM99-03 trial) with tandem autologous stem cell transplantation (IFM99-04 trial) in high risk de novo multiple myeloma. Blood 2006; 107:3474-3480 See Evidence Table.

The use of mini stem cell transplant in the treatment of multiple myeloma meets the *Kaiser Permanente Medical Technology Assessment Criteria.*

Nonablative SCT for Renal Cell Carcinoma and Melanoma

BACKGROUND
Considerable morbidity and mortality are consequences of the myeloablative chemoradiotherapy utilized in conventional allogenic marrow transplantation. This has generally restricted such potentially curative treatment to patients <50-55 years with normal organ function. Recent studies indicate that purine-analogue based non-myeloablative regimens are sufficiently immunosuppressive to facilitate allogeneic donor cell engraftment. Non-ablative (non-myeloblative) bone marrow transplantation involves engrafting an HLA-matched donor's marrow into a host to obtain a graft versus tumor effect. Engraftment is done with just immunosuppressive therapy (not high dose chemotherapy) initially and then is stopped. This procedure is not FDA-approved, but Dr. Feldman states that FDA approval is not necessary.

10/11/2000: MTAC REVIEW
Nonablative SCT for Renal Cell Carcinoma and Melanoma
Evidence Conclusion: Given the limitations of the studies presented (small sample sizes, potential selection bias, and possible toxicity associated with the procedure) there is insufficient evidence at this time to determine the efficacy of non-myeloblative allogeneic peripheral-blood stem-cell transplantation. As stated by one of the investigators "non-myeloblative allogeneic peripheral-blood stem-cell transplantation should remain an investigational approach for the treatment of metastatic renal-cell carcinoma.

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Articles: Articles were selected based on study type. There was one prospective study and one case series. Evidence tables were created for these 2 studies (attached). Review articles and commentaries were reviewed, but no evidence tables were created. *The articles selected for critical appraisal include* Childs et al. Regression of metastatic renal-cell carcinoma after non-myeloblative allogeneic peripheral-blood stem-cell transplantation. NEJM 2000; 343: 750-758. See Evidence Table Grigg et al. "Mini-allografts" for hematological malignancies: an alternative to conventional myeloblative marrow transplantation. Aust NZ J Med 1999; 29:308-314. See Evidence Table

The use of Non-ablative Stem Cell Transplantation for Melanoma and Renal Cell Carcinoma does not meet the *Kaiser Permanente Medical Technology Assessment Criteria* (fails criteria 2 for effectiveness).

12/05/2005: MTAC REVIEW
Nonablative SCT for Renal Cell Carcinoma and Melanoma
Evidence Conclusion: Peccatori and colleagues (2005), analyzed data from 70 patients who received reduced intensity stem cell transplantation for advanced renal cell carcinoma in nine European transplant centers from 1999 to 2003. The authors selected ten variables and entered them in a univariate analysis. Those significantly correlated with survival were entered in a multivariate regression analysis, which suggested three prognostic parameters according to which the authors categorized the study patients as high or low risk groups. After a median follow-up of ten months the median survival (according to Kaplan Meier estimates) was 23 months for the low-risk group, and 3.5 months for the high-risk group. The study population was a highly selected group of patients, and the therapy was not compared to an alternative strategy or to no treatment.
Articles: Peccatori J, Barkholt, Demirer, et al. Prognostic factors for survival in patients with advanced renal cell carcinoma undergoing nonmyeloablative allogenic stem cell transplantation. Cancer 2005; 104:2099-2103. See Evidence Table

The use of nonmyeloablative stem cell transplantation (mini-stem cell transplantation) in the treatment of hematologic malignancies, acute myeloid leukemia, myelodysplastic syndrome, multiple myeloma, lymphomas, and renal cell carcinoma does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Non-Myeloablative Stem Cell/Bone Marrow Transplant (Mini Transplant)
BACKGROUND
Myeloablative combination of high-dose chemo-radiotherapy followed by allogenic hematopoietic stem-cell transplantation (HSCT) is an effective treatment for various hematological malignancies resistant to conventional doses of chemotherapy. Conventional allogenic HSCT involves the use of maximally tolerated myeloablative chemotherapy and/or radiotherapy conditioning regimens to eradicate the underlying disease, while the allograft serves to rescue patients from marrow aplasia induced by the treatment (Georges 2002). However, high-dose chemo/radiotherapy with allogenic HSCT is associated with significant morbidity and mortality due to toxicity of the preparative regimen, the accompanying immunodeficiency, and graft versus host disease (GVHD). The associated toxicity and mortality have limited the use of allogenic HSCT to young medically fit patients. Many patients who may potentially benefit from the treatment are not eligible for the procedure due to age, co-morbid illnesses, poor organ function, or extensive previous chemotherapy. Several hematologic malignancies e.g. acute myelogenous leukemia, chronic myelogenous leukemia, and myeloblastic syndromes peak in the seventh decade of life, which limits the options for these older patients to palliative chemotherapy (Burroughs 2004). There are indications that the main therapeutic effect of allogenic HSCT may not be solely due to the physical elimination of all tumor cells by the high doses of conditioning regimen, but also to T-cell-mediated graft-versus tumor (GVT) or graft versus leukemia (GVL) effect. Researchers also found that donor lymphocyte infusions (DLIs) can re-induce remissions in patients who have relapsed following allogenic transplantation. This has led to the exploration of non-myeloablative allogenic stem cell transplantation (NST) as a safer alternative to conventional high-dose transplant regimens, and as a means to exploit the GVD effect to cure malignancies with elimination of the need for hazardous conditioning. Conditioning regimens are referred to as non-myeloablative if they are not given at a dose that will result in permanent marrow aplasia i.e. will not completely eradicate host hematopoiesis and immunity. They have a potent immunosuppressive effect but are only mildly myelodepressive and commonly result in induction of mixed chimerism (Shimoni, 2002). A truly nonmyeloablative regimen is defined as a regimen that allows relatively prompt hematopoietic recovery (in less than 28 days) without a transplant and upon engraftment mixed chimerism should occur (Khouri, 2004). Clinical data indicate that NST lowers the incidence and severity of GVHD which is main cause of treatment related mortality. NST regimens were originally designed for older patients or any patient ineligible for standard conditioning due to other co-morbidities or risks. Now, they may also be considered for patients where high-dose chemo/radiotherapy is unnecessary. Reduced intensity regimens usually consist of purine analogues e.g. fludarabine combined with alkylating agents such as busulfan, or cyclophosphamide. A second approach which is nonablative, consists of 2 Gy total body irradiation either alone

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or combination with fludarabine. Mini stem cell transplant was reviewed by MTAC on 4/10/2002, and 6/11/2003 and did not pass MTAC criteria. They study reviewed were all small case series with short follow-up and no control or comparison groups.

06/11/2003: MTAC REVIEW
Non-Myeloablative Stem Cell/Bone Marrow Transplant (Mini Transplant)
Evidence Conclusion: There is insufficient published literature to provide evidence on the use of non-myeloablative stem cell/bone marrow transplant for cervical cancer, myeloproliferative disease, HIV patients, severe combined immunodeficiency, Wiskott-Aldrich syndrome, amyloidosis, or other metabolic disorders. There is also insufficient evidence to determine the efficacy and outcome of mini stem cell/ bone marrow transplantation in treating hematological diseases. In addition to the small sample sizes of the series reviewed, and the relatively short follow-up duration, case series provide the lowest grade of evidence; they lack a control or comparison group and are prone to selection and observation bias.
Articles: The search yielded almost 600 articles. The majority were reviews, opinion pieces, or dealt with the technical aspects of the procedure. The literature search did not reveal any randomized controlled trials, or non-randomized comparative studies. All were small case series or case reports with small sample sizes. The search did not reveal any studies or reports on non-myeloablative transplantation for cervical cancer, amyloidosis, or other metabolic disorders. There were very few case reports with 1-8 patients each on PNP deficiency, Wiskott-Aldrich syndrome, ADA severe combined immunodeficiency, DiGeorge syndrome, and HIV infection. The search also revealed a series of 50 patients with Fanconi's anemia conditioned with a non-myeloablative regimen before the transplantation, and with six years of follow-up. Most of the series published were on leukemias, lymphomas, and multiple myeloma (MM). Mini transplant for MM was reviewed by the committee in 4/10/2002 and did not pass MTAC criteria. The case series on the individual leukemias and lymphomas were too small. The two largest series that included older patients and/or patients with other co-morbid conditions, with a variety of hematological diseases were selected for critical appraisal, as well as the series on Fanconi's anemia. *The following articles were critically appraised:* McSweeney PA, Niederwieser D, Shizuru JA, et al. Hematopoietic cell transplantation in older patients with hematologic malignancies: replacing high-dose toxic therapy with graft-versus-tumor effects. *Blood* 2001; 97:3390-3400. See Evidence Table Niederwieser D, Maris M, Shizuru JA, et al. Low-dose total body irradiation (TBI) and Fludarabine followed by hematopoietic cell transplantation (HCT) from HLA-matched or mismatched unrelated donors and postgrafting immunosuppression with cyclosporine and mycophenolate mofetil (MMF) can induce durable complete chimerism and sustained remissions in patients with hematological diseases. *Blood* 2001; 101:1620-1629. See Evidence Table Socie G, Devergie A, Girinski T, et al. Transplantation for Fanconi's anemia: long-term follow-up of fifty patients transplanted from a sibling donor after low-dose cyclophosphamide and thoraco-abdominal irradiation for conditioning. *British Journal of Hematology* 1998; 103:249-255. See Evidence Table

The use of non-myeloablative stem cell/bone marrow transplant in the treatment of cervical cancer, myeloproliferative disease, HIV patients, severe combined immunodeficiency, Wiskott-Aldrich syndrome, amyloidosis, or other metabolic disorders does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

12/05/2005: MTAC REVIEW
Non-Myeloablative Stem Cell/Bone Marrow Transplant (Mini Transplant)
Evidence Conclusion: Hematological malignancies Djulbegovic and colleagues' systematic review included 25 case series with a total of 603 patients with a wide range of hematologic malignancies. Only 4 studies included more than 10 patients with the same malignancy. The authors compiled some extractable data from the heterogeneous studies included, but apparently, they did not use standard meta-analysis techniques. The studies had different inclusion/exclusion criteria, used different conditioning, treatment, and immunosuppression regimens, and the patients had variable co-morbid conditions. The authors did not discuss any evaluation of the quality of the studies, or how they pooled the data. The results of the compiled data showed that 44% of the patients had complete response to the treatment, and that 51% developed acute GVHD, and 23% developed chronic GVHD. Some analyses were done for specific diseases. Three recent studies (Alyea 2005, Sorror 2004, and Diaconescu 2004) compared the outcomes of transplantations after nonablative and ablative regimens in different centers in the US. They were not randomized rather retrospective analysis of cohorts of patients selected to receive the nonablative conditioning regimens, and matched controls conditioned with myeloablative regimens. The results of these analyses showed that patients who received the nonablative conditioning had lower transplant related mortality, nonrelapse mortality rates, and experienced less or comparable grade II to IV toxicities despite the fact that they were older, had more advanced diseases, and more co-morbidities. The three studies had specific questions, defined inclusion/exclusion criteria, and comparison groups, yet they were only observational, and subject to bias and confounding. Randomization would have been ideal but is not an option as
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patients conditioned with nonablative regimen are not candidates for the standard ablative conditioning. Specific hematologic diseases: AML Sayer et al's article (2003) reported on 113 patients with AML treated at ten German transplant centers between February 1998 and December 2000, using reduced intensity conditioning regimens. Their ages ranged from 16-67 years, and the survivors had a median follow-up of 12 months (range 46-937 days). The authors analyzed the outcomes of this retrospective series of patients and did not include a control group. There were multiple baseline variations in the patient and disease characteristics, and according to the authors, inclusion criteria differed between centers, with no clear or accurate definition for who is or is not eligible for the standard conditioning regimen. The results of the analysis show that the estimated 2-year overall survival, and event free survival after the procedure were 32% and 29% respectively. The rate of acute GVHD grades II-IV was 42%, and that of chronic GVHD was 32.7%. The latter was extensive among 6.5% of the patients. The compiled data in Djulbegovic's systematic review (N=62) showed a 66% complete response rate, 36% acute GVHD, and 23% chronic GVHD. AML/MDS De Lima and colleagues (2004) compared the outcomes of 94 patients with AML or MDS treated with either a reduced intensity or a nonablative conditioning regimen. The average ages were 61 and 54 years in the two regimens respectively, and the median duration of the follow-up was 40 months. It was a retrospective analysis and there were several baseline variations in the patients' and disease characteristics among the recipients of the two regimens, as well as some variations in the source of transplant received. The analysis had the advantage of comparing two regimens but the disadvantage of non-randomization, which is a potential source of selection bias. The regimens were not compared to the conventional ablative regimen. Overall, the results of the study indicate a 3-year actuarial progressive free survival rate of 34%, and overall survival of 27% with no statistically significant difference between the two groups. The rate of acute GVHD grade II-IV was 36%, and that of chronic GVHD was 34% for all patients. Ho and colleagues (2004) presented the results of 62 patients who received a reduced intensity allogenic hematopoietic stem cell transplant for MDS, and AML with multilineage dysplasia, in one center in UK. The donors were either siblings or unrelated volunteers. The ages of the patients ranged from 5-60 years with a median of 53 years, and they were followed up for a median of 348 days (range 37-1,495 days). The overall survival was 89% at 100 days, 80% at 200 days, and 74% at one year. The corresponding disease-free survival rates were 84%, 67% and 62% respectively, and the nonrelapse mortality at one year was 15%. None of the related recipients, and 9% of the unrelated recipients developed acute GVHD. Extensive chronic GVHD developed in only 3% of the population. The nonmyeloablative transplantation was not compared to any other therapeutic strategy, or to no treatment. Multiple myeloma Gerull and colleagues (2005) reported the outcomes of 52 MM patients who received nonmyeloablative allogenic transplantation between September 1999 and June 2003, at the University of Heidelberg, Germany. The ages of the patients ranged from 36 to 68 years, and they were followed up for a median of 567 days, (479 days for survivors). At the time of analysis only 24 patients (46%) were alive. The results show that the estimated overall survival at 18 months was 41%, and the estimate progression free survival also at 18 months was 29.4%. 38% developed GVDH grade II-IV, and 70% developed chronic GVHD. This study only presents an analysis of a retrospective data of a heterogeneous group of patients treated at one center, followed up for a relatively short time, and the treatment was not compared to an alternative therapy or no treatment. Compiled data in Djulbegovic's systematic review on 103 patients with MM show complete response rate of 37%, acute GVHD among 59%, and chronic GVHD among 18% of the patients. NHL Khouri and colleagues (2004) reported on the results of a prospective cohort of patients treated with nonmyeloablative stem cell transplantation for advanced recurrent NHL after a prior response to conventional treatment study, in one center in Texas. Their ages ranged from 21 –68 years with a median of 55 years. 20 (41%) patients dad follicular lymphoma, 15 (31%) had transformed or de novo diffuse large cell lymphoma, and 14 (28%) had mantle cell lymphoma. All had received a prior treatment with a range of 1-4 chemotherapy regimens (median 4), and 17% had failed a previous autologous transplant. The results of the analysis show that hematopoietic recovery occurred within 25 days (median 11 days), 22% had a persistent or progressive disease after transplantation, 20% developed acute GVHD, and 36% developed chronic extensive GVHD. 2% of the patients died within 100 days and 6% after 100 days. The study was small, with potential biases, and no comparison group. Compiled data from Djulbegovic's systematic review on patients with NHL (N=103) show complete response rate of 31%, acute GVHD among 50%, and chronic GVHD among 12% of the patients. Renal cell carcinoma: Peccatori and colleagues (2005), analyzed data from 70 patients who received reduced intensity stem cell transplantation for advanced renal cell carcinoma in nine European transplant centers from 1999 to 2003. The authors selected ten variables and entered them in a univariate analysis. Those significantly correlated with survival were entered in a multivariate regression analysis, which suggested three prognostic parameters according to which the authors categorized the study patients as high or low risk groups. After a median follow-up of ten months the median survival (according to Kaplan Meier estimates) was 23 months for the low-risk group, and 3.5 months for the high-risk group. The study population was a highly selected group of patients, and the therapy was not compared to an alternative strategy or to no treatment. Conclusion: The results of the published studies do not provide strong evidence on the efficacy of nonmyeloablative stem cell transplants in improving the net health outcomes of patients with hematopoietic malignancies. The studies were all observational case series with different selection criteria. Those with comparison groups were retrospective and

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nonrandomized. There were significant differences in patients' characteristics, disease characteristics and stages, and other co-morbid conditions. Moreover, there was no clear or accurate definition for who is or is not eligible for the standard conditioning regimen. Multiple conditioning regimens, treatments, and GVHD prophylaxis regimens were used. Randomized controlled trials might not be an option among these patients who are not candidates for transplantation with the conventional conditioning regimens. Overall, the results of existing published studies, with their limitations, indicate good overall survival and disease-free survival rates, and reduced regimen-related toxicities with the nonmyeloablative stem cell transplantations despite the older age of the patients and presence of more co-morbid conditions and/or organ dysfunctions.
The search yielded more than 600 articles. The majority were reviews, opinion pieces, or dealt with the technical aspects of the procedure. The literature did not reveal any randomized controlled trials. One systematic review of case series was identified. Other published studies were small prospective or retrospective case series or case reports, and most lacked control groups. Most studies included patients with a wide range of hematologic malignancies, and only a few included cohorts of patients with a specific disease. Hematological malignancies: The search identified several case series with population sizes ranging from six patients to just over 100. There was one systematic review with some compiling of the results of smaller studies, and several other prospective and retrospective series. The systematic review, and the studies with comparison groups were selected for critical appraisal. *Specific disease results:* Acute myeloid leukemia and myelodysplastic syndrome (AML/ MDS)
The search revealed few studies on patients with AML or MDS. The series with comparison groups, large number of patients, and published in full text were reviewed.
Articles: The literature search for articles published on MM after the last review revealed a recent case series with 52 patients (Gerull 2005), and smaller series with less than 25 patients. Gerull's study was selected for critical appraisal. Lymphoma: Hodgkin's disease (HD) and Non-Hodgkin's lymphoma (NHL):
There were few small case series on either HD, and /or NHL. The largest series with 49 patients was selected for the review. Other hematopoietic diseases Studies on other hematologic conditions included small number of patients and were not critically appraised. Renal cell carcinoma (RCC): There were several reports on small case series (sizes ranging from 6-18) of patients with RCC treated with nonmyeloablative stem cell transplantation. Very recently a larger analysis of 70 patients with advanced RCC was published. The latter was critically reviewed. *The following articles were selected for critical appraisal:* Alyea EP, Kim HT, Ho V, et al. Comparative outcome of nonmyeloablative and myeloablative allogenic hematopoietic cell transplantation for patients older than 50 years of age. Blood 2005; 105:1810-1814. See Evidence Table Diaconescu R, Flowers CR, Storer B et al. Morbidity and mortality with nonmyeloablative compared with myeloablative conditioning before hematopoietic cell transplantation from HLA-matched related donors. Blood 2004; 104:1550-1558. See Evidence Table de Lima M, Anagnostopoulos A, Munsell M, et al. Nonablative versus reduced intensity conditioning regimens in the treatment of acute myeloid leukemia and high-risk myelodysplastic syndrome: dose is relevant for long-term disease control after allogenic hematopoietic stem cell transplantation. Blood 2004; 104:865-872. See Evidence Table Djulbegovic B, Seidenfeld J, Bonnel C, Kumar A. Nonmyeloablative allogenic stem-cell transplantation for hematologic malignancies. A systematic review. Cancer Control. 2003 10:17-41. See Evidence Table Gerull S, Goerner M, Benner A, et al. Long-term outcome of nonmyeloablative allogenic transplantation in patients with high –risk multiple myeloma Bone Marrow Transplant 2005;doi: 10.1038/sj.bmt.1705161 (advance online publication) See Evidence Table Ho AYL, Pagliuca A, Kenyon M, et al. Reduced intensity allogenic hematopoietic stem cell transplantation for myelodysplastic syndrome and acute myeloid leukemia with multilineage dysplasia using fludarabine, busulphan, and alemtuzumab (FBC) conditioning. Blood 2004; 104:1616-1623. See Evidence Table Khouri IF, and Champlin RE Nonmyeloablative stem cell transplantation for lymphoma. Seminars in Oncology 2004; 31:22-26. See Evidence Table Peccatori J, Barkholt, Demirer, et al. Prognostic factors for survival in patients with advanced renal cell carcinoma undergoing nonmyeloablative allogenic stem cell transplantation. Cancer 2005; 104:2099-2103. See Evidence Table Sorror ML, Maris MB, Storer B et al. Comparing morbidity and mortality of HLA-matched unrelated donor hematopoietic cell transplantation after nonmyeloablative and myeloablative conditioning: influence of pretransplantation comorbidities. Blood 2004; 104:961-968. See Evidence Table Sayer HG, Kroger M, Beyer J, et al. Reduced intensity conditioning for allogenic hematopoietic stem cell transplantation in patients with acute myeloid leukemia: disease status by marrow blasts is the strongest prognostic factor. Bone marrow transplant 2003; 31:1089-1095. See Evidence Table

The use of nonmyeloablative stem cell transplantation (mini-stem cell transplantation) in the treatment of hematologic malignancies, acute myeloid leukemia, myelodysplastic syndrome, Melanoma and Renal Cell Carcinoma, Multiple Myeloma does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Scleroderma

BACKGROUND
Scleroderma is a rare multi-system autoimmune disease notable for a pathologic fibrotic thickening of the skin and abnormalities of the vasculature and visceral organs. It is progressive, debilitating, and often fatal. There is

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no cure and treatment usually involve anti-inflammatory and immunosuppressive agents such as high dose steroids. The symptomatic improvement seen following immune suppression led investigators to propose treatment of scleroderma by destroying the immune system with high-dose chemotherapy and then restoring immune function by infusing the patient's own stem cells. The patient's stem cells are mobilized by administering cyclophosphamide and then harvested for later reinfusion. High doses of chemotherapeutic agents are then used to destroy the patient's immune system. The previously harvested stem cells are then re-infused and, in most cases, restore normal immunologic function.

8/11/1999: MTAC REVIEW

Scleroderma

Evidence Conclusion: Evidence identification was conducted by searching MEDLINE from 1995-1999 using terms multiple sclerosis, hematopoietic stem cell transplant, stem cells, and transplantation. The author of the largest case series was contacted to ascertain if there were any studies published which had not been previously identified.

Articles: The best, published scientific evidence consists of a case series of 15 patients with a history of progressive MS for a median of 6 yrs. and severe disability. Most of the patients were observed for only a few months after treatment; only 3 of the 15 patients were followed for a year or more. Six months after treatment, 3 of 13 patients had improved by at least 1.5 points on the Kurtzke Disability Status Scale (0=normal to 10=death from MS) and 1 patient had worsened by 1 point. The mean improvement was less than 1 point at 6 months. Using the Scripps Neurological Rating Scale (0-100) eight of 13 patients improved by 20 points or more at 6 months. The mean improvement was 22.5 points at 6 months. Transplant-related complications included sepsis and anaphylactic shock. This case series does not prove that high dose chemotherapy with stem cell rescue is an effective treatment for MS. Because some patients who carry the diagnosis of progressive MS may experience neurologic improvement without treatment, one cannot be certain that the clinical improvement documented in this study was the result of the therapeutic intervention. Fassas A, et al. Peripheral blood stem cell transplantation in the treatment of progressive multiple sclerosis: first results of a pilot study. *Bone Marrow Transplantation* 1997; 20:631-8 See Evidence Table

The use of stem cell transplantation in the treatment of multiple sclerosis does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Stem Cell Transplantation for Amyloidosis

BACKGROUND

Amyloid is a protein that is made by plasma cells in bone marrow. There are several forms of amyloid; one form is lighter than the others. A disease called amyloidosis occurs when too much of the light form of amyloid is produced and the proteins are deposited in the body's organs and tissues. The most common form is primary (AL) amyloidosis that mainly affects the heart, lungs, skin, tongue, nerves and intestines. The accumulation of amyloid causes progressive disruption of the normal tissue structure and ultimately leads to organ failure. Signs and symptoms of amyloidosis are generally nonspecific and are seen in a small proportion of patients. Many patients have multi-system involvement at diagnosis. The natural history of amyloidosis is that it is fatal within 2 years in about 80% of patients. It is a rare condition, affecting approximately 3000 people in the United States per year (United Kingdom Myeloma Forum, 2004; Gertz & Rajkumar, 2002; Mayoclinic.com). The standard treatment for AL amyloidosis is oral melphalan. However, this has a clinical response rate of only about 20% and is not effective for rapidly progressive disease (Dispenzieri et al., 2004; Skinner et al., 2004). The use of high-dose intravenous melphalan, followed by autologous stem cell transplantation was first described in the literature in 1996. Stem cells are collected from the patient's bone marrow before high-dose chemotherapy is administered. Early case series found a substantially higher procedure-related mortality than for patients with multiple myeloma. There is also significant risk associated with stem cell mobilization in patients with AL amyloidosis. However, positive results have been reported in patients who survive the treatment. A United Kingdom guideline does not recommend high-dose chemotherapy and stem cell transplantation for patients with any of the following: over 70 years old, more than two organ systems involved, symptomatic cardiac neuropathy or autonomic neuropathy, dialysis-dependent renal failure or a history of GI bleeding due to amyloid (United Kingdom Myeloma Forum, 2004).The amyloid patients who are eligible for high-dose chemotherapy and stem cell transplantation are a highly select group. Researchers at the Mayo Clinic reviewed their records and found that fewer than 20% of their amyloidosis patients would have theoretically been eligible for the treatment. The researchers point out that, due to the better prognosis of this group compared to other amyloidosis patients, a randomized controlled trial or study with a matched control group is needed to determine efficacy (Gertz & Rajkumar, 2002).

10/13/2004: MTAC REVIEW

Stem Cell Transplantation for Amyloidosis

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Evidence Conclusion: There is evidence from a matched case-control study (Dispenzieri) that high-dose chemotherapy and autologous stem cell transplantation improves survival in patients with amyloidosis. Two-year survival in the Dispenzieri study was 70% in the cases and 40% in controls. Matching reduces but does not eliminate the potential for selection bias. The evidence is weaker than that provided by a randomized controlled trial which can control for group differences on unmeasured characteristics. There were no appropriate randomized controlled trials or other matched studies. Experts in amyloidosis have stressed the need for randomized or matched studies because of the better prognosis of patients with amyloidosis who are eligible for high-dose chemotherapy and stem cell transplantation. The Skinner study was a descriptive analysis of one institution's experience over 8 years. It did not match patients and is therefore subject to selection bias.
The searched yielded 112 articles, many of which were reviews, opinion pieces, dealt with technical aspects of the treatment or addressed similar treatments or diseases. There was one randomized controlled trial. In the RCT, both groups received high-dose chemotherapy and stem cell transplantation, one initially and the other after two rounds of oral chemotherapy. Since there was no comparison to a different treatment, this study was not reviewed.
Articles: The best, most relevant, evidence was a matched case-control study comparing patients who did and did not receive high-dose chemotherapy and stem cell transplantation. This was critically appraised, along with the largest case series. *The two studies reviewed were:* Dispenzieri A, Kyle RA, Lacy MQ et al. Superior survival in primary systemic amyloidosis patients undergoing peripheral blood stem cell transplantation: a case-control study. *Blood* 2004; 103: 3960-3963. See Evidence Table Skinner M, Sanchorawala V, Seldin DC et al. High-dose melphalan and autologous stem-cell transplantation in patients with AL amyloidosis: An 8-year study. *Ann Intern Med* 2004; 140: 85-93. See Evidence Table

The use of stem cell transplantation in the treatment of amyloidosis does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Stem Cell Transplantation for Autoimmune Diseases

BACKGROUND
Autoimmune diseases (ADs) encompass a heterogeneous group of chronic systemic disorders with different genetic, environmental, and individual etiological factors, as well as different prognoses. They are highly prevalent, have a significant morbidity and mortality, and a considerable economic cost to the patients and the community. For most ADs the exact pathophysiology remains unclear and may vary from one disease to another. It is known however, that some immunogenic predisposition combined with environmental triggers is required to initiate most ADs (Gratwohl 2005, Tyndall 2005). Among the categories of autoimmune diseases are neurological disorders, rheumatological disorders, vasculitis, hematological immunocytopenias, gastrointestinal and others. Multiple sclerosis, systemic sclerosis, systemic lupus erythematosus, and rheumatoid arthritis are the most commonly encountered ADs. Multiple sclerosis (MS) is a chronic inflammatory disease that affects the central nervous system. It is the most frequent cause of neurologic disability in young adults in Western countries. MS is thought to be an autoimmune disease, but there are other views for its origin. The disease causes gradual demyelination and axonal degeneration in the brain and spinal cord. The clinical course of MS is widely variable ranging from isolated episodes with no clinical significance to impaired mobility, disability, and reduction of life expectancy in more severe cases (Saccardi 2005). Several therapies have been utilized, but currently immunosuppression and immunomodulation are the only recognized forms of therapy. Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease that affects predominantly young women and may range from a relatively mild condition to a severe life-threatening disease involving major organs such as the kidney, brain, lung, or the hematopoietic system. Renal involvement is the most common severe manifestation; it occurs in 30-50% of patients and. and has a 9-25% rate of end-stage renal failure. Lupus has no cure, but in the majority of cases it is responsive to treatment with immunosuppression and steroids. It was reported that more than half of the patients have permanent organ damage, much of which is due to, or increased by corticosteroids (Petri 2006). The disease often pursues a relapsing or refractory course that results in poor quality of life and reduced survival (Jayne 2004). Systemic sclerosis (SSc) also known as scleroderma, is a clinically heterogeneous autoimmune disease characterized by excessive collagen deposits in the skin and internal organs. It was found that rapidly progressive SSc, both in the cutaneous and diffuse forms, has a 5-year survival rate of 20-80%, and a 10-year survival rate of 15-65% (Farge 2004). Various treatments were tried, but none has been proven effective in preventing disease progression or reversing fibrosis. Rheumatoid arthritis (RA) is a chronic systemic inflammatory autoimmune disease of undetermined etiology that affects about 1% of the population (Snowden 2004). It primarily involves the synovial membranes and articular structures of multiple joints leading to substantial pain, joint destruction, and loss of mobility. RA often affects extra-articular tissues throughout the body including the skin, blood vessels, muscles, heart, and lungs. It is a disorder for which there is no cure, and current treatment methods focus on relieving pain, reducing inflammation, slowing joint damage and improving function, and sense of well-being. Patients with severe diseases however may not be controlled by the conventional

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methods used. In general, immunosuppression and immunomodulation are the basic therapeutic strategies for autoimmune diseases and are usually successful. However, certain patients do not respond to these therapies, and require more toxic drugs to achieve or maintain remissions (Gratwohl A, 2005). The ability to use immunosuppressive or cytotoxic therapy over longer periods of time is limited due to infections, bone marrow toxicity, and secondary malignancy. In the last decade, hematopoietic stem cell transplantation (HSCT) after intense immunosuppression has been proposed as a possible strategy for the treatment of severe or refractory autoimmune diseases. HSCT is a short name for a complex multi-step treatment aimed at resetting the dysregulated immune system of patients with severe autoimmune diseases. Various protocols have been tried depending on the underlying disease and experience of the transplant centers. The majority were based on autologous HSCT which a 3-step procedure is involving collection of hemopoietic stem cells (HSCs), treating the patient with a conditioning regimen to eliminate self-reacting lymphocytes within the body, and finally re-infusion of the previously frozen autologous stem cells. The source of stem cells may be bone marrow, cord blood, or peripheral blood. Peripheral blood stem cells harvest contains more progenitor and mature lymphocytes and gives more rapid hematological and immunological reconstitution. It is also simpler to collect than bone marrow harvests, and do not require general anesthesia (Tyndall 2005). Once mobilized, the stem cells are harvested, manipulated, and may be cryopreserved. The conditioning regimens used are designed to specifically target the lymphocytes (lymphoablative regimens) or to destroy the entire hematopoietic bone marrow compartment (myeloablative regimen). However, the goal of autologous HSCT for AD is to generate new self-tolerant lymphocytes after elimination of self or autoreactive lymphocytes within the patient, rather than ablate and reconstitute the entire hematopoietic compartment (Burt 2006). A major difference between lymphoablative and myeloablative regimens is the use of total body irradiation. The latter may have deleterious effects among patients especially those with SSc as radiation can cause microvascular damage. After conditioning the patient, the graft is thawed and infused. Hematological reconstitution occurs in 10-12 days, and immunological reconstitution takes longer. HSCT for autoimmune diseases is still in its experimental stages, it has a learning curve, and some researchers are concerned that it might not be feasible, or too toxic in immunosuppressed patients with organ involvement from the underlying AD.

04/2/2007: MTAC REVIEW
Stem Cell Transplantation for Autoimmune Diseases
Evidence Conclusion: The use of hematopoietic stem cell transplantation in the treatment of severe refractory autoimmune diseases is still in the experimental phase. All published studies were case reports or small case series that assessed the feasibility, tolerance, and efficacy of the transplant for patients with ADs. None included a control or comparison group. These cases were registered in databases, the largest of which is The European Bone Marrow transplant/European league against Rheumatism (EBMT/EULAR) registry. Gratwohl, and colleagues (2005), analyzed the data recorded in the EBMT registry up to 2003. It included records for 473 patients treated in 110 transplant centers in 21 countries in Europe and Australia. This has the advantage of studying the efficacy and safety of the procedure in a larger series of patients but has several limitations including the variations between these centers in the eligibility criteria, patient characteristics, autoimmune disorders and stage of the disease, protocol and techniques of the transplant, and experience in performing the procedure as well as others. Moreover, the analysis did not include a control or comparison group that received an alternative or no treatment. The results of the analysis show that the overall treatment mortality was 7% and with large differences between the ADs (20% for immune thrombocytopenia, 14% for SLE, and 2% for rheumatoid arthritis). The results also show that the more aggressive conditioning regimen was statistically associated with slowing down of the disease progression but was also associated with a significantly higher treatment related mortality. In conclusion the published studies to date do not provide sufficient evidence to determine the efficacy and safety and long-term net health outcome of stem cell transplantation in the treatment of autoimmune diseases.
All studies on HSCT published to date are phase I-II clinical trials (only case series with no controls). Phase III RCTs are underway in US and Europe, and none has been completed and reported to date. The published reports are mostly on one or two individual cases or small case series that either included patients with a specific autoimmune disease or grouped patients with different ADs who underwent an autologous HSCT. The inclusion/exclusion criteria, patient characteristics, protocol, and technique of the procedure, as well as the population size and duration of follow-up varied between the trials. The population sizes of the case series ranged from as low as 8 patients with miscellaneous ADs in one study with 12 months of follow-up, to 50 patients with systemic lupus erythematosus who were followed up for a mean of 29 months. The majority of the published reports collected their data from databases and had overlapping population. The largest database is The European Bone Marrow transplant/European League Against Rheumatism (EBMT/EULAR) International Stem Cell Project database. Other databases for stem transplantation include the International Bone Marrow Transplantation (IBMTR) registry, and the Autologous Blood and Marrow Transplant Registry (ABMTR) in the US, the Sylvia Lawry Center, Munich, Germany database, and the International Autoimmune Diseases stem cell Database in Basel, Switzerland.
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Articles: There is insufficient literature on reduced intensity conditioning and allogenic HSCT. The article (Gratwohl 2005) that analyzed data on the efficacy and toxicity of HSCT recorded in the EBMT database was critically appraised. Gratwohl A, Bocelli-Tyndall C, Fassa A, et al. Autologous hematopoietic stem cell transplantation for autoimmune diseases. Bone Marrow Transplantation 2005; 35:869-879. See Evidence Table

The use of stem cell transplantation in the treatment of autoimmune disorders does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Allogeneic Bone Marrow Transplantation (BMT) in Low-Grade Lymphoma (LGL) and Chronic Lymphocytic Leukemia (CLL)

BACKGROUND

Low grade lymphomas (LGL) are indolent malignancies with a high rate of initial response to treatment and median survival duration of 7-10 years. Radiation therapy or the combination of radiation and chemotherapy can produce durable remissions in some patients with stage I, II, or III disease. Patients with an advanced, recurrent or refractory disease have a poor prognosis. The use of myeloablative therapy and autologous BMT showed positive results among patients with recurrent disease, but not among those with an extensive bone marrow involvement or refractory disease. Allogenic BMT is viewed as an attractive option to treat younger patients with refractory or recurrent disease, with the idea that donor lymphoid cells can potentially mediate a graft versus lymphoma (GVL) effect and achieve a long-term disease control. Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in Europe and North America. Although it is generally considered a disease of the elderly, it is increasingly recognized in younger patients. CLL is characterized by the heterogeneity in clinical behavior and life expectancy for those affected by it. Treatment options for CLL are the use of steroids, alkylating agents, or observation. Bone marrow transplantation is not a standard therapy, but autologous and allogeneic transplants are increasingly being used. BMT which induces high remission rates, yet a small percentage of durable remissions, is an appealing treatment strategy for younger patients. The use of tumor free grafts constitutes an obvious advantage of allogeneic over autologous bone transplantation. The allogeneic transplantation, however, has considerable treatment-related complications and mortality, particularly graft-versus-host disease (GVHD) and infections. Other reasons for the infrequent use of allogeneic BMT are the frequent lack of a matched sibling donor and the higher cost of care. Many questions regarding patient selection, efficacy and outcome are still unresolved. Description: Before BMT, patients are conditioned with total body irradiation (TBI) containing regimens, which may also include cyclophosphamide. After the infusion of the bone marrow, immune suppression is generally used for GVHD. The bone marrow source is human leukocyte antigen (HLA) matched sibling, syngeneic donor, or HLA matched unrelated donor.

12/12/2001: MTAC REVIEW

Allogeneic Bone Marrow Transplantation (BMT) in Low-Grade Lymphoma (LGL) and Chronic Lymphocytic Leukemia (CLL)

Evidence Conclusion: The case series reviewed do not provide sufficient evidence to determine the efficacy and outcome of allogenic bone marrow transplantation, for low-grade lymphoma, and chronic lymphocytic leukemia. Case series provide the least grade of evidence; they lack a control or comparison group and are prone to selection bias, and confounding. The search yielded 161 articles. Articles were selected based on study type. Most of the articles were reviews, opinion pieces, editorials, letters, and commentaries.

Articles: The literature did not reveal any randomized controlled trials, or meta-analyses, only clinical reports and case series. Evidence tables were created for the following articles: van Besien, K; et al. Allogeneic bone marrow transplantation for low-grade lymphoma. Blood 1998; 92: 1832-6 See Evidence Table Toze CL, Shepherd JD, et al. Allogeneic bone marrow transplantation for low-grade lymphoma and chronic lymphocytic leukemia. Bone Marrow Transplantation 2000; 25: 605-612. See Evidence Table

The use of allogenic bone marrow transplantation in the treatment of low-grade lymphoma, and chronic lymphocytic leukemia does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Non-Medicare- Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description

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38204	Management of recipient hematopoietic progenitor cell donor search and cell acquisition
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor
38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
38211	Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
38212	Transplant preparation of hematopoietic progenitor cells; red blood cell removal
38213	Transplant preparation of hematopoietic progenitor cells; platelet depletion
38214	Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
38230	Bone marrow harvesting for transplantation; allogeneic
38232	Bone marrow harvesting for transplantation; autologous
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38241	Hematopoietic progenitor cell (HPC); autologous transplantation
38242	Allogeneic lymphocyte infusions
S2140	Cord blood harvesting for transplantation, allogeneic
S2150	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre- and posttransplant care in the global definition

Stem Cell Storage (long-term) – Considered not medically necessary unless patient is scheduled for transplant

CPT® or HCPC Codes	Description
No specific codes for storage - often submitted as *86999 Unlisted transfusion medicine procedure*	

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed	Date Last Revised
5/1996	05/04/2010 MDCRPC, 03/01/2011 MDCRPC, 01/03/2012MDCRPC, 11/06/2012MDCRPC ,09/03/2013MPC,07/01/2014MPC, 05/05/2015MPC, 03/01/2016MPC, 01/03/2017MPC, 11/07/2017MPC , 10/02/2018MPC, 10/01/2019MPC , 10/06/2020MPC , 10/05/2021MPC , 10/04/2022MPC , 10/03/2023MPC	10/17/2022

MDCRPC Medical Director Clinical Review and Policy Committee
MPC Medical Policy Committee

Revision History	Description
02/06/2018	MPC approved criteria for Mesenchymal Stem Cell Therapy for orthopedic conditions

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05/29/2018	Added coverage language for Medicare members to use Kaiser Permanente criteria for stem cell use for orthopedic conditions
05/07/2019	MPC approved to adopt KP National Criteria for Bone & Marrow Transplant
03/03/2020	MPC approved the proposed changes from KP National Transplant Services.
06/18/2020	Removing CPT codes 30206 and 30207; adding CPT codes 38206 and 38207
04/06/2021	Per National Transplant Guidelines: 1.2 added “active”
12/16/2021	Added stem cell storage policy language to criteria.
01/10/2022	MPC approved the proposed changes from KP National Transplant Services. 60-day notice is not required.
10/17/2022	Updated applicable codes

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Clinical Review Criteria

Stereotactic Radiation (Radiosurgery/Focused Beam/Gamma Knife)

- CyberKnife Robotic Radiosurgery System
- Fractionated Stereotactic Radiotherapy
- Multiple Brain Metastatic Lesions (5 or more brain metastatic lesions)
- Stereotactic Body Radiation Therapy for Prostate Cancer

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	01/15/2021 Noridian retired Stereotactic Radiosurgery (SRS) and Stereotactic Body Radiation Therapy (SBRT) (L34151).These services still need to meet medical necessity as outlined in the LCD and will require review. LCDs are retired due to lack of evidence of current problems, or in some cases because the material is addressed by a National Coverage Decision (NCD), a coverage provision in a CMS interpretative manual or an article. Most LCDs are not retired because they are incorrect. Therefore, continue to use LCD L34151 for determining medical necessity.
Local Coverage Article	None

For Non-Medicare Members

Kaiser Permanente has elected to use the Stereotactic Radiosurgery (KP-0423 06012023) MCG* for medical necessity determinations for the following indications*: trigeminal neuralgia, arteriovenous malformation, essential tremor, glomus jugulare tumor, intracranial meningioma, pituitary adenoma, vestibular schwannoma, and tumors of the prostate. This list does not include all indications covered in the criteria. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.

> **MCG*are proprietary and cannot be published and/or distributed**. However, on an individual member basis, Kaiser Permanente can share a copy of the specific criteria document used to make a utilization management decision. If one of your patients is being reviewed using these criteria, you may request a copy of the criteria by calling the Kaiser Permanente Clinical Review staff at 1-800-289-1363 or access the MCG Guideline Index using the link provided above.

If requesting this service, please send the following documentation to support medical necessity:

- Most recent medical oncology notes
- Most recent radiation oncology notes
- Most recent imaging (i.e. CT/MRI)

Service	Criteria Used
▪ Multiple Brain Metastatic Lesions (5 or more brain metastatic lesions)	There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as

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	standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.
▪ For solitary lung metastases (from any primary)	Send all cases to MD review and possible further radiation oncology consultation

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Radiosurgery can be defined as the stereotactic (precision) delivery of multiple cross-fired radiation beams to a point or volume within a configured space (Chang 2003). Stereotactic radiosurgery may also be described as a method to destroy targets using single high doses of focused ionizing radiation, administered using stereotactic guidance (Niranjan 2001). It is a combination of minimally invasive technologies administered by a multidisciplinary team consisting of surgeons, oncologists, medical physicists, and engineers.

Stereotactic radiosurgery (SRS) was originally designed to produce functional lesions in the brain. It then evolved to target benign tumors and vascular malformations in surgically inaccessible locations. These indications are continuously expanding with the rapidly evolving technology of radiosurgical systems. Currently it has become an alternative to microsurgery and conventional radiation therapy in the treatment of many lesions in the base of the skull. It is used for vascular, tumor, and functional brain surgery, including arteriovenous malformations, pituitary adenomas, acoustic neuromas, and meningiomas, as well as brain metastases. Radiosurgery was initially limited to the brain because of the requirement of a stereotactic frame attached to the skull to provide a coordinate system for tumor localization. Recent advances, however, allow radiosurgical treatment throughout the body without such frames.

A variety of methods have been developed to provide a reference system for the localization study to determine the target coordinates, including fixed frame and frameless systems, removable frame systems, and rigid masks.

Treatment can be repeated any number of times with equal precision as the target is calculated from the position of gold markers. Regardless of the number of sessions, these procedures consist of the following components:

- Head position stabilization (attachment of a frame or frameless)
- Imaging for localization (CT, MRI, or angiography, etc.)
- Computer assisted tumor localization
- Treatment planning – number of isocenters, number, placement and length of arcs, beam size and weight, etc.
- Isodose distributions, dosage prescription and calculation
- Setup and quality assurance testing
- Simulation of prescribed arcs or fixed portals
- Stereotactic intervention or treatment itself

Gamma knife, the prototype of stereotactic radiosurgery was first clinically used in 1967. It developed rapidly from the earlier A-units to B units, and in 1999 to Model C that has a robotic engineering. With the gamma knife, the patient's head is placed within a large metal collimator consisting of a dome-shaped shell with holes that transmit the radiation to the center point. A stereotactic frame is anchored to the skull with four screws that penetrate the outer table to position the head so that the desired target is at the center of the collimator. The use of the frame limited the use of the gamma knife to head lesions, and to patients who could tolerate the rigid frame fixation. Moreover, the use of fractionated treatments that extended for several days was impractical with the frame fixation (Giller 2005).

The CyberKnife is a recently developed frameless stereotactic system that consists of a modified linear accelerator mounted on a robotic arm that moves slowly around the patient. It delivers several beams of radiation at each of many stopping points while minimizing radiation exposure of surrounding tissue (Quinn 2001). Stereotactic precision is achieved without a rigid frame by means of two diagnostic x-ray cameras mounted in the CyberKnife vault and are used to acquire real-time images of the patient's internal anatomy during treatment. Any patient motion is detected by these images, and the information is used by the robot to compensate and keep the linear acceleration on target. Treatment time ranges from 45-60 minutes and can be given in one fraction, or several fractions with smaller doses given over several days, depending on the condition being treated and the size of the affected area.

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The use of the CyberKnife for radiosurgery of organs other than the brain is more challenging and requires several technical refinements. When used for spinal lesions for example, it requires the placement of internal small 2-mm stainless steel screws in the spinal lamina adjacent to the target site as “fiducial markers” (Giller 2005).

Radiosurgery has its advantages as well as risks. It is non-invasive, and can treat poor surgical candidates, and tumors inaccessible to surgery, Moreover, it can safely deliver higher doses of radiation than those used in conventional radiotherapy, while sparing the surrounding tissues from the high levels of radiation. It can thus be more effective in treating radioresistant and recurrent tumors and may be used as a boost to conventional radiotherapy. On the other hand, it was reported that its efficacy is lower and risk of complications higher in larger tumors, or those that were previously treated with radiation. Another limitation is the sensitivity of the optic nerve and chiasma to radiosurgical doses. There is also the risk of radionecrosis which is a combination of cytotoxic and microvascular tissue injury within the treated field due to radiation. This may be delayed for months, asymptomatic, severe, and /or persistent (Giller 2005).

The CyberKnife was cleared by the FDA in October 2001for radiosurgery for lesions, tumors, and other conditions in any anatomical site.

Trigeminal neuralgia (tic douloureux) is a disorder of the fifth cranial (trigeminal) nerve that causes episodes of intense, stabbing pain (separated by pain-free periods) in the areas of the face where the branches of the nerve are distributed.

The general approach to treating this disorder is to begin treatment with pharmacological agents and to initiate surgical treatment if medical treatment fails. There are 3 categories of surgical options: 1) Percutaneous procedures (glycerol injection commonly used at GHC); 2) Microvascular decompression; 3) Focused beam radiosurgery (gamma knife, LINAC). According to the MRU, GHC patients currently referred for radiosurgery on a case-by-case basis).

In gamma knife radiosurgery, magnetic resonance imaging (MRI) is used to identify the trigeminal nerve root. Subsequently, a single 4-mm isocenter of radiation is delivered to the trigeminal nerve root (just posterior to the pons). The radiation dose is 70-90 Gy. No surgical incisions are made.

Evidence and Source Documents

Gamma Knife in the treatment of Trigeminal Neuralgia
CyberKnife Robotic Radiosurgery System
Gamma Knife in the treatment of five or more brain metastatic lesions
Stereotactic Body Radiation Therapy (SBRT) for Prostate Cancer

Medical Technology Assessment Committee (MTAC)

Gamma Knife in the treatment of Trigeminal Neuralgia

04/12/2000: MTAC REVIEW

Evidence Conclusion: Since this topic was last reviewed in 1997, there have been two moderately sized case series articles published examining gamma knife radiosurgery on trigeminal neuralgia. A substantial proportion of patients improved after treatment with low rates of adverse outcomes. Case series have numerous threats to validity and provide weak evidence. If patients with trigeminal neuralgia are known to uniformly experience unrelenting pain, however, the improvement reported in these papers is more suggestive of efficacy. Even in this situation, it is not known whether alternate treatments might be as or more effective than gamma knife radiosurgery. If pain episodes tend to occur infrequently, case series results are less impressive because many patients would likely have been in remission during the initial follow-up period.

Articles: Articles were selected based on study type. For gamma knife therapy, there were no randomized control trials or meta-analyses. Several case series were sub-sets of subsequent case series. The largest and most comprehensive case series that had not been previously reviewed for the 1997 CPC evaluation were selected for critical appraisal and evidence tables were created (Kondziolka, D, Perez, B, Flickinger, JC, Habeck, M, Lunsford, D. Gamma knife radiosurgery for trigeminal neuralgia. Arch Neurol 1998; 55: 1524-1528. Young, RF, Vermeulen, S, Posewitz, A. Gamma knife radiosurgery for the treatment of trigeminal neuralgia. Stereotact Funct Neurosurg 1998; 70 (suppl 1): 192-199). The search on LINAC did not yield any additional articles. One book chapter on LINAC was located. This reported on a case series with 10 patients and was not included in this review due to the small sample size. Young, RF, Vermeulen, S, Posewitz, A. Gamma knife radiosurgery for the treatment of

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trigeminal neuralgia. Stereotact Funct Neurosurg 1998; 70 (suppl 1): 192-199. See Evidence Table. Kondziolka, D, Perez, B, Flickinger, JC, Habeck, M, Lunsford, D. Gamma knife radiosurgery for trigeminal neuralgia. Arch Neurol 1998; 55: 1524-1528. See Evidence Table.

The use of Gamma Knife in the treatment of Trigeminal Neuralgia does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

CyberKnife Robotic Radiosurgery System

06/05/2006: MTAC REVIEW

Evidence Conclusion: CyberKnife; There were no published meta-analyses or randomized controlled trials on the CyberKnife radiosurgery system. There were only case reports and small case series with no control or comparison groups. Case series have numerous threats to validity and provide the weakest grade of evidence, Chang, et al reported on their experience with radiosurgical treatment with the CyberKnife among 61 patients treated in their center at Stanford University over 3 years, and who had at least 36 months of follow-up. The treatment was not compared to an alternative therapy. Data were collected both prospectively and retrospectively, and the main outcome was the tumor response and hearing preservation. The authors did not discuss any inclusion/exclusion criteria, included a heterogeneous group of patients, and two fractionation regimens for the therapy were used. After 36 months of observation, the tumor size decreased among 48% of the patients, was stable among 50%, and increased in size in 2%. Ninety percent of those with those with measurable hearing maintained their hearing level after treatment. Gerszten and colleagues reported their experience with CyberKnife radiosurgery for spinal lesions among 115 patients with several variations in their baseline characteristics and indications for the treatment. It was also a case series with no control or comparison group and potential selection and observation biases. The median follow-up duration was 18 months, and the outcome was
improvement in pain, and tumor control. The results of the series indicate that 94% of the patients presenting with significant pain described an improvement in their pain using a 10-point scale after one month of the treatment. The condition did not progress among those who received the therapy as the primary treatment modality or those who had undergone previous surgery. In conclusion the published literature to date does not provide sufficient evidence to determine the efficacy of CyberKnife for stereotactic radiosurgery for lesions or tumors in various anatomical sites.

Articles: The search yielded 71 articles. There were no meta-analyses or randomized control trials on CyberKnife robotic surgery. There were several small case reports and series that dealt with the technology for the treatment of several lesions in different parts of the body including pituitary tumors, extracranial lesions, metastatic brain tumors, acoustic neuromas, trigeminal neuralgia, spinal lesions, lung, renal, and prostate cancer. Gerstzen et al, published two articles on the same series of patients. The largest and most comprehensive case series, and/or the series with long-term follow-up were selected for critical appraisal. Chang SD, Gibbs IC, Sakamoto GT. Staged stereotactic irradiation for acoustic neuromas. Neurosurgery. 2005; 56:1245-1263. See Evidence Table. Gerszten PC, Ozhasoglu C, Burton SA, et al. Evaluation of CyberKnife frameless real-time image-guided stereotactic radiosurgery for spinal lesions. Stereotact Funct Neurosurg. 2003; 81:84-89. See Evidence Table. Gerszten PC, Ozhasoglu C, Burton SA, et al. CyberKnife frameless stereotactic radiosurgery for spinal lesions: Clinical experience in 125 cases. Neurosurgery. 2004; 55:89-99. See Evidence Table.

The use of CyberKnife Robotic Radiosurgery System in the treatment of lesions, tumors, and other conditions in any anatomical site does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Gamma Knife in the treatment of five or more brain metastatic lesions

02/09/2015: MTAC REVIEW

Evidence Conclusion: To date, there is no direct evidence from randomized controlled trials to determine that stereotactic radiosurgery alone or in combination with WBRT for patients with more than 4 brain metastases leads to better or equivalent outcomes to those of WBRT as regards overall survival, local recurrence, need for salvage therapy, neurological functioning, quality of life, or other outcomes. The best published evidence consists of a recent large prospective observational study of patients with one to 10 brain metastases (Yamamato et al, 2014), two case-matched studies conducted by the same principal author and colleagues, that compared SRS treatment results for patients with 1-4 versus ≥ 5 tumors and 2-9 vs. >10 brain metastases (Yamamato et al, 2013 & 2014 respectively), and a number of retrospective analyses of patients for multiple brain metastases treated with SRS used alone or in conjunction with surgical excision or WBRT. The prospective study conducted by Yamamato and colleagues (2014, Evidence table 1) included 1,194 patients with 1-10 newly diagnosed brain metastasis, with a maximum lesion volume <15 mL, and a Karnofsky performance status (KPS) score of ≥70. All patients received standard stereotactic radiosurgery and the primary outcome was overall survival for which the non-inferiority margin for the comparison of outcomes in patients with two to four brain metastases with those of patients with

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five to ten brain metastases was set as the value of the upper 95% CI for a hazard ratio (HR) of 1.30. The results of the analysis showed a median overall survival after stereotactic radiosurgery of 13.9 months in the patients with one brain metastasis, 10.8 months for those with 2-4 metastases, and 10.8 months among those with 5-10 lesions). Overall survival did not differ between the patients with two to four vs. those with 5-10 lesions (HR 0.97, 95% CI 0.81-1.18). This was less than the value of non-inferiority margin set by the authors a prior. The same group of investigators performed two retrospective case matched-studies to examine whether treatment results of SRS alone for patient with five or more brain metastases differ from those for patients with 1-4 metastases in one study, and for patients with 2-9 versus 10 or more lesions in the other study (Yamamato et al 2013, 2014). Overall the analysis comparing outcomes of SRS in patients with more than 5 metastases versus 1-4 showed a minimal, but statistically significant higher survival in patients with 1-4 versus ≥ 5 metastases. There were no significant differences between the subgroups in other outcomes including death due to progression of brain disease, need for salvage WBRT, salvage surgery, repeat SRS for new tumors, neurological deterioration, or SRS-related complications. Generally similar results were observed with the comparison of outcomes among patients with 2-9 versus 10 or more brain metastases. The studies had their shortcomings including the inherent limitations of retrospective studies, as well as limitations in analyses performed. The great majority of published observational retrospective studies suggest that the number of brain metastases (exceeding one lesion) had no statistically significant impact on overall survival among patients treated with SRS given alone or in combination with WBRT. These retrospective studies include the largest series (Karlsson et al 2009) with data for 1,885 patients with 1-8 metastases treated over 30 years. The results of the analysis indicate that the median overall survival did not differ significantly between those with 2, 3-4, 5-8 or >8 brain metastatic lesions; but patients with one brain metastasis survived longer than those with multiple brain metastases. Prospective randomized controlled trials are needed to determine the efficacy of SRS with or without surgery for multiple brain metastases compared to WBRT alone or following surgical excision of the lesions. A randomized controlled study of neurocognitive outcomes in patients with five or more brain metastases treated with radiosurgery or whole-brain radiotherapy is underway. The primary aim of this study is to compare the change in neurocognitive function outcome between baseline and 6 months in WBRT versus SRS treatment groups. Conclusion: There is insufficient evidence to determine that SRS with or without whole brain radiation therapy (WBRT) has non-inferior, equivalent, or superior outcomes to WBRT in the management of patients with five or more brain metastases. There is insufficient direct evidence to determine that the outcomes of SRS in patients with five or more brain metastases are non-inferior or equivalent to those in patients with 1-4 brain metastases.

Articles: The literature search revealed over 400 articles on the use of SRS for brain metastases. The majority of published articles were studies evaluating the use of the technology for one to four brain lesions, studies comparing different radiation doses, and articles on the technical aspects of the technology. The search did not identify any randomized controlled trial (RCT) that compared SRS with or without WBRT versus WBRT. Almost all the studies that examined the efficacy of SRS in patients with five or more brain lesions were retrospective, observational studies with no comparison groups. There was one recently published prospective, observational study conducted in Japan (Yamamato, et al, 2014) among patients with up to 10 brain metastases, and two case-matched retrospective studies conducted by the same group of principal authors comparing the SRS results for patients with 1-4 versus ≥ 5 tumors in one study, and 2-9 versus 10 or more lesions in the other .The Prospective study and the case matched study comparing outcomes of SRS for 1-4 versus ≥ 5 brain metastases were critically appraised. The results of the retrospective studies published in the last 8 years were summarized and presented in Table 3. Yamamoto M, Serizawa T, Shuto T, et al, Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): A multi-institutional prospective observational study. Lancet Onclo. 2014 April; 15(4): 387–395. Evidence tables 1 and 2. Yamamoto M, Kawabe T, Sato Y, et al. A case-matched study of stereotactic radiosurgery for patients with multiple brain metastases: comparing treatment results for 1-4 vs ≥ 5 tumors: clinical article. J Neurosurg. 2013 Jun; 118(6):1258-1268. Evidence tables 1 and 2.

The use of Gamma Knife in the treatment of five or more brain metastatic lesions does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Stereotactic Body Radiation Therapy (SBRT) for Prostate Cancer

BACKGROUND

Prostate cancer is one of the most common cancers, and the second leading cause of cancer death in men in the US. There are many treatment options for a localized disease, and each has its advantages and side effects. The choice of intervention should be considered carefully, balancing the benefits and harms as they relate to the patient's age, overall health, and personal preferences. External beam radiation therapy (EBRT) is one of the standard treatment options for localized prostate cancer and research shows that there is a dose response for biochemical relapse-free survival. However, the increase in radiation dose to the prostate also results in an increase in exposure to the adjacent organs at risk (namely the bladder, urethra, and rectum). The National Comprehensive Cancer Network (NCCN) Prostate Cancer Guideline (2014) states that doses of 75.6–79.2 Gy in

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conventional fractions to the prostate are appropriate for patients with low-risk cancers, and that patients with intermediate- or high-risk disease should receive doses up to 81.0 Gy. Several advanced techniques have been developed within the last two decades to deliver these high doses of radiation to the prostate while sparing the surrounding normal tissues. Currently intensity-modulated radiation therapy (IMRT) is the most common EBRT modality used for the treatment of localized prostate cancer. IMRT involves the external delivery of multiple beams of radiation that conform to the shape of the tumor, and where the intensity of each beam can be modulated in order to spare the surrounding healthy tissue. IMRT is typically delivered in 38-45 fractions (treatment sessions) and requires 7-9 weeks of treatment (Parthan 2012, Yamazaki 2014, NCCN 2014). Slowly proliferating prostate cancer cells are thought to have a unique radiobiology that is characterized by a low α /β ratio (around 1.5 Gy as opposed to about 10 Gy for other cancers). This assumption was first promoted in 1999 by Brenner and Hall, based on their observation of 367 patients from two centers. They noted that this low α /β ratio of prostate cancer is comparable or lower than that for late-responding normal tissue (experiments on rodents suggest that α /β ratio for the rectum is 4-6 Gy). This suggests that prostate cancer cells have a high degree of sensitivity to dose per fraction, and that the use of fewer high-dose per fraction radiation treatments (hypofractionation) would improve local tumor control. This theory is controversial, supported by some investigators and questioned by others, yet it provided the biologic rationale in favor of hypofractionated radiotherapy for localized prostate cancer (Brenner 1999, Freeman 2011, McBride 2012, Bolzicco 2013, Cabrera 2013, Katz 2013, Oliai 2013, Mangoni 2014, Tan 2014). Hypofractionation may be defined as moderate (2.4-4 Gy per fraction) or extreme (6.5-10 Gy per fraction). Extreme hypofractionation with high-dose-rate brachytherapy (HDR-BT) has been used in some centers for the treatment of prostate cancer, either as a monotherapy or in combination with EBRT. HDR-BT therapy, however, is not widely adopted due to its relatively invasive nature, need for hospitalization, anesthesia, resources, and technical expertise for the planning and delivery of therapy. It also requires prolonged bed rest that increases the risk of infection and thromboembolism (Jabbari 2012, Fukudo 2014, Koh 2014). Stereotactic radiation therapy refers to non-surgical techniques that deliver precisely-targeted (within a few millimeters) external beam photon radiotherapy. Stereotactic techniques are often used to deliver much higher doses per treatment (in only a single or few treatments), compared to traditional radiation therapy. Stereotactic radiosurgery (SRS) was initially developed to treat small brain tumors and functional abnormalities of the brain. Stereotactic body radiotherapy (SBRT) has recently emerged, and is highly marketed, as a non-invasive alternative to HDR-BT for delivering hypofractionated radiotherapy to the prostate. The term ‘stereotactic’ means precise positioning of the target within three-dimensional space, and the term 'body' is used to distinguish the technique from the current terminology of SRS used for brain tumors. SRS and SBRT rely on several technologies: 1. Three-dimensional imaging and localization techniques that determine the exact coordinates of the target within the body, 2. Systems to immobilize and carefully position the patient and maintain it during therapy, 3. Highly focused gamma-ray or x-ray beams that converge on a tumor or abnormality, and 4. Image-guided radiation therapy to improve the precision and accuracy of the treatment (Freeman 2011, Radiology Info.org, Aneja 2014, Tan 2014). SBRT for prostate cancer delivers the entire course of therapy in 4-5 visits over 2-2.5 weeks, compared with up to 45 fractions over 9 weeks with conventional fractionation. Thus, it may be more convenient to patients, potentially improve their adherence to therapy, reduce staff and machine burden, and according to a number of analyses (based on modeling), may be less costly than EBRT. However, the use of SBRT for prostate cancer is an area of controversy in the radiation oncology community and is still regarded by many as an experimental treatment. The mechanism of cell kill with large hypofractionated doses is not fully understood in vivo, and many radiation oncologists have concerns over the potential toxicity of the very high ablative doses delivered per fraction, as well as the risk of disease recurrence (Hodges 2012, Parthan 2012, Cabrera 2013, Seison 2013, Tan 2014). CyberKnife® (Accuray Incorporated, Sunnyvale, CA) is one of the devices used for delivering SBRT. It is a non-gantry-based frameless robotic stereotactic radiation delivery system that consists of a 6MV linear accelerator mounted on a robotic arm, with two orthogonal X-ray imagers to track the inserted gold fiducial markers (GFM) and perform real-time corrections for target repositioning during treatment. CyberKnife delivers hundreds of individualized circular beams with a targeting error of less than 1 mm. allowing the safe delivery of highly conformal treatment plans. To date, CyberKnife has been used to treat tumors of the head and neck, lung, kidney, liver, pancreas, and prostate. The CyberKnife SBRT treatment protocol has two principal phases; treatment planning and treatment delivery. The treatment planning phase involves the implanting of three to four gold fiducial markers (GFMs) in the apex, intermediate lateral zone, and base of the prostate using TRUS for image guided positioning and motion tracking, followed by treatment planning using CT to differentiate the prostate and proximal seminal vesicles from the surrounding tissue. Treatment is then delivered to the prostate by the CyberKnife system in four or five fractions to a total of 34 -39 Gy, given on consecutive or alternating days, according to the study protocol (Freeman 2011, Chen 2013, Seisen 2013). CyberKnife was previously reviewed by MTAC in 2006 for the treatment of lesions or tumors in any anatomical site and did not meet MTAC evaluation criteria. The current review is limited to the use of CyberKnife SBRT for the treatment of prostate cancer, based on a request for coverage of the technology.

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10/20/2014: MTAC REVIEW
Stereotactic Body Radiation Therapy (SBRT)
Evidence Conclusion:
Conclusion: Overall the results of the published small observational phase I and II trials indicate that SBRT has favorable outcomes in terms of short-term biochemical control, and with acceptable toxicity. However, the literature does not provide sufficient evidence to determine the comparative effectiveness of SBRT to other conventional radiotherapy techniques, or the durability of the observed biochemical control and low toxicity associated with the treatment beyond 3-5 years. The published studies did not examine the long-term safety of SBRT or its clinical effects in terms of disease-free survival, metastases-free survival, or overall survival. Larger trials with longer follow-up duration are required to evaluate the long-term safety and effects of SBRT, especially that late toxicity could be worse with extreme hypofractionation compared to the conventional hypofractionation. A number of RCTs involving extreme hypofractionation are underway and may provide more evidence on the safety and efficacy of SBRT compared to conventional therapies for the treatment of localized prostate cancer. However, it will be several years before the results of these trials are published. These ongoing studies are: PACE (Prostate Advances in Comparative Evidence) is an ongoing international randomized phase III study comparing SBRT using CyberKnife, radical prostatectomy, and IMRT (78 Gy in 39 fractions) for low and intermediate risk prostate cancer. HYPO-RT-PC (Hypofractionated radiotherapy of intermediate risk localized prostate cancer) is a Swedish phase III trial that will compare 78Gy in 39 fractions delivered with IMRT over 8 weeks vs. SBRT 42.7 Gy in 7 fractions of 6.1 Gy over 2.5 weeks. RTOG 0938 is a randomised phase II trial that compares the health related side effects of 2 hypofractionation regimens (36.25 Gy delivered twice weekly for a total of 5 treatment sessions (7.25Gy /session) over 15-17 days versus 51.6 Gy delivered in 12 daily treatment sessions (4.3Gy per session) over 16-18 days) for low-risk patients.
Articles: The literature search revealed over 200 articles, the majority of which were reviews, description of hypofractionation radiation therapy, or studies that were unrelated to the current review. No randomized controlled trials (RCTs) comparing SBRT to conventional EBRT regimens or low dose brachytherapy for low-risk prostate cancer were identified. The published empirical studies on the use of the technology for prostate cancer were only phase I and phase II feasibility trials conducted in a number of centers in US and overseas. The search also revealed a pooled analysis (King et al, 2013) of the results of the phase II trials conducted in 8 institutions participating in a consortium for prostate SBRT, as well as a number of published systematic reviews (with no meta-analyses) for hypofractionation therapy in general, or SBRT for the treatment of localized prostate cancer. The pooled analysis by King and colleagues, and the larger phase II trials with the longest follow-up duration were selected for critical appraisal: King CR, Brooks JD, Gill H, et al. Long-term outcomes from a prospective trial of stereotactic body radiotherapy for low-risk prostate cancer. Int J Radiat Oncol Biol Phys. 2012; 82:877-882. See Evidence Table 1. King CR, Freeman D, Kaplan I, et al. Stereotactic body radiotherapy for localized prostate cancer: pooled analysis from a multi-institutional consortium of prospective phase II trials. Radiother Oncol. 2013; 109:217-221. See Evidence Table 1 . King CR, Collins S, Fuller D, et al. Health-related quality of life after stereotactic body radiation therapy for localized prostate cancer: results from a multi-institutional consortium of prospective trials. Int J Radiat Oncol Biol Phys. 2013;87(5):939-45. See Evidence Table 1 Chen LN, Suy S, Uhm S, et al. Stereotactic body radiation therapy (SBRT) for clinically localized prostate cancer: the Georgetown University experience. Radiat Oncol. 2013;8: 58.doi: 10.1186/ 1748-717X-8-58. See Evidence Table 2

Katz AJ, Santoro M, Diblasio F, et al. Stereotactic body radiotherapy for localized prostate cancer: disease control and quality of life at 6 years. Radiat Oncol. 2013;8: 118.doi: 10.1186/1748-717X-8-118. See Evidence Table 2. Oliai C, Lanciano R, Sprandio Bet al. Stereotactic body radiation therapy for the primary treatment of localized prostate cancer. J Radiat Oncol. 2013; 2:63-70. See Evidence Table 2.

The use of Stereotactic body radiation therapy (SBRT) for Prostate Cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
61796	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 simple cranial lesion
61797	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional cranial lesion, simple (List separately in addition to code for primary procedure)
61798	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 complex cranial

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	lesion
61799	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional cranial lesion, complex (List separately in addition to code for primary procedure)
61800	Application of stereotactic headframe for stereotactic radiosurgery (List separately in addition to code for primary procedure)
61781	Stereotactic computer-assisted (navigational) procedure; cranial, intradural (List separately in addition to code for primary procedure)
61782	Stereotactic computer-assisted (navigational) procedure; cranial, extradural (List separately in addition to code for primary procedure)
61783	Stereotactic computer-assisted (navigational) procedure; spinal (List separately in addition to code for primary procedure)
63620	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); 1 spinal lesion
63621	Stereotactic radiosurgery (particle beam, gamma ray, or linear accelerator); each additional spinal lesion (List separately in addition to code for primary procedure)
32701	Thoracic target(s) delineation for stereotactic body radiation therapy (SRS/SBRT), (photon or particle beam), entire course of treatment
77301	Intensity modulated radiotherapy plan, including dose-volume histograms for target and critical structure partial tolerance specifications
77371	Radiation treatment delivery, stereotactic radiosurgery (SRS), complete course of treatment of cranial lesion(s) consisting of 1 session; multi-source Cobalt 60 based
77372	Radiation treatment delivery, stereotactic radiosurgery (SRS), complete course of treatment of cranial lesion(s) consisting of 1 session; linear accelerator based
77373	Stereotactic body radiation therapy, treatment delivery, per fraction to 1 or more lesions, including image guidance, entire course not to exceed 5 fractions
77432	Stereotactic radiation treatment management of cranial lesion(s) (complete course of treatment consisting of 1 session)
77435	Stereotactic body radiation therapy, treatment management, per treatment course, to 1 or more lesions, including image guidance, entire course not to exceed 5 fractions
G0339	Image guided robotic linear accelerator-based stereotactic radiosurgery, complete course of therapy in one session or first session of fractionated treatment
G0340	Image guided robotic linear accelerator-based stereotactic radiosurgery, delivery including collimator changes and custom plugging, fractionated treatment, all lesions, per session, second through fifth sessions, maximum five sessions per course of treatment

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed	Date Last Revised
1992	06/01/2010[MDCRPC], 04/05/2011[MDCRPC], 02/07/2012[MDCRPC], 12/04/2012[MDCRPC], 05/07/2013[MDCRPC],11/05/2013[MPC], 09/02/2014[MPC], 07/07/2015[MPC], 05/03/2016[MPC], 03/07/2017[MPC], 01/09/2018[MPC], 12/04/2018[MPC], 12/03/2019[MPC], 12/01/2020[MPC], 12/07/2021[MPC],12/06/2022[MPC], 12/09/2023[MPC]	04/03/2023

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
09/08/2015	Revised LCD L34136 and added L34151
02/06/2018	MPC approved criteria for prostate cancer
4/28/2020	Added list of covered indications from KP-0423 criteria as clarification for searching
03/09/2021	Updated criteria to include clarifying language: *For cognitive sparing, an alternative consideration could be whole brain radiation therapy with hippocampal sparing and memantine.*
01/10/2023	MPC approved to adopt the revised changes to the SRS criteria to include indications for brain

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	metastasis. Requires 60-day notice effective 06/01/2023.
04/03/2023	Updated applicable codes

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Clinical Review Criteria
Subtalar Arthroereisis for the Treatment of Pes Planus (Flat Feet)

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	Medicare Benefit Policy Manual (MBPM) Chapter 15 section 290 – Foot Care, B. Exclusions from Coverage *This service is not covered per Medicare criteria.*
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article	None

For Non-Medicare Members

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage

Background

Flatfoot is a progressive developmental or acquired deformity characterized by plantar medial rotation of the talus, decrease in the medial arch height, and supination and abduction of the forefoot. The posterior tibial tendon may weaken and tear and the talo-navicular capsule, the tibio-navicular ligament, the spring ligament, the long and short plantar ligaments and the plantar aponeurosis may become stretched. There is a shift in the load from lateral column to the medial column, which may cause the medial arch to flatten further (Arangio 2007).

Flexible flatfoot is also referred to as “collapsing pes valgo planus” in which collapsing refers to the flexibility of the deformity, pes refers to the foot, planus refers to the flattened arch, and vulgus refers to the everted calcaneus (Forg 2001). It is one of the most common foot deformities in adults and can cause pain, fatigue, night cramps, and abnormal gait.

A vast majority of flexible flatfeet can be controlled with functional orthoses, but the worst deformities may require surgical intervention to reconstruct the foot deformity and reduce posterior tendon dysfunction. Many surgical procedures as tendon and muscle lengthening, osteotomies, arthrodesis, and arthroereisis have been described (Saxena 2007).

Arthroereisis was developed more than 30 years ago to be used in combination with other bone and soft tissue procedures. It involves placing various shaped implants beneath the talus to limit excessive eversion while preserving inversion. The implants are intended to block forward, downward and medial displacement of the talus, thus allowing normal subtalar joint motion but blocking excessive pronation. They do not replace reconstructive surgery but are used in conjunction with other operative soft-tissue and bony procedures (Needleman 2006, Saxena 2007).

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The operative procedure includes inserting the arthroereisis implant after correcting all parts of the flatfoot deformity and associated conditions in sequence; ankle, hindfoot, midfoot and forefoot. To date there are at least four cylindrical metallic implants (composed of titanium alloys) designed to be placed under the talus in the tarsal canal and sinus tarsi lesion. They range from 6 -14 mm in width, and 12-18 mm in length. The Futura Biomedical Subtalar Peg Implant, the Maxwell-Brancheau Arthroereisis (MBA) Sinus Tarsi Implant, the Kalix device, and the HyProCure Sinus Tarsi implant are all approved by the Food and Drug Administration for use as an internal support to primary surgical interventions in the treatment of flatfoot. The devices are contraindicated in cases of active local infection, allergic reactions to foreign bodies, poor or insufficient bone stock, the presence of clinical or functional abnormalities that would prevent the potential of achieving good results, or other conditions that may place the patient at risk.

Medical Technology Assessment Committee (MTAC)

Subtalar Arthroereisis

06/04/2007: MTAC REVIEW

Evidence Conclusion: There is insufficient published evidence to determine the efficacy and safety of Arthroereisis in the treatment of flexible flatfeet in adults. The published studies on the technology are only small case series with no comparison groups to compare the outcomes of the intervention to alternative therapies.

Articles: The search revealed around twenty articles on subtalar arthroereisis for the correction of flatfeet in adults. There were no randomized or non-randomized controlled trials that compared the procedure with an alternative therapy. The majority of the published articles reported on experimental studies performed on cadavers. The reports on human adult patients were either case reports or case series with less than 25 patients. The largest were two case series (Needleman 2006, and Viladot 2003) with 23 and 21 patients respectively, and each on a different arthroereisis implant. Both were critically appraised. Needleman RL. A surgical approach for flexible flatfeet in adults including a subtalar arthroereisis with MBA Sinus tarsi Implant. Foot &Ankle International 2006; 27:9-18. See Evidence Table. Viladot R, Pons M, Alvarez F, et al. Subtalar arthroereisis for posterior tibial tendon dysfunction. A preliminary report. Foot & Ankle International 2003; 24:600-606. See Evidence Table.

The use of Subtalar Arthroereisis in the treatment of Pes Planus does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Considered Not Medically Necessary:

CPT® or HCPC Codes	Description
0335T	Insertion of sinus tarsi implant
S2117	Arthroereisis, subtalar
0510T	Removal of sinus tarsi implant
0511T	Removal and reinsertion of sinus tarsi implant

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check.

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Date Created	Date Reviewed	Date Last Revised
06/26/2007	04/06/2007[MDCRPC], 02/07/2011 [MDCRPC], 12/04/2012 [MDCRPC], 10/01/2013 [MPC], 08/05/2014[MPC],06/02/2015[MPC], 04/05/2016[MPC], 02/07/2017[MPC], 02/07/2017[MPC], 12/05/2017[MPC], 11/06/2018[MPC], 11/05/2019[MPC], 11/03/2020[MPC], 11/02/2021[MPC], 11/01/2022[MPC], 11/07/2023[MPC]	04/6/2011

[MDCRPC] Medical Director Clinical Review and Policy Committee

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MPC Medical Policy Committee

Revision History	Description

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Date Sent: 3/29/24
These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage.
Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

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Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Pressure Reducing Support Surfaces

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Hospital Beds NCD 280.7
Local Coverage Determinations (LCD)	LCD L33830 Pressure Reducing Support Surfaces Group 1 LCD L33642 Pressure Reducing Support Surfaces Group 2 LCD L33692 Pressure Reducing Support Surfaces Group 3
Local Coverage Article	Pressure Reducing Support Surfaces - Group 1 - Policy Article (A52489) Pressure Reducing Support Surfaces - Group 2 - Policy Article (A52490) Pressure Reducing Support Surfaces - Group 3- Policy Article (A52468)

For Non-Medicare Members

Service	Policy
Pressure Reducing Support Surfaces Group 2	LCD L33642 Pressure Reducing Support Surfaces Group 2 Pressure Reducing Support Surfaces - Group 2 - Policy Article (A52490)
Pressure Reducing Support Surfaces Group 3	LCD L33692 Pressure Reducing Support Surfaces Group 3 Pressure Reducing Support Surfaces - Group 3- Policy Article (A52468)

If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Pressure relieving support surfaces are designed to prevent or promote the healing of pressure ulcers by reducing or eliminating tissue interface pressure. Most of these devices reduce interface pressure by conforming

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to the contours of the body so that pressure is distributed over a larger surface area rather than concentrated on a more circumscribed location. This clinical policy is consistent with Medicare DME MAC guidelines.

Applicable Codes

Medicare - Considered Medically Necessary when criteria in the applicable policy statements listed above are met
Non-Medicare - Group 2 and 3 - Considered Medically Necessary when criteria in the applicable policy statements listed above are met. Group 1- Medical Necessity Review not required

HCPC Codes	Description
Pressure Reducing Support Surfaces - Group 1	
A4640	Replacement pad for use with medically necessary alternating pressure pad owned by patient
E0181	Powered pressure reducing mattress overlay/pad, alternating, with pump, includes heavy-duty
E0182	Pump for alternating pressure pad, for replacement only
E0183	Powered pressure reducing underlay/pad, alternating, with pump, includes heavy duty
E0184	Dry pressure mattress
E0185	Gel or gel-like pressure pad for mattress, standard mattress length and width
E0186	Air pressure mattress
E0187	Water pressure mattress
E0188	Synthetic sheepskin pad
E0189	Lambswool sheepskin pad, any size
E0196	Gel pressure mattress
E0197	Air pressure pad for mattress, standard mattress length and width
E0198	Water pressure pad for mattress, standard mattress length and width
E0199	Dry pressure pad for mattress, standard mattress length and width
Pressure Reducing Support Surfaces - Group 2	
E0193	Powered air flotation bed (low air loss therapy)
E0277	Powered pressure-reducing air mattress
E0371	Nonpowered advanced pressure reducing overlay for mattress, standard mattress length and width
E0372	Powered air overlay for mattress, standard mattress length and width
E0373	Nonpowered advanced pressure reducing mattress
Pressure Reducing Support Surfaces - Group 3	
E0194	Air fluidized bed

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
10/28/2015	11/03/2015[MPC], 10/04/2016[MPC], 08/01/2017[MPC], 06/05/2018[MPC], 06/04/2019[MPC], 06/02/2020[MPC], 06/01/2021[MPC], 06/07/2022[MPC] , 06/06/2023[MPC] , 01/09/2024[MPC]	03/04/2024

[MPC] Medical Policy Committee

Revision History	Description
7/10/2018	Added criteria for Group 3 mattresses
10/11/2018	Removed Group 3 effective date information
06/02/2020	Added Pressure Reducing Support Surfaces Group 1 HCPC codes

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03/04/2024	Medicare coverage criteria is used for commercial criteria which is now linked directly to the Local Coverage Determinations.

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Clinical Review Criteria
Surgical Treatment of Migraine Headaches

- Surgical Deactivation of Trigger Sites

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article	None
Kaiser Permanente Medical Policy	Due to the absence of an active NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Clinical Review Criteria, ***Surgical Treatment of Migraine Headache*** for medical necessity determinations. Refer to the Non-Medicare criteria below.

For Non-Medicare Members

Kaiser Permanente has elected to use the MCG* Migraine Headache, Surgical Treatment (A-0578) for medical necessity determinations. These procedures are not covered per MCG. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.

> **The MCG* are proprietary and cannot be published and/or distributed**. However, on an individual member basis, Kaiser Permanente can share a copy of the specific criteria document used to make a utilization management decision. If one of your patients is being reviewed using these criteria, you may request a copy of the criteria by calling the Kaiser Permanente Clinical Review staff at 1-800-289-1363 or access the MCG Guideline Index using the link provided above.

If requesting this service, please send the following documentation to support medical necessity:

- Last 2 years of neurology notes
- Most recent clinical note from requesting provider

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Background

Migraine headache is a common primary headache disorders that is characterized by a variety of symptoms such as nausea, vomiting, visual disturbances, and sensitivity to light and sounds. In the United States, approximately 18% of women and 6% of men have experienced at least one migraine in the previous year. Standard treatment for migraine involves identification and avoidance of triggers, and the use of pharmacotherapy to treat acute attacks and prevent further attacks (Goadsby 2010, Silberstein 2004).

Surgical treatment for migraine headache has been proposed for patients who are not receiving adequate benefit from standard treatment options. This approach was originally discovered as an unanticipated benefit of cosmetic

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surgery. The first step to determining whether the patient is a candidate for surgery is to identify trigger sites. Most investigators use Botox to identify the trigger site; however, local nerve blocks can also be used. Patients who experience complete elimination or at least 50% improvement in intensity and/or frequency of headaches are considered candidates for surgery. The surgical approach varies by trigger site and involves removal of certain facial muscles, severing of a facial nerve, and/or surgical modification of the sinuses (Kung 2011).

Medical Technology Assessment Committee (MTAC)

Surgical Deactivation of Trigger Sites for Treatment of Migraine Headaches

02/11/2013: MTAC REVIEW

Evidence Conclusion: A RCT that included 125 subjects evaluated the safety and efficacy of surgical deactivation of migraine headache trigger sites. Patients in the treatment group were injected with Botox to identify trigger sites. Patients were eligible for surgery if they experienced at least 50% improvement in the intensity and/or frequency of headaches from the Botox lasting at least 4 weeks. Ninety-one patients out of the 100 patients in the treatment group underwent surgery. Patients in the control group receive injections of saline. After one year 31 patients in the treatment group and 3 patients in the control group experienced complete elimination. Both groups experienced significant improvement in headache intensity and duration compared to baseline; however, only the treatment group experienced a significant improvement in headache frequency. Compared to the control group, patients who received surgery experienced significantly greater reductions in headache frequency, intensity, and duration at one year. The most common surgical complications were: nasal dryness, rhinorrhea, recurrence of septal deviation, scalp itching, and minor hair loss. This study had several limitations: the inclusion and exclusion criteria were not provided, an ITT analysis was not performed, power was not assessed, the outcome data was self-reported, and it is not stated whether patients were taking pharmacotherapy during the trial (Guyuron 2005).

Headache outcomes at 1 year (Guyuron 2005)

	Treatment	Control	P-value
	Number (%)		
Complete elimination	31 (35)	3 (15.8)	<0.001
Significant improvement*	82 (92)	0 (0)	<0.001
	Mean ± SE		
Frequency (migraine/month)	3.8 ± 0.4	10.2 ± 1.7	<0.001
Intensity (0 to 10, most severe)	4.0 ± 0.3	7.0 ± 0.3	<0.001
Duration (hour)	0.35 ± 0.05	0.99 ± 0.2	0.007

*A t least 50% improvement in intensity, frequency, and/or duration.

Patients in the treatment group were followed for 5-years to determine the long-term safety and efficacy of surgery. Ten patients in the treatment group who underwent additional surgery were excluded from the analysis, leaving 69 patients. Results from this observational follow-up study suggest that the improvements in headache frequency, duration, and intensity that were achieved at 1 year were maintained at 5 years (Guyuron 2011).

Headache outcomes at baseline, 1 year, and 5 years (Guyuron 2011)

	Baseline	Year 1	Year 5
		Number (%)	
		N=89	N=69
Complete elimination	NA	31 (35)	20 (29)
Significant improvement*	NA	82 (92)	61(88)
		Mean ± SD	
Frequency (migraine/month)	10.9 ± 7.5	4.0 ± 6.4	4.0 ± 5.3
Intensity [0 to 10 (most severe)]	8.5 ± 1.2	4.0 ± 3.3	4.5 ± 3.2
Duration (days)	1.4 ± 1.4	0.42 ± 0.8	0.31 ± 0.9

*A t least 50% improvement in intensity, frequency, and/or duration.

A more recent RCT that included 75 subjects also evaluated the safety and efficacy of surgical deactivation of migraine headache trigger sites. Patients underwent injections of Botox to identify the trigger site. Patients who experienced complete elimination or at least 50% improvement in intensity and/or frequency of headaches were candidates for surgery. Patients were then randomized to receive either surgery based on migraine trigger site (frontal, temporal, or occipital) or sham surgery. Twenty-eight (57%) patients who underwent surgery experienced complete elimination compared to 1 (4%) who underwent sham surgery. Both groups experienced significant improvements in headache frequency and intensity from baseline. The treatment group also experienced a significant improvement in headache duration from baseline. The treatment group experienced significantly

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greater reductions in headache frequency and intensity compared to the control group at one year. There was no significant difference between the treatment and the control group in headache duration. The most common adverse events were temporary hollowing and intense itching. This trial had several limitations: it was a small trial and power was not assessed, outcomes were self-reported, and it is not stated whether patients were taking pharmacotherapy during the trial (Guyuron 2009).

Change from baseline to 1 year (Guyuron 2009)

	Treatment	Control	P-Value
	Number (%)		
Complete elimination	28 (57.1)	1 (3.8)	<0.001
Significant improvement*	41 (83.7)	15 (57.7)	0.014
	Mean ± SD		
Frequency (headaches/month)	-7.4† ± 5.8	-3.5† ± 5.4	0.005
Intensity (1 to 10)	-3.0† ± 3.5	-1.3† ± 2.9	0.03
Duration (days)	-0.30† ± 0.46	-0.87 ± 4.5	0.43

*At least 50% improvement in intensity, frequency and/or duration.
†Significant improvement from baseline.

Conclusion: Results from two RCTs with methodological limitations suggest that surgical treatment for migraine headaches may improve migraine headache frequency, intensity, and durations, and results in more patients achieving complete elimination compare to control (not surgery or sham surgery). However, the safety and efficacy of surgical treatment for migraine headaches compared to standard therapy is unknown and there is limited data on the long-term efficacy of this procedure.
Articles: Several observational studies and two randomized controlled trials (RCTs) were identified that evaluated the safety and efficacy of surgical treatment of migraine headaches. The two RCTs and a follow-up study of one of the RCTs were selected for review. All of these studies were conducted by the same investigator.
The following studies were selected for review: Guyuron B, Kriegler JS, Davis J, Amini SB. Comprehensive surgical treatment of migraine headaches. Plast Reconstr Surg. 2005; 115:1-9. See Evidence Table. Guyuron B, Kriegler JS, Davis J, Amini SB. Five-year outcome of surgical treatment of migraine headaches. Plast Reconstr Surg. 2011; 127:603-608. See Evidence Table. Guyuron B, Reed D, Kriegler JS, Davis J, Pashmini N, Amini S. A placebo-controlled surgical trial of the treatment of migraine headaches. Plast Reconstr Surg. 2009; 124:461-468. See Evidence Table.

The use of Surgical Deactivation of Trigger Sites for Treatment of Migraine Headaches does not meet *the Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
15824	Rhytidectomy; forehead
15826	Rhytidectomy; glabellar frown lines
21299	Unlisted craniofacial and maxillofacial procedure
30520	Septoplasty or submucous resection, with or without cartilage scoring, contouring or replacement with graft
30801	Ablation, soft tissue of inferior turbinates, unilateral or bilateral, any method (eg, electrocautery, radiofrequency ablation, or tissue volume reduction); superficial
31200	Ethmoidectomy; intranasal, anterior
31201	Ethmoidectomy; intranasal, total
31205	Ethmoidectomy; extranasal, total
31254	Nasal/sinus endoscopy, surgical with ethmoidectomy; partial (anterior)
31255	Nasal/sinus endoscopy, surgical with ethmoidectomy; total (anterior and posterior)
64732	Transection or avulsion of; supraorbital nerve
64734	Transection or avulsion of; infraorbital nerve
64744	Transection or avulsion of; greater occipital nerve
67900	Repair of brow ptosis (supraciliary, mid-forehead or coronal approach)

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With diagnosis codes	
G43.001	Migraine without aura, not intractable, with status migrainosus
G43.009	Migraine without aura, not intractable, without status migrainosus
G43.011	Migraine without aura, intractable, with status migrainosus
G43.019	Migraine without aura, intractable, without status migrainosus
G43.101	Migraine with aura, not intractable, with status migrainosus
G43.109	Migraine with aura, not intractable, without status migrainosus
G43.111	Migraine with aura, intractable, with status migrainosus
G43.119	Migraine with aura, intractable, without status migrainosus
G43.401	Hemiplegic migraine, not intractable, with status migrainosus
G43.409	Hemiplegic migraine, not intractable, without status migrainosus
G43.411	Hemiplegic migraine, intractable, with status migrainosus
G43.419	Hemiplegic migraine, intractable, without status migrainosus
G43.501	Persistent migraine aura without cerebral infarction, not intractable, with status migrainosus
G43.509	Persistent migraine aura without cerebral infarction, not intractable, without status migrainosus
G43.511	Persistent migraine aura without cerebral infarction, intractable, with status migrainosus
G43.519	Persistent migraine aura without cerebral infarction, intractable, without status migrainosus
G43.601	Persistent migraine aura with cerebral infarction, not intractable, with status migrainosus
G43.609	Persistent migraine aura with cerebral infarction, not intractable, without status migrainosus
G43.611	Persistent migraine aura with cerebral infarction, intractable, with status migrainosus
G43.619	Persistent migraine aura with cerebral infarction, intractable, without status migrainosus
G43.701	Chronic migraine without aura, not intractable, with status migrainosus
G43.709	Chronic migraine without aura, not intractable, without status migrainosus
G43.711	Chronic migraine without aura, intractable, with status migrainosus
G43.719	Chronic migraine without aura, intractable, without status migrainosus
G43.A0	Cyclical vomiting, in migraine, not intractable
G43.A1	Cyclical vomiting, in migraine, intractable
G43.B0	Ophthalmoplegic migraine, not intractable
G43.B1	Ophthalmoplegic migraine, intractable
G43.C0	Periodic headache syndromes in child or adult, not intractable
G43.C1	Periodic headache syndromes in child or adult, intractable
G43.D0	Abdominal migraine, not intractable
G43.D1	Abdominal migraine, intractable
G43.801	Other migraine, not intractable, with status migrainosus
G43.809	Other migraine, not intractable, without status migrainosus
G43.811	Other migraine, intractable, with status migrainosus
G43.819	Other migraine, intractable, without status migrainosus
G43.821	Menstrual migraine, not intractable, with status migrainosus
G43.829	Menstrual migraine, not intractable, without status migrainosus
G43.831	Menstrual migraine, intractable, with status migrainosus
G43.839	Menstrual migraine, intractable, without status migrainosus
G43.901	Migraine, unspecified, not intractable, with status migrainosus
G43.909	Migraine, unspecified, not intractable, without status migrainosus
G43.911	Migraine, unspecified, intractable, with status migrainosus
G43.919	Migraine, unspecified, intractable, without status migrainosus

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
03/05/2013	03/05/2013[MDCRPC], 11/04/2014 [MPC], 09/01/2015[MPC], 06/07/2016[MPC], 04/04/2017[MPC],	02/16/2022

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	02/06/2018[MPC], 02/05/2019[MPC], 02/04/2020[MPC], 02/02/2021[MPC] , 02/01/2022[MPC] , 02/07/2023[MPC]	

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
02/01/2022	Adopted Kaiser Permanente policy for Medicare Advantage members.
02/16/2022	Updated applicable codes

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KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Targeted Axillary Node Dissection (TAD)

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Criteria

For Medicare Members

Source)	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article	None
Kaiser Permanente Medical Policy	Due to the absence of an active NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Clinical Review Criteria, ***Targeted Axillary Node Dissection (TAD),*** for medical necessity determinations. Use the Non-Medicare criteria below.

For Non-Medicare Members

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

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Background

A significant proportion of breast cancer women have axillary metastasis which is a crucial factor in determining local and systemic treatment. The standard of care for these women is total axillary lymph node dissection. However, total axillary lymph node dissection results in morbidities (Lucci et al., 2007) including numbness and lymphedema which is an incapacitating swelling of the arm. In addition to the complications, many women undergo chemotherapy (before the total node dissection) which convert them to node-negative status in approximately 40% to 75% of cases (Boughey et al., 2013; Mittendorf et al., 2014). Yet, a high percent of women undergoes extensive surgery which may no longer be necessary. Sentinel lymph node dissection (SLND) which is an alternative to complete axillary lymph node dissection (ALND) is less invasive, is shown to be promising but it has a high false negative rate (Caudle et al., 2015). New surgery, targeted axillary node dissection (TAD), which combines SLND and identification with removal of clipped node has been the center of attention.

Description of procedure: From Shin et al., 2016 (Shin et al., 2016): At the time of diagnosis/biopsy and in patients with node disease limited to axilla, cancerous nodes are clipped. Then patients undergo chemotherapy involving anthracycline-based, taxane-based, or a combination of both. At the completion of chemotherapy, the previously clipped cancerous nodes are identified with ultrasound and 125 I-radiolabeled seeds are placed to localize them. Implantation of seed is performed one to five days before the surgery and is ultrasound-guided. Both lymph node with radioactive seed are identified with gamma probe. During the surgery, the surgeon removes the sentinel

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lymph nodes, which is sentinel lymph node dissection (SLND), and the cancerous clipped nodes. The clipped node is then sent to Pathologist for assessment. Radiography of the specimen during surgery is performed to assure the removal of lymph node and the seed. Eligible patients for TAD include women with N1 or N2 disease. In patients with N3 disease, clip placement is not performed because they need axillary lymph node dissection after chemotherapy.

Medical Technology Assessment Committee (MTAC)

Target Axillary Node Dissection

01/14/2019: MTAC REVIEW

Evidence Conclusion: In patients with biopsy-proven axillary metastasis in whom a clip placement was performed and who underwent chemotherapy, there is insufficient evidence to determine the efficacy and safety of targeted axillary node dissection (TAD) in comparison with complete axillary lymph node dissection (ALND) or Sentinel Lymph Node Dissection (SLND) in patients with axillary metastasis after chemotherapy.

Articles: PubMed was searched through September 19, 2018 with the search terms Targeted axillary lymph node dissection, TAD, clip placement, breast cancer with variations. The search was limited to English language publications and human populations. The reference lists of relevant studies were reviewed to identify additional publications. The search yielded several articles. However, three met the framework and were reviewed. These studies can be found in evidence table 1. Studies with small sample size or feasibility study were excluded. Studies with no assessment of TAD (SLND with clip placement and removal at time of surgery) were not included. See Evidence Table.

The use of Target Axillary Node Dissection does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Considered Not Medically Necessary:

CPT® or HCPC Codes	Description
No specific codes	

Date Created	Date Reviewed	Date Last Revised
02/05/2019	02/05/2019[MPC], 03/03/2020[MPC], 03/02/2021[MPC], 03/01/2022[MPC] , 03/07/2023[MPC]	

[MPC] Medical Policy Committee

Revision History	Description
02/05/2019	MPC approved to adopt criteria of no coverage for TAD; added 01/2019 MTAC review.

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Clinical Review Criteria
Transanal Endoscopic Resection of Rectal Carcinoma

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
KPWA Medical Policy	Due to the absence of a NCD, LCD, or other coverage guidance, KPWA has chosen to use their own Clinical Review Criteria, "***Transanal Endoscopic Resection of Rectal Carcinoma,***" for medical necessity determinations. Use the Non-Medicare criteria below.

For Non-Medicare Members

Transanal Endoscopic Microsurgery (TEM) will be considered medically necessary for **ONE** or more of the following indications:

1. Benign rectal tumors (adenomas)
2. Low-risk Tis and T1 rectal carcinoma
3. Small rectal carcinoids (less than 2 cm in diameter)
4. T2 cancer in someone medically unable to undergo a major operation

Kaiser Permanente Washington does not cover Transanal Endoscopic Microsurgery (TEM) for lesions that do not meet the criteria above.

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Background

Transanal endoscopic microsurgery (TEM) is a minimally invasive surgical technique that was developed to avoid the morbidity of radical surgery for adenomas and early-stage rectal cancer, while still allowing for complete removal of the lesion. TEM requires specialized instrumentation. TEM uses a natural opening (the anus) to reach the target organ, and is a valuable surgical technique with a low complication rate for patients with appropriate rectal lesions. The main advantages of TEM are preservation of the rectum, anus and fecal continence, low complication rates, short operation times, lower blood loss, shorter hospital stays, and shorter recover times. Other advantages include better exposure, magnified stereoscopic view, and greater reach into the middle and upper rectum.

Local excision (LE) alone does not offer the opportunity for lymph node biopsy and, therefore, has been reserved for patients in whom the likelihood of cancerous extension is small. LE can occur under direct visualization for

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rectal tumors within 10 cm of the anal verge and may be most appropriate for small tumors (less than 4cm) confined to the submucosa (T1, as defined by the TNM staging system). TEMS extends local excision ability to the proximal rectosigmoid junction. Adenomas, large rectal polyps (which cannot be removed through a colonoscope), retrorectal masses, small carcinoid tumors, and non-malignant conditions such as strictures or abscesses are amenable to local excision by either method. TEMS can avoid morbidity and mortality associated with major rectal surgery, including the fecal incontinence related to stretching of the anal sphincter, and can be performed under general or regional anesthesia. Use of TEMS for resection of rectal cancers is more controversial.

The most common treatment for rectal cancer is surgery, either open resection or local excision. The technique chosen depends on the size and location of the tumor, evidence of local or distal spread, and patient characteristics and goals. Open, wide resections have the highest cure rate, but may also have significant adverse effects, such as lifelong colostomy, bowel, bladder, or sexual dysfunction. The use of LE in rectal adenocarcinoma is an area of much interest; however, because LE alone does not offer the opportunity for lymph node biopsy it has been reserved for patients in whom the likelihood of cancerous extension is small. Despite this increased risk of local recurrence, local excision may be an informed alternative for patients. TEMS permits local excision beyond the reach of direct visualization equipment.

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
0184T	Excision of rectal tumor, transanal endoscopic microsurgical approach (ie, TEMS), including muscularis propria (ie, full thickness)

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
03/07/2017	03/07/2017[MPC], 05/02/2023[MPC]	

[MPC] Medical Policy Committee

Revision History	Description
03/07/2017	MPC approved to adopt criteria for TEMS

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Clinical Review Criteria
Focused Aspiration of Scar Tissue (FAST)

- Tenex
- Tenex Health TX System (Tenex Microtip, X1 MicroTip, TX2 Microtip, TXB MicroTip) for the Treatment of Tendinopathies

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article	None
Kaiser Permanente Medical Policy	Due to the absence of a NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Clinical Review Criteria, "***Focused Aspiration of Scar Tissue (FAST)***" for medical necessity determinations. Use the Non-Medicare criteria below.

For Non-Medicare Members

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies for tendonitis and soft tissue injuries.

If requesting review for this service, please send the following documentation:

- Last 6 months of clinical notes from requesting provider &/or specialist

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Tenex Health TX™ is used for the treatment of tendonitis and soft tissue injuries. This procedure — Fasciotomy and Surgical Tenotomy (may also be referred to as Focused Aspiration of Scar Tissue FAST) – is a minimally invasive, non-surgical approach for eliminating scar tissue, the source of chronic tendon pain. FAST is a minimally invasive treatment designed to remove tendon scar tissue, allowing patients to return to their athletics and active lifestyles. The Tenex system is a surgical instrument that uses ultrasonic energy to perform a percutaneous tenotomy and fasciotomy. It is intended to precisely cut and remove disease and damaged tissue that leads to natural tendon and soft-tissue function.

Hayes Review

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Hayes, Inc. Hayes Health Technology Brief. Tenex Health TX Procedure (Tenex Health) for Treatment of Tendon Pain. Lansdale, PA: Hayes Inc.; 9/2015

Medical Technology Assessment Committee (MTAC)

Tenex Health TX System (Tenex Microtip, X1 MicroTip, TX2 Microtip, TXB MicroTip) for the Treatment of Tendinopathies

BACKGROUND

Tendons are fibrous connective tissues that attach muscles to other body parts, usually bones. They play an important role in the movement by transmitting the contraction force produced by the muscles to the bone they hold. Tendons are anatomically designed to withstand extensive mechanical loading but are prone to injury through a variety of biomechanical and biological mechanisms Tendon disorders have become very common among athletic and non-athletic population and account for a considerable proportion of activity-related diseases of the musculoskeletal system. Different terms have been used to describe tendon pathology including tendinitis, tendinosis, paratendonitis, and tendinopathy. Currently, tendinopathy has become the accepted term to describe a spectrum of changes that occur in damaged and/or diseased tendons. Common tendinopathies include plantar fasciitis, Achilles tendinopathy, medial and lateral elbow epicondylitis, rotator cuff tendinopathy, and others. These are mainly characterized by pain, reduced exercise tolerance, and decreased function (Ahmad 2020, Scott 2015, Steinmann 2020).

Tendinopathy is primarily a diagnosis of clinical suspicion and can be difficult to diagnose. Imaging can be normal in pathological tendon, and asymptomatic tendon can be histologically pathological. It is thus reported that the clinical presentation and prognosis of tendinopathy can be very individualized and require detailed assessment of the extent or nature of pathology and risk factors to diagnose and manage the condition. Treatment of tendinopathy should promote repair and remodeling rather than further injury/inflammation. However, it is reported that there is no good clinical outcome measure for tendon remodeling as there is often a discrepancy between clinical improvement and structural improvement measured with clinical imaging (Ahmad 2020, Scott, 2015).

The first line treatment for a diagnosed tendinopathy consists of conservative measures such as rest and activity modification to allow the tendon to heal, bracing, and individualized rehabilitation exercises to stimulate the cellular activity and increase the blood flow in the tendon. Pharmacological therapies such as non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids may have short-term effect on reducing pain but could have negative or equivocal long-term effect. The majority of individuals will respond to conservative therapy; however, in some patients the tendinopathy is refractory (recalcitrant) to conservative therapy. Corticosteroid injections are commonly used in cases refractory to conservative therapy but have unproven efficacy, can delay healing, and may be associated with potential harms to the tendons (Ahmad 2020, Mattie 2017).

Currently, there is no universally accepted therapeutic modality for recalcitrant tendinopathies. Several non-pharmacological invasive or minimally invasive therapies have been introduced to practice or are being investigated such as laser therapy, shock-wave therapy, therapeutic ultrasound, and thermal modalities (cryotherapy and hyperthermia), platelet rich plasma (PRP) injection, stem cell therapy and others. Many of these therapies were found to have no effect, have only a short-term effect on improving symptoms and /or result in long-term damage to the tendon. Some investigators have advocated re-injuring the tendon through treatments such as intra-tendinous needling and injections, and aggressive soft tissue therapy. These approaches may improve the patient's symptoms in the short-term but could result in long-term damage to the tendon (Mattie 2017, Scott 2015, Stover 2019).

Surgery is often considered as a last option for patients with persistent pain and disability after exhausting all appropriate nonoperative options. Surgery involves the excision of degenerative tendon portions, removal of adhesions, decompression, and/or creation of multiple longitudinal tenotomies. It is reported that ideally surgical treatment of chronic tendinopathy should involve micro-resection of specific regions demonstrating mucoid degenerative tissue. However, traditional surgical techniques are based on gross and not microscopic appearance. Over the years the surgical procedures have evolved from open techniques to more minimally invasive approaches using arthroscopy, or through percutaneous incisions under ultrasound guidance. It is

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reported however, that there is insufficient evidence from high quality RCTs to determine the effectiveness of surgical interventions for the treatment of tendinopathies (Koh 2013, Ma 2020).

Ultrasound-guided percutaneous tenotomy (UGPT) (also known as percutaneous ultrasonic tenotomy [PUT]) is a relatively recent option introduced for the treatment of multiple types of tendinopathy. The therapy is based on the assumption that the removal of the pathological tissues would convert the chronic degenerative process into an acute process that introduces inflammatory growth factors and promotes tendon healing. UGPT combines ultrasound visualization with a small cutting handpiece to allow debridement of the pathological tendon tissue. It is reported however, that ultrasound scanning delivers a 2-dimensional image for a 3-D structure which may result in either failing to remove all the pathologic tissue or removing too much of the healthy tissue. In addition, the pistoning motion of the cutting handpiece can penetrate healthy tendons due to the inadequate visualization provided by the ultrasound probe (Sanchez 2017).

Tenex procedure is an ultrasound-guided percutaneous tenotomy performed with the assistance of proprietary device “TX Tissue Removal System” (Tenex Health; Lake Forest, CA). It uses both diagnostic and therapeutic ultrasound and is intended for ablating, emulsifying and removing diseased or pathologic musculoskeletal tissue to treat chronic tendon and soft-tissue injuries. The Tenex Health TX System is an ultrasonic surgical aspirator that fragments, emulsifies, and removes soft tissue. The system consists of a console, ultrasonic handpiece, inflation cuff and a foot pedal. The console provides control over the user functions including irrigation, aspiration, and ultrasonic fragmentation/emulsification. It has a large, color LCD and employs a touchscreen with a graphical user interface for selection of required settings. The console also houses the irrigation valve, the irrigation pump, and the aspiration pump. The ultrasonic handpiece has a double lumen to allow for concomitant aspiration and irrigation of emulsified tendon tissue. It connects to the console for power, as well as for delivering irrigation fluid directly to the surgical site and for aspirating emulsified tissue by way of integrated tubing set. The handpiece and tubing are single use disposable components of the system. Irrigation fluid is delivered under pressure to the surgical site by operation of an air pump residing in the console. The foot pedal is used to control each of the functions (irrigation, aspiration, ultrasonic fragmentation/emulsification) of the system (FDA website, Batista 2018).

The Tenex procedure is performed in an outpatient setting under sterile condition with local anesthesia and no sedation. A pre-procedure ultrasound is performed to identify the location and extent of the pathology. A small incision (approximately 5 mm) is then made in line with the tendon fiber to allow the introduction of the TX cutting device while limiting any iatrogenic damage to the tendon. The TX ultrasonic cutting device a needle-like point (the TX Micro Tip) is inserted into the area and high-frequency vibrations cuts and debrides the damaged scar tissue and intra-tendinous calcifications that were identified by the pre-procedural ultrasound. Once debridement is complete the skin incision is closed with adhesive bandage, an occlusive film and a compression sleeve. Post procedure protocol limits movement according to the tendon treated. (Chimenti 2019).

Sanchez, et al (2017) reported that that percutaneous ultrasound-guided tenotomy using Tenex device is a surgical procedure associated with complications similar to those of surgery including tendon tear, re-rupture, deep vein thrombosis, and worsening of healing.

10/12/2020: MTAC REVIEW

Evidence Conclusion:

There is insufficient published evidence from well-conducted randomized or non-randomized prospective observational studies to determine the safety and efficacy of Tenex Health TX system for the management of recalcitrant tendinopathies.

Low- to very low strength of evidence suggest that the intervention may lead to some improvement in pain and /or function when compared to baseline symptoms.

Articles:

The literature search did not identify any randomized controlled trials or prospective comparative study that compared the safety and efficacy of percutaneous ultrasound tenotomy, using Tenex Health TX tissue removal system versus a sham therapy or any other intervention used for the treatment of tendinopathy refractory to conservative therapy. The limited published literature consisted of small observational studies and case series the majority of which were retrospective with data obtained from chart reviews.

The use of Tenex Health TX System (Tenex Microtip, X1 MicroTip, TX2 Microtip, TXB MicroTip) for the Treatment of Tendinopathies does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

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Applicable Codes

Considered not medically necessary:

CPT® Codes	Description
23405	Tenotomy, shoulder area; single tendon
23406	Tenotomy, shoulder area; multiple tendons through same incision
24357	Tenotomy, elbow, lateral or medial (e.g., epicondylitis, tennis elbow, golfer's elbow); percutaneous
27000	Tenotomy, adductor of hip, percutaneous (separate procedure)
27306	Tenotomy, percutaneous, single tendon (separate procedure)
27307	Tenotomy, percutaneous, adductor or hamstring; multiple tendons
27605	Tenotomy, percutaneous, Achilles tendon (separate procedure); local anesthesia

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
04/04/2017	04/04/2017[MPC], 04/02/2019[MPC], 04/07/2020[MPC], 04/06/2021[MPC], 04/05/2022[MPC], 04/04/2023[MPC]	12/02/2022

[MPC] Medical Policy Committee

Revision History	Description
02/14/2019	Updated criteria set to publish
12/01/2020	Added MTAC report for Tenex Health TX System (Tenex Microtip, X1 MicroTip, TX2 Microtip, TXB MicroTip) for the Treatment of Tendinopathies. MPC approved to retain non-coverage policy. Included additional CPT codes for percutaneous tenotomy for review. Requires 60-day notice, effective date of additional codes 05/01/2021.
12/02/2022	Removed codes 28008 and 28060 fasciotomy codes as they are not applicable to this procedure.

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KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria

Therasphere and SIR Sphere for Unresectable Hepatocellular Carcinoma

- SIRT (Selective Internal Radiation Therapy)

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article	Treatment with Yttrium-90 Microspheres (A52950)

For Non-Medicare Members

I. The use of Yttrium-90 (90Y) microsphere radioembolization (SIR-Spheres® or TheraSphere®) is medically necessary if **ONE** of the following is met:
   A. Unresectable metastatic liver tumors from primary colorectal cancer (CRC)
   B. Unresectable liver-only or liver-dominant metastases from neuroendocrine tumors (NET) (e.g. carcinoid, islet cell tumor/pancreatic endocrine tumor) and **ALL** of the following:
      1. The disease is diffuse* and symptomatic (*For this medical policy, the term “diffuse” disease is defined as tumor tissue spread throughout the affected organ (e.g., diffuse liver disease)
      2. Only in persons who have failed systemic therapy with octreotide to control carcinoid syndrome (e.g., debilitating flushing, wheezing and diarrhea)
   C. Unresectable primary hepatocellular carcinoma (HCC)

II. Yttrium-90 (90Y) microsphere radioembolization is not covered for any other indication because its clinical utility has not been established.

If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world, and the third most common cause of cancer-related mortality. It is responsible for more than half a million deaths across the globe each year. Treatment options for patients diagnosed with hepatocellular carcinoma (HCC) are limited. Less than 15% are candidates for surgical resection at presentation, and the use of external beam radiation is limited due to the intolerance of normal liver parenchyma to tumoricidal radiation doses (the dose required to destroy solid tumors (>70 Gy) is much higher than the liver tolerance dose of 35 GY). In addition, systematic chemotherapy was found to have little impact on survival and negative impact on the health-related quality of life due to the toxicity to other

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organs and systems. These limitations have led to the emergence of local and regional treatments such as radiofrequency ablation, local administration of cytostatic drugs like hepatic arterial infusion and isolated hepatic infusion, or intrarterial embolization techniques such as transarterial chemo-embolization and selective intrarterial radioembolization therapy (Steel 2003, Salem 2004, Ibrahim 2008, Bult 2009, Riaz 2009).

Yttrium-90 (90Y) intra-arterial radiotherapy also known as radioembolization, is an emerging technique for the treatment of patients with unresectable primary or metastatic liver tumors. It is a minimally invasive catheter-based therapy that delivers internal radiation via the arterial vessels that feed the tumor. The technology takes advantage of the dual blood supply of the liver as the normal hepatic tissue obtains more than 70% of its blood supply through the portal vein, while intrahepatic malignancies derive their blood supply almost entirely from the hepatic artery i.e. arterial rather than portal circulation. The concept of intra-arterial radioembolization was first explored by injecting yttrium-90 containing microspheres in the hepatic artery of rabbits with liver tumor. The first clinical trial on selected patients was conducted in the mid 1980s, but was discontinued due to the several patient deaths of myelosupressions due to leaching (leakage) of the microspheres (Vente 2009).

In an attempt to overcome the problem of leaching, yttrium containing solid glass microspheres were developed (TheraSphere®, MDS Nordion. Ottawa, Ontario, Canada). These consist of microscopic glass beads 20-30 μ in diameter embedded with the radionuclide yttrium-90. The glass microspheres are delivered into the liver tumor through a catheter placed into the hepatic artery and subsequently get lodged in the microvasculature surrounding the tumor. Their size causes them to be trapped in the tumor capillary bed where they deliver very high irradiation doses to the tumors while sparing the surrounding liver parenchyma. Once inside the liver neither the medical personnel nor the family members can be irradiated. The microspheres are not biodegradable; they have a half-life of 64.1 hours (2.67 days) and emit pure beta-radiation with a mean tissue penetration of 2.5 mm and a maximum of 1 cm. The therapy is given as an outpatient interventional radiology procedure, and lasts from 30 to 40 minutes (Carr 2004, Ibrahim 2008, Bult 2009).

Another 90Y product available for clinical use is SIR-Spheres® (SIRTeX Medical Ltd., Sydney, Australia). These consist of biodegradable resin-based microspheres containing Yttrium-90 (90Y) and have an average size of 35 μ in diameter. Upon administration of the spheres in vivo, they are permanently implanted. Similar to TheraSphere, SIR-Spheres emit pure β-radiation with a half life of 2.67 days. Both types of microspheres have shown to preferentially localize to abnormally vascularized liver tumors, where they exert intense localized radiation, while limiting radiation exposure to the uninvolved hepatic parenchyma (Ibrahim 2008, Bult 2009).

Radioembolization is not without complications; it may lead to post-radioembolization syndrome which includes fatigue, nausea, vomiting, anorexia, fever, abdominal pain and cachexia. More serious adverse events include radiation induced liver toxicity, vascular injury when introducing the catheter, radiation pneumonitis from microspheres shunting around the liver and into the lungs, and gastrointestinal tract ulceration. Absolute contraindications for the use of 90Y microspheres include pretreatment with 99mTc macroaggregated albumin scan demonstrating significant hepatopulmonary shunts, and inability to prevent deposition of the microspheres to the gastrointestinal tract with modern catheter techniques (Ibrahim 2008, Riaz 2009).

TheraSphere (MDS Nordion, Ottawa, Canada) was approved by the FDA in 1999 under the Humanitarian Device Exemption Guidelines for the treatment of unresectable hepatocellular carcinoma.

SIR-Spheres® (SIRTeX Medical Ltd., Sydney, Australia) received FDA premarket approved in 2002 for the treatment of colorectal cancer metastasized in the liver with adjuvant floxuridine administered via the hepatic artery.

Medical Technology Assessment Committee (MTAC)

Therasphere in the Treatment of Unresectable Hepatocellular Carcinoma

04/10/2002: MTAC REVIEW

Evidence Conclusion: There is insufficient published evidence to determine the effectiveness of Therasphere for the treatment of unresectable hepatocelluar carcinoma (HCC). Many of the empirical studies were done with animals. Only small case series (four studies, each with n<20) with human populations were available.
Articles: The search yielded 24 articles, many of which dealt with technical aspects of the procedure. There were no randomized controlled trials or meta-analyses. There were several case series, all with small sample sizes (n<20). None of the empirical articles were considered of sufficient quality to be evaluated.

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The use of Therasphere in the treatment of unresectable hepatocellular carcinoma does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

06/05/2006: MTAC REVIEW
Therasphere in the Treatment of Unresectable Hepatocellular Carcinoma
Evidence Conclusion: The empirical studies published before the previous MTAC review of the TheraSphere in 2002, were very small case series with less than 20 patients. For this review the literature search identified a small comparative non-controlled trial and few additional relatively larger series, many of which were published by the same group of investigators. In the comparative trial 28 patients received either TheraSphere therapy or Cisplatin. The patients were not randomized to the treatment groups, the study was unblinded, and the authors did not discuss how the patients were selected for each of the two therapies. The trial was not powered to detect significant differences between the study groups, had a short follow-up duration, and the 6-months data were available for only 50% of the patients. Its results indicate that patients treated with 90-Yttrium microspheres reported significantly higher scores on physical, functional, and social well-being vs. those treated with cisplatin. There was no significant difference in survival between the two groups according to Kaplan Meier curves.

The other case series reviewed was relatively small, had no control or comparison group, included a heterogeneous group of patients with different comorbidities, and the therapy received was not uniform for all patients. Its results indicate that 47% of the patients and 51% of the lesions had a greater than 50% reduction in size. The median survival was 20.8 months among non-high risk patients, and 11.1 month for those at high risk. In conclusion, the evidence published after the previous review is still insufficient to determine the effectiveness and safety of TheraSphere for the treatment of unresectable hepatocelluar carcinoma (HCC).
Articles: The search yielded 27 articles, many of which dealt with technical aspects of the procedure. No randomized controlled trials or meta-analyses were identified. There was a small non-randomized cohort study that compared TheraSphere treatment with Cisplatin, as well as several small prospective and retrospective case series with sizes ranging from 15 to less than 90 patients. The study with a comparison group, as well as a prospective case series with no patient overlap with the comparative trial, and clinically important outcomes, were selected for critical appraisal. Steel J, Baum A, and Carr B. Quality of life in patients diagnosed with primary hepatocellular carcinoma: hepatic arterial infusion of cisplatin versus 90-Yttrium microspheres (TheraSphere)® Psycho-Oncology 2004;13;73-79. See Evidence Table. Salem R, Lewandowski RJ, Atassi B, et al. Treatment of unresectable hepatocellular carcinoma with use of 90Y microspheres (TheraSphere): safety, tumor response, and survival J Vasc Interv Radiol. 2005;16:1627-1639 See Evidence Table.

The use of Therasphere in the treatment of unresectable hepatocellular carcinoma does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

07/06/2010: MTAC REVIEW
Therasphere in the Treatment of Unresectable Hepatocellular Carcinoma
Evidence Conclusion: *TheraSphere* The literature search did not reveal any published randomized controlled trials on TheraSphere after the last 2006 review. At the time the published empirical studies consisted of one small comparative non-randomized trial with 28 patients and a number of case series, many of which were published by the same group of investigators. In the comparative trial, 28 patients received either TheraSphere therapy or cisplatin. The patients were not randomized to the treatment groups, the study was unblinded, and the authors did not discuss how the patients were selected for each of the two therapies. The trial was not powered to detect significant differences between treatments, had a short follow-up duration, and the 6-month data were available for only 50% of the patients. Its results indicate that patients treated with Yttrium-90 microspheres reported significantly higher scores on physical, functional, and social well-being vs. those treated with cisplatin. There was no significant difference in survival between the two groups according to Kaplan Meier curves. The recently published meta-analysis (Vente 2009) pooled the results of the case series with no comparison or control group and do not provide any additional evidence to determine the efficacy and safety of TheraSphere in the treatment of unresectable hepatocellular carcinoma. *Sir-spheres*: The results of the two randomized trials on Sir-Spheres (Gray 2001 and Van Hazel 2004) provide some but insufficient evidence on the benefits of Sir-Spheres combined with regional chemotherapy vs. regional chemotherapy alone in improving the response rate and time to progression. The common toxicities associated with the treatment were generally mild and the rate of grade 3 and 4 toxicities did not differ significantly between the treatment arms in Gray et al's trial. These results, however may not generalized as the chemotherapies use in the trials are not the standard regimens currently used as a first-line treatment, and the response rates in the control arms (0% in Gray et al's trial and 18% in Van Hazel and colleagues trial) were much lower than usually observed. Moreover, the trials were too small, and had insufficient power to determine whether radioembolization has any mortality benefit. *Conclusion:* There is insufficient published evidence to determine efficacy and toxicity of TheraSphere in the treatment of unresectable liver cancer
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when given alone or in combination with systemic or regional chemotherapy. There is insufficient published evidence to determine the efficacy and toxicity of Sir-Spheres in the treatment of liver metastases from colorectal cancer when given alone or in combination with systemic or regional chemotherapy.
Larger RCTs are randomizing patients to first line chemotherapy with or without ^{90}Y microsphere radioembolization are currently underway and may provide more evidence on the benefits of adding radioembolization therapy to first line chemotherapy.
Articles: The literature search yielded around 200 articles; many were review articles or publications that dealt with technical aspects of the procedure. There was one meta-analysis of studies (Vente 2009) on patients with primary or secondary liver malignancies treated with 90Y glass or resin microspheres, and another Cochrane review (Townsend 2009) of RCTs on radioembolization for liver metastases from colorectal cancer. Vente meta-analysis pooled the data from case series but presented a summary result for each of the RCTs separately. The Cochrane review also presented the results of the same 2 trials separately. The search also identified two phase-2 randomized trials conducted by the same research group in Australia that compared Sir-Spheres plus chemotherapy vs. chemotherapy alone for treating patients with liver metastases from primary colorectal cancer. The first published RCT (Gray 2001) compared Sir-Spheres with regional chemotherapy vs. regional chemotherapy alone in 74 patients, and the second (Van Hazel 2004) compared Sir-Spheres combined with systemic chemotherapy vs. systemic chemotherapy alone in 21 patients. The two trials were included in both meta-analyses. The search did not reveal any randomized controlled trials on TheraSphere.
The majority of other published studies were prospective or retrospective case series including patients with HCC or hepatic metastatic colorectal cancer (mCRC). A small number of case series reported on patient with liver metastases secondary to neuroendocrine or breast cancers. The following meta-analysis and the larger RCT were selected for critical appraisal: Vente MAD, Wondergem M, van den Bosch MAAJ, et al. Yttrium-90 microsphere radioembolization for the treatment of liver malignancies: a structured meta-analysis. Europ Radiol 2009;19:951-959. See Evidence Table. Gray B, Van Hazel G, Burton M, et al. Randomized trial of SIR-Spheres® plus chemotherapy vs. chemotherapy alone for treating patients with liver metastases from primary large bowel cancer. Ann Oncol 2001;12:1711-1720. See Evidence Table.

The use of Therasphere in the treatment of unresectable hepatocellular carcinoma does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

The use of SIRsphere in the treatment of unresectable hepatocellular carcinoma does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

02/13/2012: MTAC REVIEW
Therasphere in the Treatment of Unresectable Hepatocellular Carcinoma
Evidence Conclusion: The best evidence published to date, after the last 2010 MTAC review, consisted of one small phase III randomized controlled trial on radioembolization using SIR-Spheres in patients with liver metastatic colorectal cancer, and two comparative efficacy analyses conducted to compare of the safety and efficacy of yttrium 90 (^{90}Y) radioembolization in patients with unresectable hepatocellular carcinoma. In all published series and studies the radioembolization were performed by highly trained professionals in specialized centers.
TheraSphere: Salem and colleagues (2011) recently published a comparative analysis of the outcomes of two relatively large cohorts of patients (total N= 463) with unresectable HCC who were treated in a single center with either transarterial chemotherapy (TACE) or radioembolization using ^{90}Y microspheres (TheraSphere). The study was not a randomized trial, nor designed to determine equivalence between the two therapies. The authors indicated that treatment response and survival were calculated from first treatment, and follow-up duration was longer for TACE. They also explained that patients undergoing TACE were younger and more likely to receive it as a bridge to transplantation. The overall results of the analysis showed longer time to progression with radioembolization using^{90}Y microspheres. There was no significant difference between the two therapies in time to response or survival. The study was not designed as an equivalence study, and lack of significant difference does not indicate that the two therapies are equivalent. An analysis performed by the authors showed that a randomized trial with 1000 patients would be required to establish equivalence in survival. There were no statistically significant differences in major toxicities between the two therapies. Patients treated with chemoembolization were more likely to experience abdominal pain and higher hepatic transaminase elevation. Lance et al's (2011) comparative analysis only included 73 patients treated with either chemoembolization or radioembolization with glass or resin ^{90}Y microspheres. The results did not show survival advantage with radioembolization but found higher rates of hospitalization in the chemoembolization group due to the postembolization syndrome.
Sir-Sphere: Hendlisz and colleagues' (2010), RCT compared the efficacy and safety of intravenous fluorouracil (FU) given alone or with of intra-arterial 90Y-resin microspheres (SirSpheres) in 46 patients with liver-limited
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metastatic colorectal cancer (mCRC) who failed other chemotherapies. The trial was randomized, controlled, and multicenter. However, it was conducted among a highly selected group of patients; it was not blinded and allowed patients in the FU alone group who had documented progression to cross-over to the radioembolization plus FU group at the investigators' discretion. As a result, 70% of those in the FU alone group also received radioembolization, which is significant source of bias, but the authors performed an intention to treat analysis (ITT), ie.analyzed the patients in the groups they were randomized to. The overall results of the study indicate that radioembolization with yttrium 90 resin microspheres in addition to intravenous fluorouracil significantly improved the response to therapy and time to liver progression compared to FU alone among the selected patients included in the trial. Radioembolization was not associated with more toxicity than chemoembolization. The effect on survival was not statistically significant, which could be attributed to the small sample size, especially with the high cross-over that could have improved the outcomes in the FU only group.

Articles: The literature search for studies published after the last review revealed one Phase III trial that compared IV fluorouracil infusion alone or with radioembolization with SIR-Spheres for a specific indication, two retrospective comparative analyses that compared radioembolization with TheraSphere vs. transcathether chemoembolization, and a number of retrospective and prospective single center case series with different population sizes. The largest case series and the larger comparative analyses were published by the same group of authors (Salem et al. 2010, 2011) and had a potential population overlap. The comparative analysis, as well as the Phase III trial, were selected for critical appraisal. Salem R, Lewandowski RJ, Kulik L, et al. Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma. *Gastroenterology.* 2011;140:497-507. See Evidence Table. Hendlisz A, den Eynde M V, Peeters M, et al. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. *J Clin Oncol.* 2010;28:3687-3694. See Evidence Table.

The use of Therasphere in the treatment of unresectable hepatocellular carcinoma does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

The use of SIRsphere in the treatment of unresectable hepatocellular carcinoma does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
C2616	Brachytherapy source, nonstranded, yttrium-90, per source
Q3001	Radioelements for brachytherapy, any type, each
S2095	Transcatheter occlusion or embolization for tumor destruction, percutaneous, any method, using yttrium-90 microspheres ***S codes not covered by Medicare***
37243	Vascular embolization or occlusion, inclusive of all radiological supervision and interpretation, intraprocedural roadmapping, and imaging guidance necessary to complete the intervention; for tumors, organ ischemia, or infarction
75894	Transcatheter therapy, embolization, any method, radiological supervision and interpretation
With diagnosis codes	
C22.0	Liver cell carcinoma
C22.1	Intrahepatic bile duct carcinoma
C22.3	Angiosarcoma of liver
C22.4	Other sarcomas of liver
C22.7	Other specified carcinomas of liver
C22.8	Malignant neoplasm of liver, primary, unspecified as to type
C22.9	Malignant neoplasm of liver, not specified as primary or secondary

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check.**

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Date Created	Date Reviewed	Date Last Revised
04/10/2002	07/16/2010 MDCRPC, 05/03/2011 MDCRPC, 03/06/2012 MDCRPC, 04/03/2012 MDCRPC, 02/05/2013 MDCRPC ,12/03/2013 MPC, 10/07/2014MPC, 08/04/2015MPC, 06/07/2016MPC, 04/04/2017MPC, 02/06/2018MPC, 01/08/2019MPC, 01/07/2020MPC, 01/05/2021MPC, 01/04/2022MPC, 01/10/2023MPC	02/16/2022

MDCRPC Medical Director Clinical Review and Policy Committee

MPC Medical Policy Committee

Revision History	Description
02/28/2018	Added Noridian coverage article
02/16/2022	Updated applicable codes

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Clinical Review Criteria
Tinnitus Masking/Retraining Therapy

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article	None
Kaiser Permanente Medical Policy	Due to the absence of an active NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Clinical Review Criteria, ***"Tinnitus Masking/Retraining Therapy"*** for medical necessity determinations. Use the Non-Medicare criteria below.

*Codes for auditory assessment and rehabilitation are covered by Medicare.

For Non-Medicare Members

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies or provides better long-term outcomes than current standard services/therapies.

If requesting review for this service, please send the following documentation:

- Last 6 months of clinical notes from requesting provider &/or specialist

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Tinnitus is the perception of sound in the absence of an acoustic source (Luxon 1993). The perceived sound can vary from simple sounds such as whistling or humming to complex sounds such as music. Tinnitus may be perceived as a single sound or multiple sounds, unilateral or bilateral, within the head or outside the body, and intermittently or constantly. The American Tinnitus Association estimates that 50 million Americans have some degree of tinnitus with about 16 million of those experiencing significant enough symptoms to seek medical care and 2 million of them suffering so much that it ultimately interrupts normal day to day function. Tinnitus can occur at any age but its incidence increases by the age of 40 and peaks between 65 to 79 years (Hobson, Chisholm et al. 2012). The tinnitus experience is consistently higher among men and is strongly related to hearing loss but may be experienced by individuals with normal hearing as well. Acute tinnitus, which can last for days or weeks, may be caused by ear infection, medication, ear wax, exposure to excessive sound or changes in blood pressure. Chronic tinnitus, experienced by 10 to 15% of adults, persists for six or more months and may be caused by almost any disorder involving the outer, middle or inner ear, or the auditory nerve (Davis, Paki et al. 2007). In any

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case, tinnitus can be debilitating because it is difficult to describe, predict and manage and can lead to disruption of sleep, inability to concentrate, and depression.

Tinnitus is not a condition itself, rather, it is a symptom of an underlying condition and, therefore, management should include diagnosis and elimination of the factors precipitating tinnitus. In many cases, the cause of tinnitus cannot be identified warranting treatment of the symptom itself. At present, no universal treatment has been found effective in all patients and options are heavily dependent on the severity and perception of the condition. Treatment might range from counseling and dietary modification to acupuncture and relaxation therapy. Optimal management techniques seek to minimize the detrimental effects on activities of daily life and might include a variety of strategies. The use of medications and surgical interventions are rarely successful.

Tinnitus masking instruments have been clinically employed for alleviating symptoms for decades. These devices are worn behind or in either the same or the opposite ear affected by tinnitus and generate a noise based on the principle of distraction. The idea being that the level of noise, usually white noise, is introduced and can reduce the contrast between the tinnitus signal and background activity in the auditory system, with a decrease in the patient's perception of their tinnitus (Vernon 1977). The characteristics and circumstances of the tinnitus determine the kind of masking noise and instruments that might bring relief. No side effects or significant morbidities have been reported, to date, from the use of maskers or hearing aids as treatment for tinnitus and no substantial risks of sound therapy have been demonstrated.

Tinnitus instruments such as maskers and hearing aids are approved by the Food and Drug Administration (2009) for alleviating the symptoms associated with tinnitus and are classified as a Class III device.

Medical Technology Assessment Committee (MTAC)

Tinnitus Masking Devices

02/10/1999: MTAC Review

Evidence Conclusion: *Masking*: One small randomized controlled crossover study reports no decrease in self report of tinnitus intensity but statistically significant improvement in both specific and nonspecific effects of masking on tinnitus. Another study of patients randomized to masking or hearing aid devices and then allowed to choose which device to continue using demonstrated that 60% chose to continue using a masking device and 20% discontinued the use of any device. *Retraining Therapy*: A single small RCT demonstrated a statistically significant reduction (1-point improvement on a 10-point visual analogue scale) in subjective tinnitus loudness and discomfort following behavioral training as compared to a no treatment control group.
Articles: Erlandsson, S, et. Al. Treatment of Tinnitus: A Controlled Comparison of Masking and Placebo, British *J Audiol*. 1987, 21, 37-44. See Evidence Table Mehlum, D et. Al. Prospective Crossover Evaluation of Four Methods of Clinical Management of Tinnitus, *Otolaringol. Head Neck Surg*. 1984: 92: 448-453 See Evidence Table Scott, B. Et. Al. Psychological Treatment of Tinnitus: An Experimental Group Study. Scand. Audiol. 1985, 14: 223-230 See Evidence Table

The use of Tinnitus Masking Devices for treatment of tinnitus does not meet *Kaiser Permanente Medical Technology Assessment Criteria.*

Tinnitus Masking Devices

6/17/2013: MTAC REVIEW

Evidence Conclusion: Henry et al 2006 study recruited 800 US military veterans via advertisements. Following screening, 172 candidates were enrolled into the study; those not eligible were not convinced that their tinnitus was sufficiently severe, or they were not motivated to comply with the study requirements. A further 49 subjects were excluded in secondary screening resulting in a total of one hundred and twenty-three patients commencing treatment. Candidates were quasi-randomly assigned to a tinnitus masking (TM) device or tinnitus retraining therapy group (TRT). The mean age in the sound therapy group was 61 (SD 9.6) and in the tinnitus retraining group it was 58.7 (SD 10.5). Baseline audiometry was performed and the Tinnitus Handicap Inventory (THI), Tinnitus Handicap Questionnaire (THQ) and Tinnitus Severity Index (TSI) were administered. Both groups used a combination of noise generators, hearing aids and combination instruments. Audiometry and questionnaires were evaluated at 3, 6, 12 and 18 months. The results show that for patients with 'moderate' problems, sound therapy resulted in a statistically significant improvement in the THQ at six months but tinnitus retraining therapy (TRT) appeared to offer superior results. For patients who described their tinnitus as a 'big' problem, there was an across the board significant improvement in the three instruments at all time points except three months, which is comparable to the TRT group. Looking at the effect sizes, for sound therapy these ranged from 0.18 to 0.59 in

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the 'moderate group and did not show a systematic improvement over time. For those with a 'big' problem, the effect sizes for sound therapy ranged from 0.46 to 0.86 and whereas the THI and TSI improved over time the THQ effect size remained unchanged. For those with a 'very big' problem the effect of sound therapy seemed greater at three months, with a trend of effect sizes becoming progressively smaller through 18 months. Based on effect size, both groups showed considerable improvement overall but whereas the benefits of sound therapy tended to remain constant over time, the effect of tinnitus retraining improved incrementally. Currently, the literature on maskers and/or hearing aids for the treatment of tinnitus in adults is limited. First and foremost, the lack of an established universal tool for baseline and follow-up assessment of outcome measures restricts the ability to produce valid data and make comparisons. Additionally, due to the often "off label" use of hearing aids as tinnitus treatments there has been a dearth of driving forces for undertaking large randomized controlled trials. Henry and colleague's study demonstrate some of these limitations; although the study claims to be controlled, the two groups being investigated do not make an attempt to treat both groups similarly. Different instruments are used across the study, and even within each group, and patient contact time differs by 1.4 hours between the TM and TRT groups. In addition to these limitations, the study was quasi-randomized which allows for a greater risk of selection bias. The study also notes that the devices were more apt to break in the TRT group compared to the TM group and variation in treatment specialists for each method might result in clinician differences. While some of the studies included in the Cochrane Review report that patients experienced a decrease in tinnitus with use of masking devices there is no conclusive evidence to validate the effectiveness. On the whole, the studies included in the review demonstrate either no or limited improvement in tinnitus perception. Furthermore, the quality of the studies is, generally, low. With several different devices employed throughout the studies and marked methodological heterogeneity including numerous measures of evaluation of tinnitus severity and outcome all with different scores, scales, tests and questionnaires, comparisons and further analysis are complicated. Small sample sizes also contribute to the low quality leading to the inability to generalize findings.
Conclusions: Although some patients report a decrease in tinnitus with the use of masking devices, there is no conclusive evidence from randomized trials to demonstrate effectiveness. The limited data from the included studies show that sound therapy on its own is of unproven benefit in the treatment of tinnitus, although the effect may be better than placebo. Thus far, no adverse outcomes or significant morbidity from using sound-generating (masking) devices have been reported, and furthermore, the literature is unable to demonstrate any substantial risks.
Articles: Henry JA, Schechter MA, Zaugg TL, Griest S, Jastreboff PJ, Vernon JA, Kaelin C, Meikle MB, Lyons KS, Stewart BJ. Clinical trial to compare tinnitus masking and tinnitus retraining therapy. *Acta Oto-Laryngologica*, 2006;126:64-69. See Evidence Table

The use of Tinnitus Masking Devices for treatment of tinnitus does not meet *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Considered Not Medically Necessary:

CPT® Codes	Description
92626	Evaluation of auditory function for surgically implanted device(s) candidacy or postoperative status of a surgically implanted device(s); first hour
92627	Evaluation of auditory function for surgically implanted device(s) candidacy or postoperative status of a surgically implanted device(s); each additional 15 minutes (List separately in addition to code for primary procedure)
92630	Auditory rehabilitation; prelingual hearing loss
92633	Auditory rehabilitation; postlingual hearing loss
ICD-10 Codes	**Description**
H93.11-H93.19	Tinnitus-right ear, left ear, bilateral and unspecified

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
12/1998	04/04/2011 MDCRPC, 02/07/2012 MDCRPC, 12/04/2012 MDCRPC, 08/06/2013MPC, 06/03/2014MPC, 04/07/2015MPC, 02/02/2016MPC, 12/06/2016MPC, 10/03/2017MPC, 09/04/2018MPC, 09/03/2019MPC, 09/01/2020MPC, 09/07/2021MPC, 09/06/2022MPC , 09/05/2023MPC , 01/09/2024MPC	09/01/2020

MDCRPC Medical Director Clinical Review and Policy Committee
MPC Medical Policy Committee

Revision History	Description
09/01/2020	Added KPWA Medical Policy statement under Medicare section

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Clinical Review Criteria
Total Knee Arthroplasty
- Inpatient Knee Arthroplasty &
- Knee Arthroplasty Medical Necessity Criteria

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	Total Knee Arthroplasty (L36577) *–Not subject to medical necessity review, refer to Inpatient versus Ambulatory/Outpatient Level of Care requests* Total Knee Arthroplasty (TKA) Removal from the Medicare Inpatient-Only (IPO) List and Application of the 2-Midnight Rule
Local Coverage Article (LCA)	None
MLN Matters Article	Total Knee Arthroplasty (TKA) Removal from the Medicare Inpatient-Only (IPO) List and Application of the 2-Midnight Rule
Inpatient versus Ambulatory/Outpatient Level of Care requests	***Inpatient* Total Knee Arthroplasty** For elective total knee replacement (27438, 27446, 27447) to be approved as inpatient, **ONE of the following** criteria must be met: 1. Bilateral knee replacement 2. Coexisting neurologic condition (such as multiple sclerosis, hemiparesis, severe Parkinson's, or other neurologic conditions that would likely seriously affect ambulation) where the expected length of stay is planned to be longer than 2 midnights. ***Ambulatory* Total Knee Arthroplasty** can be approved without medical necessity review ****Effective 01/01/2022*—The following knee revision codes-27486, 27487, 27488 are listed in the Medicare inpatient only (IPO) list and should not be reviewed for ambulatory or outpatient status.**

For Non-Medicare

I. *Level of Care*

***Inpatient* Total Knee Arthroplasty (for ambulatory/outpatient requests, proceed to II.)**

A. For elective total knee replacement (27438, 27446, 27447) or revision/replacement of a knee arthroplasty (27486, 27487, or 27488) to be approved as inpatient, **ONE of the following** criteria must be met:
   1. Bilateral knee replacement

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2. Coexisting neurologic condition (such as multiple sclerosis, hemiparesis, severe Parkinson's, or other neurologic conditions that would likely seriously affect ambulation) where the expected length of stay is planned to be longer than 2 midnights.

If the patient qualifies for inpatient status, must also meet the following:

II. Non-Medicare only request for ALL Total Knee Arthroplasty (includes ambulatory & inpatient) must meet the Medical Necessity Criteria:

A. Total knee and unicompartmental (partial) arthroplasty may be considered medically necessary for degenerative joint disease when **ALL of the following** are met:

1. Treatment is needed because of functional disabling pain of at least 3 months duration which interferes with the ability to carry out activities of daily living

AND

2. Radiographic imaging or arthroscopic evidence of moderate or severe osteoarthritis as evidenced by **ONE of the following**:
   a. Moderate multiple osteophytes, definite narrowing of joint space, some sclerosis and possible deformity of bone contour (Kellgren-Lawrence Grade 3)
   b. Large osteophytes, marked narrowing of joint space, severe sclerosis, and definite deformity of bone contour (Kellgren-Lawrence Grade 4)
   c. Exposed subchondral bone (full thickness cartilage loss with underlying bone reactive changes) noted on arthroscopy or MRI (Outerbridge Grade IV)

AND

3. Patients must have three months of non-operative, conservative treatment as demonstrated by a trial of one or more of the following medications:
   a. Non-steroidal anti-inflammatory drugs (oral or topical)
   b. Acetaminophen
   c. Intra-articular injection of corticosteroids as appropriate

AND

4. A trial of Physical Therapy* in the last 12 months, which should include some of the following features:
   a. Supervised Physical therapy, attendance at >75% of sessions
   b. Flexibility and muscle strengthening exercises
   c. Reasonable restriction of activities

**If Physical Therapy is not appropriate, the medical record must clearly document why such an approach is not reasonable.*

AND

5. All patients who meet the above criteria to undergo standard elective surgery must also meet **ALL of the following**:
   a. BMI < 35: if BMI is > 35, optimization efforts must be documented, demonstrating active attempts towards weight loss as shown by sustained weight loss over 3-6 months OR stagnant weights despite documented active participation in a weight loss or exercise program. Formal nutritional counseling must be documented. If optimization attempts are unsuccessful, the surgeon and patient may proceed if there is documentation of understanding of the risks through shared decision making. However, BMI > 40 is a relative contraindication. Despite not achieving this BMI, if the provider has documented adequate efforts to improve these parameters, the case will be reviewed on a case-by-case basis by a medical director.
   b. No diabetes, or diabetes with HbA1c < 7.5 (with the presence of heart disease, no lower than 7.5). Members who have an A1C >7.5 must actively be involved with medical management and demonstrate a reduction in A1c over 3-6 months. If optimization attempts are unsuccessful, the surgeon and patient may proceed if there is documentation of understanding of the risks through shared decision making. A1c > 8.0 is a relative contraindication. Despite not achieving this A1c, if the provider has documented adequate efforts to improve these parameters, the case will be reviewed on a case-by-case basis by a medical director.
   c. Members who use nicotine/tobacco must be actively involved in a nicotine cessation program and must be nicotine/tobacco-free for a minimum of 30 days prior to surgery or have a 90% reduction in nicotine/tobacco use. If nicotine/tobacco reduction attempts are unsuccessful, the surgeon and patient may proceed if there is documentation of understanding of the risks through shared decision making. No changes in nicotine/tobacco use is a relative contraindication.

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B. Knee arthroplasty may **ALSO be considered medically necessary**, after failure of nonoperative interventions, for the following diagnoses:
   - Distal femur fracture repair in a patient with osteoporosis
   - Failure of a previous proximal tibial or distal femoral osteotomy
   - Hemophilic arthroplasty
   - Limb salvage for malignancy
   - Posttraumatic knee joint destruction
   - Avascular necrosis (osteonecrosis) of tibial or femoral condyle
   - Inflammatory Arthritis

***Kellgren-Lawrence Classification of Osteoarthritis**

Grade	Description
grade 0 (none)	definite absence of x-ray changes of osteoarthritis
grade 1 (doubtful)	doubtful joint space narrowing and possible osteophytic lipping
grade 2 (minimal)	definite osteophytes and possible joint space narrowing
grade 3 (moderate)	moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends
grade 4 (severe)	large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends

Osteoarthritis is deemed present at grade 2 although of minimal severity.
Reference: Pai, V., Knipe, H. Kellgren and Lawrence system for classification of osteoarthritis. Reference article, Radiopaedia.org. (accessed on 29 Mar 2022) https://doi.org/10.53347/rID-27111

Outerbridge
Outerbridge 0: Cartilage is normal
Outerbridge 1: Cartilage shows chondromalacia,
Outerbridge 2: Cartilage shows partial thickness fibrillation
Outerbridge 3: Cartilage shows deep fibrillation
Outerbridge 4: Full thickness cartilage loss

If requesting these services, please send the following documentation to support medical necessity:
- Last 6 months of clinical notes from requesting provider &/or specialist, including a history & physical
- If the orthopedist has a patient who does not meet one of the criteria above but has determined that the procedure should be performed in an inpatient setting, the orthopedist can submit a separate explanation with the request that will be reviewed by clinical staff on a case-by-case basis.
- If a patient is approved for ambulatory status under the prior authorization request but ends up staying longer than expected, the inpatient claim could be adjusted to inpatient if deemed appropriate.

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Background

Joint replacement surgery has been performed on millions of people over the past several decades and has proved to be an important medical advancement in the field of orthopedic surgery. The hip and knee are the two most commonly replaced joints. The knee is the largest joint in the body and includes the lower end of the femur, the upper end of the tibia and the patella. The knee joint has three compartments, the medial, the lateral and the patellofemoral. The surfaces of these compartments are covered with articular cartilage and are bathed in synovial fluid. The bones of the knee joint work together, allowing the knee to function smoothly.

The most common reason for total knee replacement surgery is arthritis of the knee joint. Types of arthritis include:

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• osteoarthritis,
• rheumatoid arthritis and
• traumatic arthritis (arthritis which occurs as a result of injury).

Arthritis causes a severe limitation in the activities of daily living (ADLs), including difficulty with walking, squatting, and climbing stairs. Pain is typically most severe with activity and patients often have difficulty getting mobilized when seated for a long time. Other findings include chronic knee inflammation or swelling not relieved by rest, knee stiffness, lack of pain relief after taking non-steroidal anti-inflammatory medications and failure to achieve symptom improvement with other conservative therapies such as steroid injections and physical therapy.

Osteonecrosis and malignancy are additional reasons to proceed with total knee replacement surgery. The use of TKR in patients with malignancy must be weighed against considerations of life expectancy and possible alternative procedures to relieve pain. The goal of total knee replacement surgery is to relieve pain and improve or increase patient function.

Occasionally, there may be a need to perform a reoperation on a previous total knee replacement. This is often referred to as a revision total knee.

Circumstances that lead to the need for a revision Total Knee Arthroplasty continued disabling pain, continued decline in function which can be attributed to failure of the primary joint replacement. Failure can be due to infection involving the joint, substantial bone loss in the structures supporting the prosthesis, fracture, aseptic loosening of the components and wear of the prosthetic components.

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:
Total Knee:

CPT® or HCPC Codes	Description
27438	Arthroplasty, patella; with prosthesis
27446	Arthroplasty, knee, condyle and plateau; medial OR lateral compartment
27447	Arthroplasty, knee, condyle and plateau; medial AND lateral compartments with or without patella resurfacing (total knee arthroplasty)
27486	Revision of total knee arthroplasty, with or without allograft; 1 component
27487	Revision of total knee arthroplasty, with or without allograft; femoral and entire tibial component
27488	Removal of prosthesis, including total knee prosthesis, methylmethacrylate with or without insertion of spacer, knee

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
05/03/2022	05/03/2022[MPC], 05/02/2023[MPC]	05/15/2023

[MPC] Medical Policy Committee

Revision History	Description
05/03/2022	MPC approved to adopt criteria for Inpatient-Total Knee for non-Medicare members. Requires 60-day notice, effective date 10/01/2022.
06/21/2022	Added clarification around Medicare inpatient only list

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09/15/2022	Updated criteria effective date to 10/25/2022.
10/13/2022	Added preexisting inpatient criteria for total knee.
10/18/2022	Moved Medicare IPO applicable codes up under Medicare Criteria for more clarity
02/06/2023	Add clarification on when Medicare IPO list of codes was updated 1/1/2022.
03/24/2023	Clarified Level of Care requirement for Medicare and Non-Medicare members.
05/15/2023	Clarified PT episode of care timeframe

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KAISER PERMANENTE®

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Clinical Review Criteria

Transcatheter Aortic or Pulmonary Valve Replacement (TAVR/TPVI)

- Valve-in Valve Transcatheter Aortic Valve Implantation (VI-TAVI) in Failed Bioprosthetic Aortic Valves Transcatheter Valve-in Valve Implantation (TAVIV)
- Transcatheter Aortic Valve in Surgical Aortic Valve (TAV-in-SAV)
- Transcatheter Pulmonary Valve Implantation (TPVI)

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Transcatheter Aortic Valve Replacement (TAVR) (20.32)
Local Coverage Determinations (LCD)	None
Local Coverage Article	None
Kaiser Permanente Medical Policy	Due to the absence of an active NCD, LCD, or other coverage guidance for transcatheter valve-in-valve replacement or transcatheter pulmonary valve implantation, Kaiser Permanente has chosen to use their own Clinical Review Criteria, ***Valve-in-Valve Transcatheter Aortic Valve Implantation*** *and* ***Transcatheter Pulmonary Valve Implantation (TPVI)*** for medical necessity determinations. Refer to the Non-Medicare criteria below.

For Non-Medicare Members

I. Transcatheter Aortic Valve Replacement (TAVR)

A. Transcatheter aortic valve replacement is medically necessary when **ALL of the following** are true:

1. Use of an FDA approved device
2. Documentation of severe, symptomatic aortic valve stenosis
3. The patient (preoperatively and postoperatively) is under the care of a heart team: a cohesive, multi-disciplinary, team of medical professionals. The heart team concept embodies collaboration and dedication across medical specialties to offer optimal patient-centered care. The heart team includes the following:
   a. Cardiac surgeon and an interventional cardiologist experienced in the care and treatment of aortic stenosis who have:
      I. independently examined the patient face-to-face, evaluated the patient's suitability for surgical aortic valve replacement (SAVR), TAVR or medical or palliative therapy;
      II. documented and made available to the other heart team members the rationale for their clinical judgment.
   b. Providers from other physician groups as well as advanced patient practitioners, nurses, research personnel and administrators.

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4. The heart team's interventional cardiologist(s) and cardiac surgeon(s) must jointly participate in the intra-operative technical aspects of TAVR.
5. TAVR must be furnished in a hospital with the appropriate infrastructure that includes but is not limited to:
   a. On-site heart valve surgery and interventional cardiology programs,
   b. Post-procedure intensive care facility with personnel experienced in managing patients who have undergone open-heart valve procedures,
   c. Appropriate volume requirements per the applicable qualifications below:

There are two sets of qualifications; the first set outlined below is for hospital programs and heart teams without previous TAVR experience and the second set is for those with TAVR experience.

Qualifications to begin a TAVR program for hospitals without TAVR experience:

The hospital program must have the following:

a. ≥ 50 open heart surgeries in the previous year prior to TAVR program initiation, and;
b. ≥ 20 aortic valve related procedures in the 2 years prior to TAVR program initiation, and;
c. ≥ 2 physicians with cardiac surgery privileges, and;
d. ≥ 1 physician with interventional cardiology privileges, and;
e. ≥ 300 percutaneous coronary interventions (PCIs) per year.

Qualifications to begin a TAVR program for heart teams without TAVR experience:

The heart team must include:

a. Cardiovascular surgeon with:
   i. ≥ 100 career open heart surgeries of which ≥ 25 are aortic valve related; and,
b. Interventional cardiologist with:
   i. Professional experience of ≥ 100 career structural heart disease procedures; or, ≥ 30 left-sided structural procedures per year; and,
   ii. Device-specific training as required by the manufacturer

Qualifications for hospital programs with TAVR experience:

The hospital program must maintain the following:

a. ≥ 50 AVRs (TAVR or SAVR) per year including ≥ 20 TAVR procedures in the prior year ; or,
b. ≥ 100 AVRs (TAVR or SAVR) every 2 years, including ≥ 40 TAVR procedures in the prior 2 years; and,
c. ≥ 2 physicians with cardiac surgery privileges; and,
d. ≥ 1 physician with interventional cardiology privileges, and
e. ≥300 percutaneous coronary interventions (PCIs) per year; and,

Participation in the STS/ACC TVT Registry is required.

All other indications are not covered as there is insufficient evidence to support effectiveness.

II. Valve-in-Valve Transcatheter Aortic Valve Implantation

A. Valve in Valve TAVR is medically necessary when **ALL of the following** are meet:
   1. Use of an FDA approved device
   2. The patient (preoperatively and postoperatively) is under the care of a heart team: a cohesive, multi-disciplinary, team of medical professionals.
   3. Documentation of a failed aortic tissue prosthesis resulting in symptomatic stenosis or regurgitation.

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III. Transcatheter Pulmonary Valve Implantation (TPVI)

A. Transcatheter pulmonary valve implantation is considered medically necessary for patients with congenital heart disease and current right ventricular outflow tract obstruction (RVOT) or regurgitation including the following indications:
- Individuals with right ventricle-to-pulmonary artery conduit with or without bioprosthetic valve with at least moderate pulmonic regurgitation **OR**
- Individuals with native or patched RVOT with at least moderate pulmonic regurgitation **OR**
- Individuals with right ventricle-to-pulmonary artery conduit with or without bioprosthetic valve with pulmonic stenosis (mean RVOT gradient at least 35 mm Hg) **OR**
- Individuals with native or patched RVOT with pulmonic stenosis (mean RVOT gradient at least 35 mm Hg)

All other indications are not covered as there is insufficient evidence to support effectiveness.

If requesting these services, please send the following documentation to support medical necessity:
- Last 6 months of clinical notes from requesting provider &/or specialist

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Background

Aortic stenosis (AS) is one of the most frequent degenerative valve diseases in developed countries with a prevalence of approximately 5% in individuals over the age of 75 years. The absolute numbers continue to increase with the increase in life expectancy. Aortic stenosis has a long latency period followed by a rapid progression after the appearance of symptoms. It is estimated that up to 2.9% of adults between the ages of 75 and 86 years have severe aortic stenosis, and that the two-year mortality among adults with severe symptoms is as high as 50% (Leon 2010, Rajani 2011, Amonn 2012).

Currently, surgical aortic valve replacement (SAVR) is the treatment of choice in patients with symptomatic severe aortic stenosis in the absence of severe co-morbid conditions. It is the only treatment that has been shown to reduce symptoms and improve functional status and survival in patients with severe aortic stenosis. The conventional surgical aortic valve replacement is performed via sternotomy using cardiopulmonary bypass. The procedure is associated with low operative mortality; however, at least 30% of the patients with severe symptomatic aortic valve stenosis are not suitable candidates for open SAVR due to advanced age, left ventricular dysfunction, concomitant coronary artery disease, and/or other pre-existing conditions. Historically these high surgical risk patients were treated with palliative medical therapy or aortic valve balloon valvuloplasty (BAV) (Leon 2010, Rajani 2011, Amonn 2012, Staubach 2012).

Transcatheter aortic valve replacement (TAVR) has emerged as an alternative minimally invasive treatment option for elderly patients with aortic stenosis who are at high surgical risk. The first transcatheter aortic valve implantation in humans was performed by Alain Cribier in France ten years ago and has developed rapidly and tremendously since then. Over 50,000 patients in 500 European centers have undergone the procedure after two prosthetic valves (Edwards SAPIEN and Medtronic CoreValve) was approved by the Conformité Européenne (CE) in 2007. TAVR involves the insertion of a bioprosthetic aortic valve through a catheter and implanting it within the diseased native aortic valve. Patients are treated off-pump i.e. on a beating heart, and the new prosthesis is implanted within the calcified native valve leaflets that remain in place while being squeezed aside. In most patients the prosthetic valve is inserted through the groin and advanced to the heart using X-ray guidance (retrograde approach). In patients who cannot undergo catheterization of the femoral artery due to vessel disease, the valve can be delivered from the left ventricular apex (antegrade approach) through a small chest incision between the ribs (Amonn 2012, Walther 2012).

Currently, TAVR is indicated for the management of high-risk patients with severe aortic stenosis who are not candidates for open surgical valve replacement. However, some patients are at too high risk even for TAVR, and patient selection plays a crucial role in the success of the procedure. Patients have to be evaluated thoroughly for their risk and anatomical suitability for the procedure. A heart team comprised of clinical cardiologists, cardiac

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surgeons, interventionists, anesthesiologists, geriatricians, and imaging specialists, is essential for the patient selection and performance of the procedure. The collaboration of such a multidisciplinary team is reported to be a key to the success of the procedure and achievement of optimal clinical outcomes (Piazza 2012, Vahanian 2012).

TAVR is not without complications; the increased risk of stroke is a significant safety concern of the procedure. Other major vascular complications, valve embolization, complete heart block, and moderate to severe paravalvular aortic regurgitation have also been reported. In addition, once the transcatheter aortic valve is implanted, it cannot be removed, and may lead to performing other risky procedures. Researchers are investigating different approaches to reduce the occurrence of these TAVR-related complications e.g. through better screening of the candidates for the intervention; refinement of the implantable devices and their delivery systems; improving the techniques in valve sizing and positioning; use of embolic protection devices as cerebral filters, carotid filters, or membrane covering of the carotid ostia; modification of periprocedure and postoperative antiplatelet strategies; use of antiarrhythmic treatment, and others (Vahanian 2012, Cribier 2012).

Over the years, different prostheses have become available for performing TAVR. The Edward SAPIEN (Edwards Lifesciences, Irvine, CA, USA) prosthesis consists of bovine pericardial leaflets mounted on a balloon-expandable cobalt-chromium stent. It is available in 2 sizes (23 mm and 26 mm) and can be inserted by either the retrograde or antegrade approach. The prosthesis was approved by the US Food and Drug Administration in 2011 based on data from the inoperable cohort of PARTNER study, for its use patients with severe aortic stenosis who have been determined by a cardiac surgeon to be inoperable for open aortic valve replacement, and in whom existing co-morbidities would not preclude the expected benefit from correction of the aortic stenosis (FDA website). The FDA requested two post-approval studies to assess the long-term safety and effectiveness of the TAVR, as well as adherence to the indication of SAPIEN utilization. Other devices including the COREValve ® (Medtronic, Minneapolis, MN, USA), ACURATE TATM valve, and JenaValveTM, haves received CE approval, but have not been approved by the USA FDA to date.

Medical Technology Assessment Committee (MTAC)

Transcatheter Aortic Valve Replacement (TAVR)

6/18/2012: MTAC REVIEW

Evidence Conclusion:

Conclusion: PARTNER Cohort A showed that transcatheter aortic valve replacement was non-inferior to open heart surgical aortic valve replacement for all-cause mortality at one year in patients with severe aortic stenosis at high-risk of operation. PARTNER Cohort B showed a 19% absolute mortality reduction at one year after transcatheter aortic valve replacement (number needed to treat of 5) when compared to standard medical therapy in patients with severe aortic stenosis and symptoms who are not suitable candidates for surgery. In the two cohorts TAVR was associated with a higher risk of neurological and cardiovascular events. The follow-up duration in the two cohorts of PARTNER may be insufficient to determine long-term safety and durability of the prosthesis, and whether the benefits observed with TAVR will be sustained over time.

Articles: The literature search revealed several publications on the PARTNER trial; another small trial (STACCATO trial); a meta-analysis that pooled the results of 16 heterogeneous studies; and a large number of case series, feasibility studies, and registry data. The pivotal PARTNER trial was selected for critical appraisal. The STACCATO study, a randomized controlled trial conducted on operable elderly patients with aortic stenosis, was not selected for critical appraisal due to its small size and premature termination. The meta-analysis was not reviewed further due to the heterogeneity of studies it included. The following studies were critically appraised:
Leon MB, Smith CR, Mack M, for the PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med. 2010; 363:1597-607. See Evidence Table
Smith CR, Leon MB, Mark MJ, for the PARTNER trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med .2011;364:2187-2198.
See Evidence Table

The use of TAVR does meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Valve-in Valve Transcatheter Aortic Valve Implantation (VI-TAVI) in Failed Bioprosthetic Aortic Valves [Transcatheter Valve-in Valve Implantation (TAVIV), transcatheter aortic valve in surgical aortic valve (TAV-in-SAV)]

BACKGROUND

Degenerative aortic stenosis is one of the most common and most serious acquired valvular heart diseases among adults. Surgical aortic valve replacement (SAVR) has been the standard treatment for symptomatic severe aortic stenosis for over forty years. SAVR is an open-heart procedure that involves removing the

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diseased aortic valve and replacing it with either a man-made mechanical valve or a biological valve. Mechanical valves are strong and long-lasting, but patients receiving them will need to use a blood thinning medication for the rest of their lives. In the last two decades, there has been a shift toward the use of biological (bioprosthetic) valve implants rather than mechanical valves. These are tissue valves made from human aortic valves (homografts) or more commonly from animal tissue (xenografts). The latter are made from porcine valve leaflets, bovine pericardium, or less frequently from porcine pericardium. Surgical bioprosthesis are commonly stratified into stented and stentless valves. Compared with mechanical valves, bioprosthetic valves are associated with a lower risk of thromboembolic events and do not require long-term anticoagulation. However, these tissue valves have a limited durability, and the majority deteriorates within 10-20 years leading to structural dysfunction. Valve failure may present as stenosis due to calcification, pannus or thrombosis; regurgitation secondary to wear and tear or infection; or as a combination of both stenosis and regurgitation (Seiffert 2010, Bapat 2012, Webb 2013, Dvir 2014).

Treatment of patients with failed bioprosthetic valve is a clinical challenge. Re-operation is considered the standard of care, but a repeat cardiac surgery is associated with high risk of morbidity and mortality, not only of the complexity of the procedure, but also because of the comorbidities and advanced age of the patients who usually need it. The operative mortality for elective redo valve surgery is reported to range from 2-7% and may increase to more than 30% among those at high-risk. Patients who are considered inoperable have no other effective treatment option; supportive medical therapy is associated with poor prognosis, and balloon valvuplasty is not recommended for stenotic bioprosthetic valves due to the high risk of tearing of the leaflets (Seiffert 2010, Bapat 2012, Dvir 2014).

Transcatheter aortic valve replacement (TAVR), also known as transcatheter aortic valve implantation (TAVI) has become an alternative less invasive treatment modality for patients with severe native aortic valve stenosis who are at high surgical risk due to advanced age, significant comorbidities, frailty, prior chest radiation and other factors. The current widespread use and success of TAVI in high-risk patients together with the major complications of redo aortic valve surgery in these patients; have led to considering the valve-in-valve TAVI (VIV-TAVI) (also referred to as TAV-in-SAV) approach as an option for patients with degenerated failed bioprosthetic heart valve. TAVI is performed with a beating heart and avoids the risks associated with using cardioplegia and cardiopulmonary bypass during redo surgery. Currently, the main transcatheter valves used for valve-in-valve procedures are the Edwards SAPIEN or SAPIEN XT (Edwards Lifesciences, Irvine, California), and the CoreValve (Medtronic, Minneapolis, Minnesota) (Eggebrecht 2011, Linke 2012, Dvir 2014).

Edwards SAPIEN XT Transcatheter Heart Valve (SAPIEN XT THV) system consists of a transcatheter aortic valve and the accessories used to implant it. The valve is made of cow tissue attached to a balloon-expandable, cobalt-chromium frame for support, and comes in three sizes: 23 mm, 26 mm, and 29 mm. The valve is compressed and placed on the end of a balloon catheter, which is then inserted through either the femoral artery or a small cut between the ribs and advanced through the blood vessels until it reaches the failed valve. The SAPIEN XT valve is then expanded with the balloon until it anchors to the failed valve (valve-in-valve). Once the new valve is in place, it opens and closes properly, allowing the blood to flow in the correct direction. According to the FDA The Edwards SAPIEN XT THV is indicated for patients with symptomatic heart disease due to either severe native calcific aortic stenosis, or more recently (in 2015) due failure of a surgical bioprosthetic aortic valve who are judged by a heart team to be at high or greater risk for open surgical therapy (i.e. Society of Thoracic Surgeons operative risk score ≥8% or at a ≥15% risk of mortality at 30 days). It is contraindicated in patients who cannot tolerate an anticoagulation/antiplatelet regimen, have a mechanical artificial aortic valve, or have active bacterial endocarditis or other active infections in the heart or elsewhere (FDA and the manufacturer's webpages).

The CoreValve system consists of a catheter-based artificial aortic heart valve and the accessories used to implant it. The valve is made of pig tissue attached to a flexible, self-expanding, nickel-titanium frame for support. The CoreValve is compressed and placed on the end of a delivery catheter, which is then inserted through the femoral artery. If the femoral arteries are not suitable, the valve can be inserted through other arteries or through the aorta. The catheter is pushed through the blood vessels until it reaches the diseased aortic valve. The valve is then released from the catheter, expands on its own and anchors to the diseased valve. The CoreValve functions the same as a normal valve, allowing the blood flow in the correct direction. The CoreValve System had been previously approved by the FDA to treat patients whose native aortic valve has become severely narrowed as a result of calcium buildup and who are considered to be at "extreme risk" or "high risk" for surgical aortic valve replacement. In March 2015 the FDA expanded the use of CoreValve system for aortic valve-in valve replacement inpatients who need replacement of a failed tissue aortic valve but are at extreme or high risk of death or serious complications from traditional open-heart surgery based on the

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judgement of a heart medical team. The CoreValve System use is contraindicated in patients with a mechanical aortic heart valve, have any infection, cannot tolerate blood thinning medicines; or have sensitivity to titanium or nickel or contrast media (FDA News Release March 30, 2015).

Reported adverse events with of VIV-TAVI include death, stroke, acute kidney injury, myocardial infarction, major bleeding, and the need for a permanent pacemaker. Other limitations associated with VIV-TAVI are the increase risk of coronary obstruction (especially in patients with stentless valves); high residual gradients which may result from under expansion of the result transcatheter heart valve in smaller surgical bioprothesis; and paravalvular leaks between the surgical and transcatheter valves. Successful outcome of the VIV procedure is thus dependent on patient selection, knowledge of prior cardiac surgery, internal diameter and material of the degenerated bioprosthetic valve as well as mode of valve failure, anticipation of complication, procedural planning, and experience of the cardiac team with TAVI (Bapat 2012, Webb 2013, Verhoye 2015, Phan 2016)

In 2015, the US Food and Drug administration (FDA) expanded the approved use of the SAPIEN XT (Edwards Lifesciences) and CoreValve System (Medtronic) to include "valve-in-valve" repair in patients who failed surgical bioprosthetic heart and are at high or extreme risk for complications associated with traditional open-heart surgery.

06/20/2016: MTAC REVIEW
Evidence Conclusion:
Conclusion:

- There is fair evidence from a number of observational studies that valve-in-valve implant in a failed aortic prosthetic valve is feasible and relatively safe.
- There is insufficient direct evidence to determine whether the outcomes of valve-in-valve implantation in a failed aortic prosthetic valve are equivalent or superior to the outcomes of a redo conventional operation to replace the valve.
- There is insufficient published evidence to determine the long-term efficacy and durability of valve-in-valve implant in a failed aortic prosthetic valve.

Articles: The literature search for studies on valve-in-valve transcatheter aortic valve replacement in high risk patients with failed bioprosthetic valves identified a number of observational studies and case series from single institutions as well as registries for patients receiving a VIV-TAVI in various countries (Canadian registry, German registry, Italian registry, Germany/Switzerland registry, and a global registry that collects data form more than 60 countries worldwide). A recent systematic review with meta-analyses (Chen 2016) pooled the results of studies reporting on clinical outcomes of transcatheter VIV in failed surgical bioprosthetic aortic and mitral valves. Two other systematic reviews (with no meta-analyses) that summarized the results of studies on VIV-TAVI published through July 2014 were also identified (Tourmousoglou, et al, 2015, and Raval et al, 2014). To date, there are no published randomized controlled trials that directly compared the VIV-TAVI to surgical reoperation in patients with failed bioprosthetic aortic valves. The search identified a recent systematic review and meta-analysis (Phan, et al, 2016) that indirectly compared VIV-TAVI versus surgical valve redo operation (i.e. TAV-in-SAV versus SAV-in-SAV), and Erlebach et al, 2015 study that compared retrospective data on postoperative outcomes for patients with failing bioprosthetic valve who received a VIV-TAVI or underwent a redo aortic surgery in a single center in the period from January 2001 through October 2014. The two United States pivotal studies that were the basis of the FDA approvals of the systems are not published to data but are available at the FDA website. The meta-analysis that pooled the results of the cohort studies on VIV-TAVI and the analysis that compared VIV-TAVI with reoperation, as well as the global VIVID registries and the two pivotal studies submitted to the FDA were selected for critical appraisal. Chen HL, Liu K. Clinical outcomes for transcatheter valve-in-valve in treating surgical bioprosthetic dysfunction: A meta-analysis. *Int J Cardiol*. 2016 Mar 18; 212:138-141. (See Evidence Table 1) Phan K, Zhao DF, Wang N, et al. Transcatheter valve-in-valve implantation versus re-operative conventional aortic valve replacement: a systematic review. *J Thorac Dis.* 2016 Jan; 8 (1): E83-93. (See Evidence Table 2) Dvir D, Webb JG, Bleiziffer S, et al. Transcatheter aortic valve implantation in failed bioprosthetic surgical valves. JAMA. 2014 Jul; 312(2):162-170. (See Evidence Table 3).

The use of Valve-in Valve Transcatheter Aortic Valve Implantation does meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

01/13/2020: MTAC REVIEW
Evidence Conclusion:

- Overall the results of the two pivotal RCTs (PARTNER 3 and Evolut Low Risk trial) that compared the outcomes of TAVR with those of SAVR in low-surgical risk patients with

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severe aortic stenosis (excluding those with a bicuspid valve) show that TAVR is non-inferior to surgical valve replacement with respect to the primary composite endpoint as defined in each trial. PARTNER 3 trial defined the primary endpoint as a composite of death from any cause, stroke, or rehospitalization at 1 year after the procedure, while Evolut Low Risk trial defined it as a composite of all-cause mortality or disabling stroke in TAVR vs. SAVR at 24 months.

- PARTNER 3 trial is the only published trial, to date, that suggests that TAVR is superior to SAVR in reducing the composite rate of death from any cause, stroke, or rehospitalization at 1-year in low-surgical risk patients with severe aortic stenosis. However, there was no significant difference between the two procedures when each of the components was considered individually.
- The published results of Evolut Low-Risk trial are for interim analysis; the 1-year and 2-year event rates were derived from estimates not true observed incidence.
- Meta-analyses pooling the results of the two pivotal trials with NOTION study and with or without SURTAVI/low risk showed conflicting results: Anantha-Narayana et al's analysis showed that all-cause mortality was significantly lower with TAVR at 30 days, but not with long-term follow-up, Al-Abdouh et al, also found no statistically significant difference between TAVR and SAVR in all-cause mortality at one year, while Kolte et al's analysis showed a significantly lower rate of all-cause mortality at one year with TAVR vs. SAVR.
- The overall 1-year results of trials in low-risk patients indicate that compared to surgery, TAVR is associated with significantly lower risk of stages II &III acute kidney injury, new onset atrial fibrillation and life threatening or disabling bleeding. However, it is associated with a statistically significant higher risk of the need for permanent pacemaker implantation, and moderate -severe paravalvular leak compared to SAVR.
- The trials had strict legibility criteria that may limit generalization of their results.
- There is no long-term follow-up data from large RCTs to determine the long-term efficacy and safety of TAVR, the performance and durability of the TAV, potential formation of subclinical leaflet thrombosis, and long-term difference between the surgical and transcatheter valves with respect to their durability and structural degeneration.
- To date the only published long-term follow-up data is provided by the 5-year results of NOTION trial that shows no difference between TAVR and SAVR in the composite primary endpoint of all-cause mortality, stroke or myocardial infarction in mostly low surgical risk patients. The trial was small, and the lack of statistically significant differences does not indicate that the two interventions are equivalent. In addition, the study used the first generation CoreValve as well as earlier SAVR techniques, which may limit generalization of the results.
- The rapid progress in technology and continuous improvements in the design of the devices as well as the surgical and implant techniques, would be a common limitation for the pivotal studies with planned 10-year follow-up, as well as any other interventional study with 5-10 years follow-up duration.

Articles: The literature search revealed the recently published trials: PARTNER 3 trial, Evolut Low Risk trial, and the 5-year follow-up of NOTION trial, as well as 3 meta-analyses of RCTs comparing TAVR vs SAVR in low-risk patients with symptomatic severe aortic stenosis. Three other meta-analyses identified by the search pooled the results of RCTs and observational studies on TAVR for patients with low-intermediate risk. The PARTNER 3 and Evolut Low Risk trials were selected for critical appraisal. The NOTION trial and the three meta-analyses of trials in low-risk patients were summarized. The meta-analyses including observational studies and /or trials on intermediate- risk patients were excluded. See Evidence Table.

The use of Transcatheter aortic valve replacement (TAVR) for low-surgical risk patients with aortic valve stenosis does meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

Transcatheter aortic valve replacement (TAVR/TAVI)

CPT®	Description

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Codes	
33361	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; percutaneous femoral artery approach
33362	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; open femoral artery approach
33363	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; open axillary artery approach
33364	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; open iliac artery approach
33365	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; transaortic approach (eg, median sternotomy, mediastinotomy)
33366	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; transapical exposure (eg, left thoracotomy)
33367	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; cardiopulmonary bypass support with percutaneous peripheral arterial and venous cannulation (eg, femoral vessels) (List separately in addition to code for primary procedure)
33368	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; cardiopulmonary bypass support with open peripheral arterial and venous cannulation (eg, femoral, iliac, axillary vessels) (List separately in addition to code for primary procedure)
33369	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; cardiopulmonary bypass support with central arterial and venous cannulation (eg, aorta, right atrium, pulmonary artery) (List separately in addition to code for primary procedure)

Transcatheter pulmonary valve implantation (TPVI)

CPT® Codes	Description
33477	Transcatheter pulmonary valve implantation, percutaneous approach, including pre-stenting of the valve delivery site, when performed

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed	Date Last Revised
07/03/2012	07/03/2012[MDCRPC], 05/07/2013[MDCRPC], 09/03/2013[MPC], 07/01/2014[MPC], 05/05/2015[MPC], 03/01/2016[MPC], 09/02/2016[MPC], 04/04/2017[MPC], 06/05/2018[MPC] ,06/04/2019 [MPC], 06/02/2020[MPC], 06/01/2021[MPC], 06/07/2022[MPC], 06/06/2023[MPC]	06/01/2021

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
05/05/2015	Changed ejection fraction from >15% to >20%
03/01/2016	Added two indications to criteria
08/02/2016	Added MTAC review for Valve-in Valve Transcatheter Aortic Valve Implantation
09/06/2016	New policy for Valve-in-Valve Implantation was adopted
04/04/2017	Added indication for TAVR to clarify risk score and the ability for 2 cardiac surgeons to override risk scoring
12/03/2019	MPC approved to adopt the updated Medicare indication requiring one cardiologist and one interventional cardiologist for commercial members, however KPWA will retain the high-risk restriction.

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02/04/2020	MPC approved to adopt clinical indications for Transcatheter Pulmonary Valve Implantation
03/03/2020	MPC approved to endorse coverage policy for TAVR for low-surgical risk patients with aortic valve stenosis. Added January 2020 MTAC review.
05/05/2020	MPC approved to adopt updates to the clinical indications for Non-Medicare. Requires 60-day notice, effective date 9/1/2020.
06/01/2021	Retitled to include TPVI.

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KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Transition of Care

- Requests by new enrollees for continuing care with Providers outside of the member's Kaiser Permanente Health Plan Network
- Continuing inpatient coverage for terminating Kaiser members while currently hospitalized

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Criteria

No Washington State RCW or WAC applies to new members joining Kaiser Permanente, in reference to transition of care.

This document applies to members who are inpatient status at the time of enrollment or at the time of disenrollment***

This document does not apply to existing KPWA members whose provider's contract has been terminated – see Continuity of Care Policy

Line of Business	Criteria
Medicare Members	The ***transition of care clinical criteria*** is intended to prevent disruption of an already initiated treatment plan. For the purpose of this policy, a treatment plan is considered already initiated when the member is receiving the service or has already been scheduled to receive that service. Similarly, a consultation is considered already initiated when it has been scheduled. When a consultation has occurred or is scheduled to occur, for the purpose of considering a particular service, that service shall not be considered initiated if it has not yet been provided or scheduled at the time that the members new Medicare Advantage policy becomes active. A. Continued coverage for new Medicare Advantage enrollees with a non-network provider may be covered of the health plan when **all of the following** criteria are met: 1. Has completed a Transition of Care request form within 90 days of enrollment in a Kaiser Permanente plan (only required for new enrollees). 2. The most recent documentation of care provided by the treating practitioner/clinic outlines the need for ongoing care related to an active** course of treatment. 3. The member is undergoing an active** course of treatment for a chronic or acute medical condition with this requested provider. In this circumstance, the member may be permitted to receive coverage until the acute phase is resolved or up to 90 days whichever is shorter. 4. Discontinuity could cause a recurrence or worsening of the condition under treatment and interfere with anticipated outcomes, based on clinical notes and KPWA Medical Director's clinical judgment. B. ***Members currently in the hospital when ***joining*** KPWA 1. See the following links for Codes of Regulations:

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	• *42 CFR § 422.318 Special rules for coverage that begins or ends during an inpatient hospital stay.* • *42 CFR § 422.320 Special rules for hospice care.* C. **Outpatient Prescription Drugs** Within 90 days of enrollment, members may fill up to a 30-day supply of medication, including nonformulary drugs and with waiver of Kaiser Permanente's step therapy and prior authorization requirements. This 30-day supply does not include excluded drugs and specialty products and does not override quantity limits that are in the place for quality or safety reasons. ***Active course of treatment: a patient is actively seeing a provider and following the prescribed or ordered course of treatment as outlined by the provider for a particular medical condition.*
Non-Medicare Members	A. Continued coverage for new enrollees with a non-network provider may be covered ***at the discretion*** of the health plan when **all of the following** criteria are met: 1. Has completed a Transition of Care request form within 30 days of enrollment in a Kaiser Permanente plan (only required for new enrollees). 2. The most recent documentation of care provided by the treating practitioner/clinic must be provided and support need for ongoing care. 3. The member is undergoing an active** course of treatment for a chronic or acute medical condition with this requested provider. In this circumstance, the member may be permitted to receive coverage until the acute phase is resolved or up to 30 days whichever is shorter. 4. Discontinuity could cause a recurrence or worsening of the condition under treatment and interfere with anticipated outcomes, based on clinical notes and KPWA Medical Director's clinical judgment. 5. The above indications (1-4) are not applicable to PPO and POS members who may continue to see former providers using their out-of-network benefit. B. ***Members currently in the hospital when ***joining*** KPWA** 1. The hospital stay prior to joining KPWA is the financial responsibility of the prior insurance or the patient. 2. KPWA will cover medically necessary hospital stays starting day of enrollment 3. At KPWA discretion, patient may be transferred to in-network hospital C. ***Members currently in the hospital when ***terminating*** KPWA Coverage** Continuation of Inpatient Services: Members who are receiving covered services past their health plan termination date will no longer be covered. Members will be responsible for all charges incurred. D. As an exception, pregnancy related services: If the member is at 32 weeks or beyond in their pregnancy at the time of their enrollment with Kaiser Permanente. In this case, the member will be permitted to receive continued coverage with her previously established obstetric provider for the remainder of her pregnancy through the postpartum period (six weeks after the delivery date). E. **Outpatient Prescription Drugs** Within 90 days of enrollment, members may fill up to a 30-day supply of medication, including nonformulary drugs and with waiver of Kaiser Permanente's step therapy and prior authorization requirements. This 30-day supply does not include excluded drugs and specialty products and does not override quantity limits that are in the place for quality or safety reasons. ***An active course of treatment is defined as a program of planned services to correct or treat a diagnosed condition for a defined number of services or treatment period*

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	until care is completed or a transfer of care with relevant clinical information required to ensure continuity can be initiated. The following situations will be directed to an in-network provider: 1. Scheduled elective procedure following enrollment to a Kaiser Permanente plan 2. Physical examination 3. Elective service and procedures 4. Second opinion evaluations 5. Home care services 6. Routine monitoring of a chronic condition **Note:** The above criteria do not include routine monitoring for a chronic condition

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Transition of Care for New Enrollees: The criteria were developed to promote consistency in identifying the clinical situations where the practitioner may continue to provide care for a Kaiser Permanente enrollee for the time required to complete the course of treatment. Kaiser Permanente will assist members in planning for continued care in selected case-specific situations where the member is changing from another health plan to a Kaiser Permanente plan.

Date Created	Date Reviewed	Date Last Revised
12/19/2001	07/6/2010[MDCRPC], 05/03/2011[MDCRPC], 03/06/2012[MDCRPC], 01/08/2013[MDCRPC], 11/05/2013[MPC], 09/02/2014[MPC], 08/04/2015[MPC], 06/07/2016[MPC], 04/04/2017[MPC], 02/06/2018[MPC], 11/06/2018[MPC], 11/05/2019[MPC], 11/03/2020[MPC], 11/02/2021[MPC], 11/01/2022[MPC], 11/07/2023[MPC]	10/03/2023

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
08/04/2015	MPC approved to merge policies to speak to continued coverage with a non-network provider. It is compliant with NCQA and Medicare regulations for transition of care.
01/11/2016	Added Medicare link
02/07/2017	MPC approved to adopt minor changes to criteria to specify **Outpatient** Mental Health Services & approval for no more than **3 visits** within 30 days.
04/04/2017	Added indication to clarify this policy only applies to HMO members receiving outpatient care
04/07/2020	Added additional language per WAC 284-170-360, regarding continuing primary care for Access PPO and POS members when a network provider is termed with no cause.
01/05/2021	MPC approved the changes related to Pregnancy services to include the member is at 32 weeks or beyond in their pregnancy at the time of their enrollment with Kaiser Permanente or at the time their provider changes network status. Requires 60-day notice, effective date 06/01/2021.
02/01/2022	MPC approved updates to the Transition of Care Policy that is specific for members who are new enrollees for continuing care with Providers outside of the member's Kaiser Permanente Health Plan Network and as well as guidance on continuing inpatient coverage for terminating Kaiser members while currently hospitalized.
11/11/2022	Updated Criteria to reflect the EOC language effective 01/01/2023.
10/01/2023	MPC approved changes to clinical criteria in efforts to comply with CMS 2024 Final Rule for Medicare and Non-Medicare; Effective January 1, 2024.

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KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Treatments of Sleep Apnea (Surgical & Non-Surgical)

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Continuous Positive Airway Pressure (CPAP) Therapy for Obstructive Sleep Apnea (OSA) (240.4)
Local Coverage Determinations (LCD)	Positive Airway Pressure (PAP) Devices for the Treatment of Obstructive Sleep Apnea (L33718) Oral Appliances for Obstructive Sleep Apnea (L33611) Surgical Treatment of Obstructive Sleep Apnea (OSA) (L34526) Hypoglossal Nerve Stimulation for the Treatment of Obstructive Sleep Apnea (L38312)
Local Coverage Article	Positive Airway Pressure (PAP) Devices for the Treatment of Obstructive Sleep Apnea - Policy Article (A52467) Oral Appliances for Obstructive Sleep Apnea (A52512) Surgical Treatment of Obstructive Sleep Apnea (OSA) (A56905) Billing and Coding: Hypoglossal Nerve Stimulation for the Treatment of Obstructive Sleep Apnea (A57949)
Kaiser Permanente Medical Policy	For services that are not covered by the above NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Clinical Review Criteria, "***Treatments of Obstructive Sleep Apnea for Mandibular Advancement Surgery***" for medical necessity determinations. Use the Non-Medicare criteria below. Due to the absence of a NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Clinical Review Criteria, "***Laser Treatments for Snoring & Sleep Apnea***", for medical necessity determinations. Use the Non-Medicare criteria below. Due to the absence of an active NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Clinical Review Criteria, "***Uvulopalatopharyngoplasty***", for medical necessity determinations. Use the Non-Medicare criteria below.

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For Non-Medicare Members

Non-Surgical Treatments	Criteria Used
Positive Airway Pressure Devices (PAP Devices)	Has one of the following indications: 1) AHI of 15 events or greater per hour 2) AHI between 5 and 15 events per hour with documented excessive daytime sleepiness, impaired cognition, mood disorders or insomnia, or documented hypertension, ischemic heart disease or history of stroke. 3) A Sleep Apnea Clinical Score (SACS) greater than 15 and meets all of the following: a) Completed a baseline Stanford Sleepiness Score b) Completed a 3-night auto titration PAP c) Reported one of the following: i) A positive response to initial auto titration* ii) A negative response to initial auto titration but has completed a polysomnography test and met either of the two initial criteria above. **If there is a positive response to initial auto titration, subsequent polysomnography is only covered if documentation in the medical records indicates the study is medically necessary.* The AHI (Apnea-Hypopnea Index) is equal to the average number of episodes of apnea and hypopnea per hour and must be based on a minimum of 2 hours of sleep recorded by polysomnography using actual recorded hours of sleep (not projected or extrapolated). Apnea is defined as a cessation of airflow for at least 10 seconds. Hypopnea is defined as an abnormal respiratory event lasting at least 10 seconds with at least a 30% reduction in thoracoabdominal movement or airflow as compared to baseline, and with at least a 4% oxygen desaturation. Respiratory disturbance index is a term previously used for the measure to determine eligibility for PAP. It used the same parameters as the AHI. The more current term is AHI. Because some coverage requests are received with an RDI, the definition is included to help reviewers.
Mandibular Advancement Devices for Treatment of Obstructive Sleep Apnea	Medical Necessity review is not required for this service.
Nasal Expiratory Positive Airway Pressure for Obstructive Sleep Apnea (Included but not limited to the following devices: Provent® Sleep Apnea Therapy, Ventus Medical Inc., Bongo) **Oral Pressure Therapy (OPT) for the treatment of Obstructive Sleep Apnea** (Including but not limited to the following devices: Winx System, iNAP)	There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

Surgical Treatments	Criteria Used
Hypoglossal Nerve Stimulation, Implantable	**Effective until June 1, 2024** Kaiser Permanente has elected to use the Hypoglossal Nerve Stimulation, Implantable (A-0973) MCG* for medical necessity determinations. This service is not covered per MCG* for medical necessity determinations. For access to the

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Surgical Treatments	Criteria Used
	MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access. **Effective June 1, 2024** **Hypoglossal Nerve Stimulation, Implantable** FDA-approved hypoglossal nerve neurostimulation is considered medically reasonable and necessary for the treatment of moderate to severe obstructive sleep apnea when all of the following criteria are met: 1. Patient is 22 years of age or older; and 2. Body mass index (BMI) is less than 32 kg/m2; and 3. A polysomnography (PSG) is performed within 24 months of first consultation for HGNS implant; and 4. Patient has predominantly obstructive events (defined as central and mixed apneas less than 25% of the total AHI); and 5. AHI is 15 to 65 events per hour; and 6. Patient has documentation that demonstrates CPAP failure (defined as AHI greater than 15 despite CPAP usage) or CPAP intolerance (defined as less than 4 hours per night, 5 nights per week or the CPAP has been returned) including shared decision making that the patient was intolerant of CPAP despite consultation with a sleep expert: and 7. Absence of complete concentric collapse at the soft palate level as seen on a drug-induced sleep endoscopy (DISE) procedure; and 8. No other anatomical findings that would compromise performance of device (e.g., tonsil size 3 or 4 per standardized tonsillar hypertrophy grading scale). **Limitations** 1. The following are considered not reasonable and necessary and therefore will be denied: 2. Hypoglossal nerve neurostimulation is considered not medically reasonable and necessary for all other indications. 3. Non-FDA-approved hypoglossal nerve neurostimulation is considered not medically reasonable and necessary for the treatment of adult obstructive sleep apnea due to insufficient evidence of being safe and effective. • Hypoglossal nerve neurostimulation is considered not medically reasonable and necessary when any of the following contraindications are present: • Patient with central and mixed apneas that make up more than one-quarter of the total AHI. • Patient with an implantable device could experience unintended interaction with the HGNS implant system. • Neuromuscular disease • Hypoglossal-nerve palsy • Severe restrictive or obstructive pulmonary disease • Moderate-to-severe pulmonary arterial hypertension • Severe valvular heart disease • New York Heart Association class III or IV heart failure • Recent myocardial infarction or severe cardiac arrhythmias (within the past 6 months) • Persistent uncontrolled hypertension despite medication use • An active, serious mental illness that reduces the ability to carry out Activities of Daily Living (ADLs) and would interfere with the patient's ability to operate the HNS and report problems to the attending provider. • Coexisting nonrespiratory sleep disorders that would confound functional sleep assessment • Patients who are, or who plan to become pregnant. • Patients who require Magnetic resonance imaging (MRI) with model

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Surgical Treatments	Criteria Used
	3024. • Patients, who require Magnetic resonance imaging (MRI) with model 3028, can undergo MRI on the head and extremities if certain conditions and precautions are met. Please refer to the Manufacturer Guidelines for this model and future models for more information. • Patients who are unable or do not have the necessary assistance to operate the sleep remote. • Patients with any condition or procedure that has compromised neurological control of the upper airway.
Uvulopalatopharyngoplasty (UPPP)	Kaiser Permanente has elected to use the MCG* Uvulopalatopharyngoplasty (KP-0245) for medical necessity determinations. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.
Drug-Induced Sleep Endoscopy (DISE) (CPT 42975)	**Effective until June 1, 2024** Not covered **Effective June 1, 2024** **If being requested for anything besides Sleep apnea or HGNS review is not required.* The Drug-Induced Sleep Endoscopy (DISE) is considered medically reasonable and necessary for the workup of Hypoglossal nerve stimulator in patient with moderate to severe obstructive sleep apnea when all of the following criteria are met: 1. Patient is 22 years of age or older; and 2. Body mass index (BMI) is less than 32 kg/m2; and 3. A polysomnography (PSG) is performed within 24 months of first consultation for HGNS implant; and 4. Patient has predominantly obstructive events (defined as central and mixed apneas less than 25% of the total AHI); and 5. AHI is 15 to 65 events per hour; and 6. Patient has documentation that demonstrates CPAP failure (defined as AHI greater than 15 despite CPAP usage) or CPAP intolerance (defined as less than 4 hours per night, 5 nights per week or the CPAP has been returned) including shared decision making that the patient was intolerant of CPAP despite consultation with a sleep expert: and 7. No other anatomical findings that would compromise performance of device (e.g., tonsil size 3 or 4 per standardized tonsillar hypertrophy grading scale).
Maxillo-mandibular Advancement Surgery for Sleep Apnea **Geniohyoid Advancement Myotomy Combined with Hyoid Re-Suspension**	Kaiser Permanente has elected to use the Maxillomandibular Osteotomy and Advancement Surgery (A-0248) MCG* for medical necessity determinations. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access. **If requesting this service, please send the following documentation to support medical necessity:** • For sleep related issues, please send initial sleep study and all follow up notes. • For congenital malformation, submit all cranial facial clinic notes (oral surgeon, ENT, Orthodontist)
Laser Treatments for Snoring and Sleep Apnea	There is insufficient evidence in the published medical literature to show that this service/therapy is as safe and/or provides better long-term outcomes than current standard services/therapies. These

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Surgical Treatments	Criteria Used
• Cautery-Assisted Palatal Stiffening Operation (CAPSO) • Laser-Assisted Uvulopalatoplasty (LAUP) • Repose Procedure • Somnoplasty	treatments are found to be effective in the treatment of snoring; however, no Kaiser Permanente or Kaiser Permanente Options, Inc. plan covers interventions for the treatment of snoring.
Pillar Implants for Obstructive Sleep Apnea and Snoring	There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

The MCG Manuals are proprietary and cannot be published and/or distributed. However, on an individual member basis, Kaiser Permanente can share a copy of the specific criteria document used to make a utilization management decision. If one of your patients is being reviewed using these criteria, you may request a copy of the criteria by calling the Kaiser Permanente Clinical Review staff at 1-800-289-1363 or access the MCG Guideline Index using the link provided above.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Sleep-disordered breathing includes a spectrum of disorders ranging from primary snoring to obstructive sleep apnea (OSA). Obstructive sleep apnea syndrome (OSAS) is defined as an apnea-hypopnea index of more than five events per hour, and often also has mental or physical effects such as excessive daytime sleepiness. Potential health consequences of OSAS are cardiovascular diseases, neuropsychiatric problems, injuries and increased mortality. Obstructive sleep apnea results from a combination of a structurally small upper airway and a loss of upper airway muscle tone.

Patients with primary snoring have an apnea-hypopnea index of fewer than five events per hour and no complaints of daytime sleepiness. Snoring is believed to be caused by loss of tissue integrity of the soft palate. Because tissues lack support, they stretch and collapse as muscles relax during sleep. This results in a narrowed airway and causes the soft palate to vibrate, causing snoring sounds. Primary snoring can be socially disruptive but is not harmful to the health of the patient.

There has been increasing recognition of a continuum of sleep disordered breathing disorders, ranging from simple snoring to obstructive sleep apnea (OSA). OSA refers to recurrent episodes of breathing cessation during sleep due to mechanical blockage of the airway. The diagnosis of OSA requires a minimum of 30 episodes of apnea, each lasting at least 10 seconds, during 6-7 hours of sleep. OSA patients are generally obese and the cardinal symptom is excessive daytime sleepiness. Upper airway resistance syndrome (UARS), a term first used in 1993, is a form of sleep-disordered breathing that is also associated with daytime sleepiness. Patients do not meet diagnostic criteria for OSA and are generally non-obese. Recent investigations suggest that UARS may have different pathophysiology than OSA, for example UARS patients may have increased airway collapsibility and craniofacial abnormalities. Common polysomnographic findings for UARS include apnea-hypopnea index (AHI) <5, minimum oxygen saturation >92%, increase in alpha rhythm and a relative increase in delta sleep (Bao & Guilleminault).

Continuous Positive Airway Pressure (CPAP) is widely used as first-line therapy for UARS, although there is a lack of high-grade evidence supporting its effectiveness. CPAP is also often used as a tool to diagnose UARS by seeing whether patients respond to a trial of CPAP treatment. Other treatment alternatives include oral appliances, septoplasty and radiofrequency reduction of enlarged nasal inferior turbinates. Classic surgical

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procedures used for OSA are considered by many clinicians to be too aggressive for treatment of UARS (Bao & Guilleminault).

Other methods of treating snoring and OSA include weight loss, nasal continuous positive airway pressure (CPAP), laser-assisted uvula palatoplasty (LAUP), uvulopalatopharyngoplasty (UPPP) and radiofrequency tissue ablation. Disadvantages of the surgical procedures are that they can be painful and are often associated with side effects. Radiofrequency ablation generally requires multiple treatment sessions.

A **CPAP** is defined as a device that provides constant air pressure to keep the airway open and allows patients to breathe unassisted. It is prescribed for patients with obstructive sleep apnea. The immediate clinical effectiveness of CPAP for patients with obstructive sleep apnea is well documented.

There are currently more than 35 different oral appliances on the market for OSA and/or snoring. The most widely used type of oral device is **mandibular advancement devices (MAD)** which act to keep the pharyngeal airspaces open by moving the mandible forward by advancing or downwardly rotating the mandible (Schoem, 2000).

Hypoglossal nerve stimulation is a new treatment for obstructive sleep apnea (OSA). It addresses the issue of tongue prolapse into the pharynx which causes airway blockage. Tongue prolapse may be due to decreased neuromuscular activity in the genioglossus muscle, the principal tongue protrusion muscle. Electrical stimulation of the hyoglossus muscle my result in activation of the genioglossus muscle, increasing tongue protrusion and opening the pharynx (Eisele, 1997).

A review article published in 1999 (Loube) mentioned that there is a multicenter clinical trial underway on the feasibility of a hypoglossal nerve stimulator (Inspire system; Medtronic), but that the trial has been slowed due to technical issues. The most recent entry on hypoglossal nerve stimulation on the Medtronic Web site was in 1997.

A **new nasal expiratory positive airway pressure device** (Provent® Sleep Apnea Therapy, Ventus Medical Inc.) has recently been approved by the FDA for the treatment of OSA. The Provent® Sleep Apnea Therapy device is a disposable, nightly-use device that consists of a one-way valve surrounded by a ring of soft foam. The device is placed just inside the nostrils and is held in place with adhesive. It works by limiting the airflow out of the nose during expiration, which increases pressure in the upper airway to keep it open for subsequent inspiration. During inspiration, the patient breaths freely through the nose and/or mouth (Kaiser 2010).

The **Pillar Palatal Implant System** (Restore Medical; St Paul, MN) is a treatment option for snoring and obstructive sleep apnea (OSA). Three implants made of braided polyester filaments are placed in the soft palate to help stiffen the soft palate and increase structural integrity. The implant system also includes a disposable delivery tool that is used for positioning and placement of the implant. Pillar implants are inserted during a single office visit under local anesthesia.

Evidence and Source Documents

CPAP
Hypoglossal Nerve Stimulation
Nasal Expiratory Positive Airway Pressure Device
Pillar implants for obstructive sleep apnea and snoring
Oral pressure therapy (OPT) for the treatment of obstructive sleep apnea
Mandibular Advancement Devices for Treatment of Obstructive Sleep Apnea
Maxillomandibular Advancement Surgery for Sleep Apnea
Laser Treatments for Snoring and Sleep Apnea
Uvulopalatopharyngoplasty (UPPP)
Laser Treatments for Snoring and Sleep Apnea

Medical Technology Assessment Committee (MTAC)

Positive Airway Pressure Device (CPAP)

BACKGROUND

The criteria set previously used by Kaiser Permanente (from 1/1/92 through 3/96) were a direct adoption of the Medicare criteria. Changes in testing equipment have made it possible to test with greater specificity in a shorter testing period. In addition, many tests are now done using a split study, which uses half the test time for actual testing, and the other to titrate the most beneficial CPAP fit to affect the apnea previously documented. Since

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most of the Kaiser Permanente coverage contracts include a benefit for coverage of CPAP devices at 50-80% level, the existing criteria were reviewed and modified to allow for shorter testing periods and use of the in-home testing. Throughout 1996 and 1997 with experience in managing sleep anomaly cases, a new patient population has been identified that would benefit from the use of CPAP: The Upper Airway Resistance Syndrome (UARS). Dr. Jim DeMaine requested in April 1998 that the criteria be expanded to allow use of CPAP in such cases. Although there is no clinical evidence of benefit for such treatment, there is significant expert opinion and practice that would support such a change in the criteria. In addition, Kaiser Permanente Northwest has decided to cover CPAP for UARS as long as the patient has durable medical equipment coverage (DME). While the Kaiser Permanente plan criteria were modified in May 1998 to allow inclusion of UARS patients, this is not true for the private Medicare patients seen by Kaiser Permanente providers. It is still important to check coverage before ordering this treatment option so that the patient understands the financial obligation represented by the treatment option selected. A CPAP is defined as a device that provides constant air pressure to keep the airway open and allows patients to breathe unassisted. It is prescribed for patients with obstructive sleep apnea. The immediate clinical effectiveness of CPAP for patients with obstructive sleep apnea is well documented. REFRENCES Fairbanks, David N.F., Fairbanks, David W.: Obstructive Sleep Apnea: Therapeutic Alternatives. American Journal of Otolaryngology. 13: 265-270, 1992. Effective treatment of Obstructive Sleep Apnea is contingent on the establishment of a correct diagnosis and the identification of pathophysiologic conditions affecting the upper airway. CPAP is a forceful stream of air delivered to the collapsible oropharyngeal airway acting as a splint to keep the airway open. Almost all OSA patients can benefit from this treatment except those with obstructed nasal airways. Short-term compliance is 90%. Long-term compliance (2-4 yr.) is 50 - 80%. Over 300 devices are patented as “anti-snore” remedies: chin strap, whip-lash type collar, psychological conditioning devices, custom made orthodontic devices, and the tongue retaining device are examples of a few. Most of these have not been proven efficacious for sleep apnea. Surgical treatments include nasal surgery (often disappointing as a solitary treatment for severe OSA), uvulopalatopharyngoplasty, UPPP (Highly effective, 80-90%, for simple snoring in young patients, but if bulky tongue, receding chin, nasal airway obstruction, or pronounced obesity exists it is less effective a single therapy), mandibular-maxillary advancement phase 1 and 2 (97% when combined with UPPP and nasal surgery), tongue surgery (limited studies but results are promising), and tracheostomies (most successful treatment but has been almost entirely replaced by CPAP). Watson, Robert K., Thompson, A. Siobhan: Treatment Outcome of Sleep Apnea. CONN Med. 56: 125-129, 1992.101 patients. Interviewed over 12-24-month period. CPAP most often treatment used with results of improved daytime alertness (84%). Patients with moderate OSA often had surgery which led to 85% improved daytime sleepiness, and patients with mild OSA were treated with sleep position change and weight loss with 64 - 66% improved daytime alertness. Kryger, Meir: Management of Obstructive Sleep Apnea. Clinics in Chest Medicine 13: 481-492, September 1992 Diagnosis with increased risk of death (chronic respiratory failure or obtundation) the patient should be hospitalized and monitored in ICU. Do Dx Sleep Study ASAP. O2 treatment may result in severe CO2 retention. If severe OSA Dx -- treat with urgent CPAP therapy. Mechanical ventilation recommended for patients with hypercapnia that are difficult to arouse or obtunded. BiPAP is used when all night treatment with CPAP is found to be ineffective. ATS Board of Directors: Indications and Standards for Use of Nasal Continuous Positive Airway Pressure (CPAP) in Sleep Apnea Syndromes. American Journal of Respiratory Critical Care Medicine 150: 1738-1745, 1994 Indications for CPAP: Effective in the treatment of patients with clinically important obstructive sleep apnea/hypopnea syndrome. Treatment is indicated when there is documented sleep-related apnea/hypopnea and evidence of clinical impairment. CPAP may be effective in the treatment of patients with clinically significant Cheyne Stokes respiration or central apnea with clinical impairment. Limited data to substantiate the later. CPAP is not routinely indicated in individuals with simple snoring that is not associated with pauses in respiration or with clinical impairment. CPAP is a safe, effective for therapy with rare contraindications. Relative contraindications include patients with bullous lung disease and recurrent sinus or ear infections. There are no absolute contraindications. Greater than 5-10 episodes of apnea or hypopnea per hour is considered beyond the board limits of normal. Strollo, Patrick J. and Rogers, Robert M.: Obstructive Sleep Apnea. The New England Journal of Medicine 334: 99-104, 1996 Affects 2-4% of middle age adults.

Positive airway pressure, delivered through mask, is the initial treatment of choice in clinically important sleep apnea. The following are conditions associated with the varieties of Sleep Apnea:

Obstructive Sleep Apnea: Cessation of airflow for greater than or equal to 10 seconds despite continued ventilatory effort. 5 or more episodes per hour Usually associated with a decrease of greater than or equal to 4% in oxyhemoglobin saturation. Obstructive sleep hypopnea: Decrease of 30-50% in airflow for greater than or equal to 10 seconds 15 or more episodes per hour of sleep May be associated with a decrease of greater than or equal to 4% in oxyhemoglobin saturation. Upper-airway resistance: No significant decrease in airflow (snoring is usual) 15 or more episodes of arousal per hour of sleep No significant decrease in oxyhemoglobin saturation Features Common to all three: Arousal associated with increasing ventilatory effort (as measured by esophageal balloon) Excessive daytime sleepiness Sleep 1996 Nov; 19(9 Suppl):S101-S110, Management of simple snoring, upper airway resistance syndrome, and moderate sleep apnea syndrome. Levy P, Pepin JL, Mayer P, Wuyam B, Veale

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These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage.
Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

D; Sleep and Respiration Unit, Grenoble University hospital, France. The spectrum of respiratory sleep disorders has been extended in the last years to include conditions that are less well defined than severe obstructive sleep apnea (OSA). Moderate OSA< snoring, and upper airway resistance syndrome (UARS) represent three clinical questions. Therefore, the therapeutic approach remains unclear. We have tried to define these entities and to review the respective indications and efficacy of pharmacological treatment, weight loss, sleep posture, oral appliances, upper airway surgery, and finally, continuous positive airway pressure (CPAP). From these data, we also aim to define strategies of treatment for moderate OSA, snoring, and UARS. However, these conditions are likely to be particularly appropriate for randomized trials comparing different modalities of treatment that may be the only way to validate these treatment strategies. Sleep1993 Aug; 16(5):403-408, Significance and treatment of non-apneic snoring. Strollo PJ Jr, Sanders MH, Wilford Hall Medical Center, Lackland Air Force Base, Texas. Snoring has been associated with an increased risk of vascular morbidity and mortality and with the complaint of excessive daytime sleepiness. Much of this risk may be attributable to concomitant sleep apnea or hypopnea. Recent work suggests that in certain individuals, snoring without apnea or hypopnea can lead to sleep disruption. This appears to be due to augmented ventilatory effort in response to an increased “internal” resistive load that results in repetitive arousals from sleep. This condition has been termed the upper airway resistance syndrome (UARS). Identification of load-related arousals in patients with the UARS may require the addition of esophageal pressure monitoring to the diagnostic polysomnogram. Nasal continuous positive airway pressure (CPAP) effectively eliminates snoring, hypopnea and apnea and, therefore, may be useful in treating this form of sleep-disordered breathing. The diagnostic criteria and indications, if any, for chronic treatment of these non-apneic snorers with nasal CPAP as well as long-term compliance remain to be determined.

Sleep Apnea: Hypoglossal Nerve Stimulation

BACKGROUND

Hypoglossal nerve stimulation is a new treatment for obstructive sleep apnea (OSA). It addresses the issue of tongue prolapse into the pharynx which causes airway blockage. Tongue prolapse may be due to decreased neuromuscular activity in the genioglossus muscle, the principal tongue protrusion muscle. Electrical stimulation of the hyoglossus muscle my result in activation of the genioglossus muscle, increasing tongue protrusion and opening the pharynx (Eisele, 1997). A review article published in 1999 (Loube) mentioned that there is a multicenter clinical trial underway on the feasibility of a hypoglossal nerve stimulator (Inspire system; Medtronic), but that the trial has been slowed due to technical issues. The most recent entry on hypoglossal nerve stimulation on the Medtronic web site was in 1997.

08/08/2001: MTAC REVIEW
Sleep Apnea: Hypoglossal Nerve Stimulation
Evidence Conclusion: There is insufficient evidence on which to base conclusions about the effect of hypoglossal nerve stimulation on health outcomes associated with obstructive sleep apnea.
Articles: The search yielded 113 articles. Most of the articles were on uvulopalatopharyngoplasty or glossectomy. There was one empirical article on hypoglossal nerve stimulation. This was a small case series which included only 5 patients with sleep apnea (also included were 15 patients that were undergoing a surgical procedure involving the neck). Because of the small number of sleep apnea patients and a dearth of clinical outcomes, this study was not reviewed.

The use of hypoglossal nerve stimulation in the treatment of sleep apnea does not meet the Kaiser Permanente *Medical Technology Assessment Criteria*.

07/08/2019: MTAC REVIEW
Hypoglossal Nerve Stimulation
Evidence Conclusion:

- Although hypoglossal nerve stimulation surgery with the implantable device Inspire improves AHI, ODI, FOSQ, ESS in patients with moderate-to-severe obstructive sleep apnea (OSA) who failed or intolerant to CPAP, the evidence is insufficient to draw conclusions on its effectiveness and safety.
- Comparative studies with higher quality are warranted.

Articles: PubMed was searched from inception through April 23, 2019 with the following search terms (Hypoglossal OR (upper AND airway)) AND (neurostimulation OR neurostimulator OR stimulation OR stimulator OR inspire)) AND ((obstructive sleep apnea OR sleep apnea) OR (sleep AND apnea)). The search was limited to English language publications and human populations. The reference lists of relevant studies were reviewed to identify additional publications. PubMed search was performed for the comparison between hypoglossal nerve stimulation and uvulopalatopharyngoplasty or mandibular advancement devices or maxillomandibular advancement surgery or preimplantation measures. See Evidence Table.

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The use of the Hypoglossal Nerve Stimulation does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Nasal Expiratory Positive Airway Pressure for Obstructive Sleep Apnea

BACKGROUND

Obstructive sleep apnea (OSA) is a relatively common disorder that is characterized by recurrent episodes of complete (apnea) or partial (hypopnea) upper airway obstruction during sleep, with recurrent arousals and sleep fragmentation. Patients with OSA often experience daytime sleepiness, fatigue, or poor concentration, and have signs of sleep disturbance such as snoring and restlessness. If untreated OSA is associated with an increased risk of hypertension, cardiovascular complications, diabetes, and motor vehicle accidents (Balk 2012). A new nasal expiratory positive airway pressure device (Provent® Sleep Apnea Therapy, Ventus Medical Inc.) has recently been approved by the FDA for the treatment of OSA. The Provent® Sleep Apnea Therapy device is a disposable, nightly-use device that consists of a one-way valve surrounded by a ring of soft foam. The device is placed just inside the nostrils and is held in place with adhesive. It works by limiting the airflow out of the nose during expiration, which increases pressure in the upper airway to keep it open for subsequent inspiration. During inspiration, the patient breaths freely through the nose and/or mouth (Kaiser 2010).

10/16/2012: MTAC REVIEW

Nasal Expiratory Positive Airway Pressure for Obstructive Sleep Apnea

Evidence Conclusion: In 2010, Kaiser reviewed the safety and efficacy of a nasal EPAP device. Based on data from two case-series, Kaiser concluded that there was insufficient evidence to determine whether the device is a medically appropriate treatment for obstructive sleep apnea (Kaiser 2010).

A recent randomized controlled trial (RCT) evaluated the safety and efficacy of a nasal EPAP device compared to a sham device in 250 subjects with newly diagnosed or previously untreated obstructive sleep apnea. Polysomnography was performed on 2 non-consecutive nights (random order: device-on, device-off) at week1 and after 3 months of treatment. Results from this study suggest that after 3 months patients using the EPAP device had significantly greater improvements in Apnea Hypoxia Index (AHI) compared to the sham group. Adherence to treatment was determined by self-report and was approximately 88% in the EPAP group and 92% in the sham group. The most common device related adverse events were nasal congestion, nasal discomfort, dry mouth, exhalation difficultly, and discomfort with the device. There was no serious device related adverse events. This study had several limitations: power was not assessed, the intent to treat analysis did not include all randomized patients, results are not generalizable to previously treated patients, and the study was funded by the manufacturer (Berry 2011).

AHI results at week 1 and month 3 (Berry 011)

	EPAP		Sham		
	Device-off	Device-on	Device-off	Device-on	P-value*
	Median (25th to 75th quartiles)				
Week 1	13.8 (5.3 to 22.6)	5.0† (1.7 to 11.6)	11.1 (4.8 to 21.8)	11.6 (4.0 to 21.0)	<0.001
Month 3	14.4 (5.5 to 21.4)	5.6† (2.1 to 12.5)	10.2 (3.4 to 19.3)	8.3 (4.2 to 20.6)	<0.001

*P-value (EPAP vs. Sham).

†P<0.001 EPAP device-on vs. EPAP device off.

Conclusion: Results from an RCT that compared the safety and efficacy of a nasal EPAP device compared to a sham device found that after 3 months of use patients using the EPAP device had significantly greater improvements in Apnea Hypoxia Index (AHI) compared to the sham group. This trial had several limitations. Additionally, the safety and efficacy of this device compared to CPAP is unknown.

Articles: The literature search revealed 6 studies (1 randomized controlled trial and 5 observational studies) that evaluated the safety and effectiveness of the EPAP device. Studies were excluded if they had severe methodological limitations, less than 25 subjects, or less than 30 days of follow-up. The following studies were selected for review: Berry RB, Kryger MH, Massie CA. A novel nasal expiratory airway pressure (EPAP) device for the treatment of obstructive sleep apnea: a randomized controlled trial. *Sleep.* 2011; 34:497-485. See Evidence Table . Kaiser Permanente. Provent Nasal Resistance Device for obstructive sleep apnea. September 2010. http://pkc.kp.org/national/cpg/intc/topics/03_07_112.html.

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The use of nasal expiratory positive airway pressure for obstructive sleep apnea does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Pillar Implants for Obstructive Sleep Apnea and Snoring

BACKGROUND

Sleep-disordered breathing includes a spectrum of disorders ranging from primary snoring to obstructive sleep apnea (OSA). Obstructive sleep apnea syndrome (OSAS) is defined as an apnea-hypopnea index of more than five events per hour, and often also has mental or physical effects such as excessive daytime sleepiness. Potential health consequences of OSAS are cardiovascular diseases, neuropsychiatric problems, injuries and increased mortality. Obstructive sleep apnea results from a combination of a structurally small upper airway and a loss of upper airway muscle tone. Patients with primary snoring have an apnea-hypopnea index of fewer than five events per hour and no complaints of daytime sleepiness. Snoring is believed to be caused by loss of tissue integrity of the soft palate. Because tissues lack support, they stretch and collapse as muscles relax during sleep. This results in a narrowed airway and causes the soft palate to vibrate, causing snoring sounds. Primary snoring can be socially disruptive but is not harmful to the health of the patient. The Pillar Palatal Implant System (Restore Medical; St Paul, MN) is a treatment option for snoring and obstructive sleep apnea (OSA). Three implants made of braided polyester filaments are placed in the soft palate to help stiffen the soft palate and increase structural integrity. The implant system also includes a disposable delivery tool that is used for positioning and placement of the implant. Pillar implants are inserted during a single office visit under local anesthesia. Other methods of treating snoring and OSA include weight loss, nasal continuous positive airway pressure (CPAP), laser-assisted uvula palatoplasty (LAUP), uvulopalatopharyngoplasty (UPPP) and radiofrequency tissue ablation. Disadvantages of the surgical procedures are that they can be painful and are often associated with side effects. Radiofrequency ablation generally requires multiple treatment sessions. The Restore Medical Web site claims that pillar implants are cleared by the FDA for treatment of snoring and OSA. The review request noted that approval could not be confirmed on the FDA Web site.

12/05/2005: MTAC REVIEW

Pillar Implants for Obstructive Sleep Apnea and Snoring

Evidence Conclusion: *Obstructive sleep apnea*: There is no published evidence on the effect of pillar implants on health outcomes for patients with obstructive sleep apnea. *Snoring:* The only published studies on the effectiveness of pillar implants for treating primary snoring were case series. The two studies with the largest sample sizes and longest follow-up periods were reviewed. The authors of the larger study (Kuhnel et al., 2005, n=106) did not clearly list their outcome variables and may have selectively reported positive outcomes. They reported a significant decrease in daytime sleepiness and a reduction in the snoring index after treatment. The smaller study (Maurer et al., 2005, n=40) reported a significant reduction in bed-partner-reported snoring and self-reported daytime sleepiness a year after treatment. There was no significant change when recordings of snoring were evaluated recordings were available for only half of the patients. No serious adverse effects were reported in either study. The efficacy of the intervention compared to an alternative treatment or no treatment can be evaluated.

Articles: *Obstructive sleep apnea:* No empirical studies were identified. The Kaiser review stated, “there were no studies published in the Medline literature reporting use of palatal implant in patients with obstructive sleep apnea.” *Snoring:* No randomized controlled trials or non-randomized comparative studies were identified. There were several case series. The two largest case series, which also had the longest follow-up, were critically appraised. The articles were by a similar team of German researchers, but there does not appear to be overlap in the patients included in the two studies. The two articles critically appraised are: Kuhnel TS, Heln G, Hohenhorst W, Maurer JT. Soft palate implants: a new option for treating habitual snoring. Eur Arch Otorhinolaryngol 2005; 262: 277-280. See Evidence Table. Maurer JT, Hein G, Verse T. Long-term results of palatal implants for primary snoring. Otolaryngology-Head and Neck Surgery 2005; 133: 573-578. See Evidence Table.

The use of Pillar implants in the treatment of obstructive sleep apnea and snoring does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Oral pressure therapy (OPT) for the Treatment of Obstructive Sleep Apnea

BACKGROUND

Obstructive sleep apnea (OSA) is a common medical condition that affects approximately 2-4% of middle-age men and women in the United States. It is characterized by recurrent episodes of partial or complete collapse or obstruction of the upper airways during sleep. This leads to repeated momentary cessation of breathing (apnea) or significant reductions in breathing amplitude (hypopnea) resulting in significant hypoxemia and hypercapnia. The apnea /hypopnea index (AHI) describes the total number of apnea/hypopnea episodes per hour of sleep which is usually <5 in normal individuals. AHI scores of 5-15, 15-30, and >30 categorize patients with sleep apnea

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as mild, moderate, and severe, respectively. OSA is often associated with loud snoring, increasing respiratory effort, intermittent arterial oxygen desaturation, observed apnea, and disrupted sleep. Other symptoms include excessive daytime sleepiness, sleep attacks, and non-restorative sleep. OSA is a serious disorder that may significantly increase morbidity and mortality. Its potential health consequences include hypertension, arrhythmia, cerebrovascular disease, neuropsychiatric problems. It may also be associated with motor vehicle accidents, as well as social and work-related problems (Farid-Moayer 2013, van Zeller 2013, Badran 2014, Jordan 2014, Ward 2014). Conservative treatments for OSA include weight loss, modification of the patient's sleep position, medications to relieve nasal obstruction, as well as avoidance of evening alcohol, sleep medications, and sedatives. For those who fail these measures, night-time continuous positive airway pressure (CPAP) via nasal or face mask is the recommended standard and effective treatment for OSA. This positive airway ventilation stabilizes the whole upper airway reduces the AHI, normalizes the oxyhemoglobin saturation, and reduces the cortical arousals associated with the apnea /hypopnea events. However, CPAP is not well tolerated by patients, is contraindicated in claustrophobic patients, and may be associated by a number of side effects. It was reported that up to 30% of OSA patients refuse CPAP treatment, and only 50% of those who accept it can tolerate its long-term use. When adherence is defined as more than 4 hours nightly use, 46-83% of patients have reported to be non-adherent (Sawyer 2011, Zeller 2013, Jordan 2014). Alternative therapies for cases who cannot tolerate or do not respond to CPAP therapy, include the use of oral and nasal appliances, surgical procedures, laser treatment, or tracheotomy when all other treatments fail. Despite the range therapeutic options available for managing OSA, there is no treatment that is both completely effective and fully tolerated by all patient (Farid-Moayer 2013, Colrain 2013). Oral pressure therapy (OPT) is a new concept for relieving airway obstruction to treat OSA. It is a novel noninvasive treatment modality that applies vacuum in the mouth to stabile upper airway tissue in patients with OSA. The commercially available OPT system is composed of three components: an oral interface, a bedside console containing a pump, and tubing set. The oral interface is a mouthpiece that incorporates a lip seal and a connector. The pump applies continuous negative pressure to the oral interface and consists of a vacuum pump, a controller, and pressure measurement component. The tubing set connects the pump to the oral interface. The negative pressure in the oral cavity is intended to create a pressure gradient to draw the soft palate anteriorly into contact with the tongue to improve the airway flow during sleep. The patient breathes normally through the nose while sleeping, thus nasal patency to allow closed-mouth breathing is required for the use of that device (Colrain 2013, Farid-Moayer 2013). The Attune Sleep Apnea System and the Winx Sleep Therapy System (that has an additional data management software application) were approved by US Food and Drug Administration in 2012 for home use in the treatment of obstructive sleep apnea (OSA) in adults.

06/16/2014: MTAC REVIEW

Oral pressure therapy (OPT) for the Treatment of Obstructive Sleep Apnea

Evidence Conclusion: The published studies on the oral pressure therapy for obstructive sleep apnea were conducted by the same group of investigators who had financial ties to ApniCure the manufacturer of the device, which also funded the studies. These were only observational studies where the patients acted as their own controls. The first (Farid-Moayer et al, 2013) was a feasibility study conducted among 71 patients from a single center, and the second (ATLAST study, Colrain et al, 2013) was a larger multicenter study initially, but included only a limited number of patients in the final analysis. The authors of ATLAST described the study as a prospective, randomized, crossover study. However, as they indicated, randomization was for the "first-night order of control versus treatment". The study did not have a control group, and OPT therapy was not compared to CPAP therapy, sham therapy, or any other treatment for OSA. The control subjects were those who underwent their baseline PSG before OPT while the treatment group had their PSG in the first treatment night. After the first night PSG, all participants received OPT for 28 days. The study included highly selected and motivated individuals with OSA, and only 14% of those who signed the consent were included in the analysis cohort. PSG was only performed at 2 nights at baseline and after 28 days of therapy. This does not allow for excluding the effect of the night to night variations in PSG or evaluating the long-term efficacy safety, or tolerability of the OPT. Conclusion: There is insufficient published evidence to date to determine the safety, efficacy, long term effect, tolerability and compliance with the oral pressure therapy for the treatment of obstructive sleep apnea.

Articles: The literature search for studies on oral pressure therapy for the treatment of obstructive sleep study revealed two publications for a feasibility study, and a larger observational study. All were conducted by the same group of authors. The two published feasibility studies were conducted by the same group of investigators in the same center, with similar inclusion/exclusion criteria and patient characteristics, which makes it hard to determine if there is patient overlap between the studies. The authors indicate that in one study the mouthpiece was individually customized to the subjects, while it was only selected from 10 available fits in the other. The first feasibility study and the multicenter study were critically appraised. Colrain IM, Black J, Siegel LC, Bogan RK, A multicenter evaluation of oral pressure therapy for the treatment of obstructive sleep apnea. Sleep Med. 2013; 14:830-837. See Evidence Table. Farid-Moayer M, Siegel LC, Black J. A feasibility evaluation of oral pressure therapy for the treatment of obstructive sleep apnea. Ther Adv Respir Dis. 2013; 7:3-12. See Evidence Table.

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The use of Oral pressure therapy (OPT) for the treatment of obstructive sleep apnea does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Mandibular Advancement Devices for Treatment of Obstructive Sleep Apnea

BACKGROUND

There has been increasing recognition of a continuum of sleep disordered breathing disorders, ranging from simple snoring to obstructive sleep apnea (OSA). OSA refers to recurrent episodes of breathing cessation during sleep due to mechanical blockage of the airway. The diagnosis of OSA requires a minimum of 30 episodes of apnea, each lasting at least 10 seconds, during 6-7 hours of sleep. OSA patients are generally obese and the cardinal symptom is excessive daytime sleepiness. Upper airway resistance syndrome (UARS), a term first used in 1993, is a form of sleep-disordered breathing that is also associated with daytime sleepiness. Patients do not meet diagnostic criteria for OSA and are generally non-obese. Recent investigations suggest that UARS may have different pathophysiology than OSA, for example UARS patients may have increased airway collapsibility and craniofacial abnormalities. Common polysomnographic findings for UARS include Apnea-hypopnea index (AHI) <5, minimum oxygen saturation >92%, increase in alpha rhythm and a relative increase in delta sleep (Bao & Guilleminault). Continuous Positive Airway Pressure (CPAP) is widely used as first-line therapy for UARS although there is a lack of high-grade evidence supporting its effectiveness. CPAP is also often used as a tool to diagnose UARS by seeing whether patients respond to a trial of CPAP treatment. Other treatment alternatives include oral appliances, septoplasty and radiofrequency reduction of enlarged nasal inferior turbinates. Classic surgical procedures used for OSA are considered by many clinicians to be too aggressive for treatment of UARS (Bao & Guilleminault). There are currently more than 35 different oral appliances on the market for OSA and/or snoring. The most widely used type of oral device is mandibular advancement devices (MAD) which act to keep the pharyngeal airspaces open by moving the mandible forward by advancing or downwardly rotating the mandible (Schoem, 2000).

12/13/2000: MTAC REVIEW

Mandibular Advancement Devices for Treatment of Obstructive Sleep Apnea

Evidence Conclusion: There is insufficient evidence to permit conclusions about the effect of oral appliances on health outcomes. Since there are over 35 OAs, each needs to be considered separately. Only one commercially available oral appliance (Herbst device, Bloch RCT) was evaluated in the recent studies. The Bloch RCT was subject to threats to validity including small sample size, absence of a placebo controlled-group, no washout period between treatments, short intervention period (one week per treatment) and inappropriate p-value cut-off (i.e. did not adjust for multiple comparisons). The other new RCT, Wilhelmsson, used a custom-made oral appliance rather than a commercially available device. There were no long-term data on the effectiveness of any oral device. There were also no long-term data from RCTs on potential adverse effects associated with long-term use of oral devices. A cross-sectional study (Clark) suggests that there may be a high prevalence of adverse effects; this study was not able to measure the severity of complications.

Articles: Since the articles reviewed for the previous MTAC evaluation, there were two new RCTs (one was a cross-over trial), one cross-sectional study examining long-term use of an oral appliance and one case series. The randomized cross-over study compared two types of oral appliances and a no-treatment control group. The other RCT compared an oral appliance with uvulopalatopharyngoplasty (UPPP). *Evidence tables were created for two RCTs and the cross-sectional study:* Bloch KE, Jinnong AI, Zhang N, Kaplan V, Stohckli PW, Russi EW. A randomized, controlled crossover trial of two oral appliances for sleep apnea treatment. Am J Respir Crit Care Med 2000; 162: 246-51. See Evidence Table. Clark GT, Sohn JW, Hong, CN. Treating obstructive sleep apnea and snoring: Assessment of an anterior mandibular positioning device. JADA 2000:131: 765-771. See Evidence Table. Wilhelmsson B, Tegelberg A, Walker-Engstrom ML, Ringqvist M, Andersson L, Krekmanov L, Ringqvist I. A prospective randomized study of a dental appliance compared with uvulopalatopharyngoplasty in the treatment of obstructive sleep apnea. See Evidence Table.

The use of the Herbst, and Monbloc mandibular advancement devices for the treatment of obstructive sleep apnea meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

06/06/2005: MTAC REVIEW

Mandibular Advancement Devices for Treatment of Obstructive Sleep Apnea

Evidence Conclusion: There was only one empirical study evaluating the safety and efficacy of MAD for UARS, a case series with 32 patients (Yoshida, 2002). The investigators created an oral device for patients diagnosed with UARS. They assessed clinical variables using polysomnography at baseline, and 14-60 days after first use of the device. The investigators found statistically significant improvement in most of the polysomnography outcomes at follow-up, including a significant reduction in daytimes sleepiness according to the Epworth

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sleepiness scale. The study is limited by the small size and case series design—patients were not blinded and there was no comparison or control group. Improvement could have been due to the natural history of the condition or to a placebo effect. In addition, the performance of the devices may differ from other custom-made or commercially available mandibular advancement devices.

Articles: Only one empirical study was identified. This was a case series with 32 patients and was critically appraised: Yoshida K. Oral device therapy for the upper airway resistance syndrome patient. *J Prosthet Dent* 2002; 87: 427-30. See Evidence Table.

The use of the Herbst, and Monbloc mandibular advancement devices for the treatment of upper airway resistance syndrome does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Maxillomandibular Advancement Surgery for Sleep Apnea

BACKGROUND

Sleep apnea is characterized by repeated apnea or hypopnea during sleep. Apnea, which is the cessation of airflow for ten or more seconds, could be central or obstructive. If respiratory efforts persist despite cessation of airflow, the apnea is obstructive. Obstructive sleep apnea syndrome (OSAS) is defined by the presence of at least a minimum number of apneas or hypopneas per hour, and the presence of mental or physical effects or both. Potential health consequences of OSAS are cardiovascular diseases, neuropsychiatric problems, injuries, and increased mortality. Obstructive sleep apnea results from a combination of a structurally small upper airway and a loss of upper airway muscle tone. Methods of treating OSA include weight loss, nasal continuous positive airway pressure (CPAP), surgical or laser resection of the uvula, tonsils or soft palate, and tracheostomy when all other treatments fail. Surgical treatment approach varies, and the results are affected by age, cause of obstruction, and severity of disease. The best method to of treatment remains controversial. Maxillomandibular advancement (MMA) pulls forward the anterior pharyngeal tissues attached to the maxilla, mandible, and hyoid to increase the posterior airway space. It is a currently accepted treatment for OSAS; however, its indication is unsettled and is often limited to the severe cases where other surgeries have failed.

08/09/2001: MTAC REVIEW

Maxillomandibular Advancement Surgery

Evidence Conclusion: Maxillomandibular advancement (MMA) may be successful, and safe for treating selected patients with OSA. However, these series do not provide sufficient evidence to determine the efficacy of MMA in the treatment of obstructive sleep apnea. Case series offer the lowest grade of evidence and have several internal threats to their validity.

Articles: The search yielded 113 articles. Most of the articles were on uvulopalatopharyngoplasty or glossectomy. Three articles were found on maxillomandibular advancement (MMA). All three were case series, two small (n=19 and n=21), and a bigger series (n=50). *Critical appraisal was made for the following articles:* Hochban W, Brandenburg. et al. Surgical Treatment of Obstructive Sleep Apnea by Maxillomandibular Advancement. Sleep 1994; 17 (7): 624-629 See Evidence Table. Nimkarn Y, Miles PG, Waite PD. Maxillomandibular Advancement Surgery in Obstructive Sleep Apnea Syndrome Patients: Long – Term Surgical Stability. *J Oral Maxillofac Surg* 1995; 53:1414-1418 See Evidence Table. Prinsell JR. Maxillomandibular Advancement Surgery in a Site-Specific Treatment Approach for Obstructive Sleep Apnea in 50 Consecutive Patients. *Chest* 1999; 116: 1519-1529 See Evidence Table.

The use of the Maxillomandibular Advancement Surgery does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Laser Treatments for Snoring and Sleep Apnea

BACKGROUND

Sleep-disordered breathing includes a spectrum of disorders ranging from primary snoring to obstructive sleep apnea (OSA). Obstructive Sleep Apnea Syndrome (OSAS) is defined as an apnea-hypopnea index of more than five events per hour, and often also have mental or physical effects such as excessive daytime sleepiness. Potential health consequences of OSAS are cardiovascular diseases, neuropsychiatric problems, injuries and increased mortality. Obstructive sleep apnea results from a combination of a structurally small upper airway and a loss of upper airway muscle tone.

Methods of treating OSA include weight loss, nasal continuous positive airway pressure (CPAP), surgical or laser resection of the uvula, tonsils or soft palate, or tracheostomy when all other treatments fail. Surgical treatment approach varies, and the results are affected by age, cause of obstruction, and severity of the disease. The best method of treatment remains controversial.

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08/08/2001: MTAC REVIEW
Cautery-Assisted Palatal Stiffening Operation (CAPSO)
Evidence Conclusion: Only a single small case series is available to evaluate CAPSO for treating obstructive sleep apnea. This represents insufficient evidence to draw conclusions about the effect of CAPSO on health outcomes related to sleep apnea.
Articles: The search yielded 113 articles. Most of the articles were on uvulopalatopharyngoplasty or glossectomy. There were two empirical articles on CAPSO, both were case series. One of the case series (n=25) included patients with obstructive sleep apnea, while the other, report (n=206) included patients who complained of excessive habitual snoring, no attempt was made to diagnose sleep apnea. An evidence table was created for the case series with sleep apnea patients. Wassmuth Z, Mair E, Loube D, Leonard D. Cautery-assisted palatal stiffening operation for the treatment of obstructive sleep apnea syndrome. Otolaryngol Head Neck Surg 2000; 123: 55-60. See Evidence Table.

The use of cautery-assisted palatal stiffening operation (CAPSO) in the treatment of sleep apnea does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

08/08/2001: MTAC REVIEW
Repose Procedure
Evidence Conclusion: The existing scientific evidence does not permit conclusions about the efficacy of the Repose procedure on health outcomes. The best evidence is a case series of 16 individuals with data available on 14 of these. This report is subject to the limitations of case series (selection and observation bias likely).
Articles: The search yielded 113 articles. Most of the articles were on uvulopalatopharyngoplasty or glossectomy. There were three articles on the Repose procedure, one review/discussion piece and two small case series (n=9 and n=15). Because it was the best available evidence, an evidence table was created for the larger case series. DeRowe A, Gunther E, Fibbi A, Lehtimake K, Valatalo K., Maurer J, Ophir D. Tongue-based suspension with a soft tissue-to-bone anchor for obstructive sleep apnea: Preliminary clinical results of a new minimally invasive technique. Otolaryngol Head Neck Surg 2000; 122: 100-3. See Evidence Table.

The use of repose procedure in the treatment of sleep apnea does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

04/14/1999: MTAC REVIEW
Somnus Somnoplasty System
Evidence Conclusion: Evidence identification was conducted by searching MEDLINE from 1990 to February 1999 using the terms: somnoplasty, sleep apnea and radiofrequency. The Somnus Company was aware of only one published article related to the use of the Somnoplasty system for obstructive sleep apnea. This article (summarized below) reports data from a single case series of 22 patients treated for snoring, daytime sleepiness and mild obstructive sleep apnea. Results from this study show no changes in Respiratory Distress Index (RDI*) following somnoplasty, statistically significant improvements in partner report of snoring and an improvement of 3.3 points (24-point scale) in self-report of sleepiness.
Articles: Powell, NB, et al *Chest,* 1998:113:1163-74. See Evidence Table

The use of the Somnus Somnoplasty System for the treatment of obstructive sleep apnea has been approved by the FDA and therefore meets *Kaiser Permanente Medical Technology Assessment Criteria.*

08/08/2001: MTAC REVIEW
Base of Tongue Somnoplasty in the Treatment of Sleep Apnea
Evidence Conclusion: The evaluated study does not provide sufficient evidence to determine the efficacy of base of tongue somnoplasty, in the treatment of sleep apnea, due to its small sample size, together with the other limitations of case series.
Articles: The search yielded 113 articles. Most of the articles were on uvulopalatopharyngoplasty or glossectomy. There was a pilot study done for base of tongue somnoplasty on humans, and another study made on animals. *The best available article for critical appraisal was the pilot study:* Powell N B, Riley R W, et al. Radiofrequency Tongue Base Reduction in Sleep- Disordered Breathing: A Pilot Study. *Otolaryngol Head Neck Surg* 1999: 120: 656-64. See Evidence Table.

The use of base of tongue somnoplasty in the treatment of sleep apnea does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

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12/05/2005: MTAC REVIEW
Radiofrequency Tissue Ablation (Somnoplasty)
Evidence Conclusion: There is insufficient evidence on single level base of tongue somnoplasty to draw conclusions about the efficacy of the procedure compared to placebo or the standard treatment, CPAP. There were no RCTs on single level somnoplasty. One non-randomized comparative study did not find significant between-group differences on subjective outcomes. There is evidence from one RCT that multilevel (base of tongue and soft palate) does not improve outcomes compared to sham treatment or placebo. The RCT did not identify significant between-group differences in two of three primary outcomes including the objective outcome, slowest reaction time. Findings from case series suggest that there is a relatively low complication rate, at least in institutions with extensive experience with the technology.
Articles: See Evidence Table. Stewart DL, Weaver EM, Woodson BT. Multilevel temperature-controlled radiofrequency for obstructive sleep apnea: Extended follow-up. Otolaryngol Head Neck Surg 2005; 132; 630-635. Woodson BT, Nelson L, Mickelson S et al. A multi-institutional study of radiofrequency volumetric tissue reduction for OSAS. Otolaryngol Head Neck Surg 2001; 125: 303-311. See Evidence Table. Kezirian EJ, Powell NB, Riley RW, Hester JE. Incidence of complications in radiofrequency treatment of the upper airway. Laryngoscope 2005; 115: 1298-1304. See Evidence Table. Stuck BA, Starzak K, Verse T et al. Complications of temperature-controlled radiofrequency volumetric tissue reduction for sleep-disordered breathing. Acta Otolaryngol 2003; 123: 532-535. See Evidence Table.

The use of Radiofrequency tissue ablation (somnoplasty) in the treatment of sleep apnea does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

eXciteOSA® for Snoring and Mild Obstructive Sleep Apnea (OSA)
12/2022: MTAT REVIEW
Evidence Conclusion: A Hayes, Inc. evidence review (Dec. 2022) identified three single-arm studies of poor or very poor quality that suggested the intervention may be associated with reduced snoring. Device-related adverse events were typically mild and self-limiting. A key limitation of the identified studies was a maximum follow-up period of six weeks. The INTC consented to no further review of eXciteOSA®. The Hayes report can be referenced to inform KP decision-making on eXciteOSA® at this time. The INTC may review the topic again should more substantial evidence become available. Two ongoing randomized controlled trials (RCTs) are in progress. Written clinical input was not obtained from PMG experts from across the KP program. However, clinical experts within KP have noted they are still exploring the technology at medical professional society meetings in 2023.

Uvulopalatopharyngoplasty (UPPP)
Background

Sleep-disordered breathing includes a spectrum of disorders ranging from primary snoring to obstructive sleep apnea (OSA). Obstructive Sleep Apnea Syndrome (OSAS) is defined as an apnea-hypopnea index of more than five events per hour, and often also have mental or physical effects such as excessive daytime sleepiness.
Potential health consequences of OSAS are cardiovascular diseases, neuropsychiatric problems, injuries and increased mortality. Obstructive sleep apnea results from a combination of a structurally small upper airway and a loss of upper airway muscle tone.

Methods of treating OSA include weight loss, nasal continuous positive airway pressure (CPAP), surgical or laser resection of the uvula, tonsils or soft palate, or tracheostomy when all other treatments fail. Surgical treatment approach varies, and the results are affected by age, cause of obstruction, and severity of the disease. The best method of treatment remains controversial.

Uvulopalatopharyngoplasty (UPPP) is a surgical procedure used to treat sleep apnea or snoring. It removes excess tissue in the throat in an attempt to widen the airway. The soft tissue removed may include the uvula, tonsils, adenoids, tongue or roof of the month. It takes 2 to 3 weeks to recover from the surgery.

1997 Literature Search
Articles: Based on the literature below there is limited evidence of the value of LAUP or UPPP in the treatment of OSAS (Obstructive Sleep Apnea Syndrome). While there is strong evidence supporting the value of CPAP in the treatment of OSAS, compliance in the use of the CPAP device remains a problem. Anand-V-K,

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Ferguson-P-W, Schoen-I-S, Obstructive sleep apnea: comparison of continuous positive airway pressure and surgical treatment, Otolaryngology-Head-Neck Surgery. Sept: 105(3) 382-90. Retrospective review, 400 cases of patients diagnosed with OSA (Obstructive Sleep Apnea). A comparative analysis with polysomnography revealed superior cures with CPAP, although long term compliance remains problematic. Conclusion was use of CPAP as initial therapy in- patients with no clinically apparent causes for obstruction: nasal polyps, deviated nasal septum, or obstructive tonsillar hypertrophy. Mickelson, SA., Laser-Assisted Uvulopalatoplasty for Obstructive Sleep Apnea, Laryngoscope: 106(I Pt 1): 10-3, 1996 Jan. Study Size 34, Consecutive prospective patients; Improved RDI by at least 50% in 53.8% of the study group. Snoring was reduced by 92.3%. Conclusion: Results suggest that LAUP MAY be efficacious in management of OSAS. Vaidya AM. Petruzzelli GJ., McGee D., Gopalsami C., Identifying obstructive sleep apnea in patients presenting for laser-assisted uvulopalatoplasty, Laryngoscope: 106(4): 431-7 1996 Apr. 850 patients with snoring evaluated. While body mass index, falling asleep while driving, snoring every night, and stopping breathing during sleep were found to correlate strongly with increasing RDI (Respiratory Disease Index), it was strongly recommended that a referral for PSG (polysomnography Study) be initiated if there is any suspicion of OSAS. Walker RP. Grigg-Damberger MM. Gopalsami C, Totten MC., Laser-assisted uvulopalatoplasty for snoring and obstructive sleep apnea: results in 170 patients, Laryngoscope. 105(9 Pt 1): 938-43, 1995 Sept July 1993 - December 1994, 541 consecutive patients referred for treatment of snoring. 274 had LAUP treatments. As of January 1995 LAUP, treatment courses were completed for 170 patients.105 had diagnosis of snoring and 65 had diagnosis of OSAS based on preoperative polysomnography. Of the 65 OSAS patients 16 cases achieved success as measured on post-op polysomnography. Conclusion: LAUP may be a viable surgical option for patients with snoring and mild sleep apnea. Schecthtman KB. Sher AE., Piccirillo JF., Methodological and statistical problems in sleep apnea research: the literature on Uvulopalatopharyngoplasty. Sleep 18(8): 659-66 1995 Oct. A comprehensive review of the literature on surgical treatment of sleep apnea found 37 appropriate papers (total n = 992) on UPPP. Problems identified: 1) There were no randomized studies and few (n=4) with control groups. 2) Median sample size was only 21.5; thus statistical power was low and clinically important associations were routinely classified as "not statistically significant". 3) Only one paper presented the confidence bounds that might distinguish between statistical and clinical significance. 4) Because of short follow-up times and infrequent repeat follow-ups, little is known about whether UPPP results deteriorate in time. 5) In at least 15 papers, bias caused by retrospective designs and nonrandom loss to follow-upraised questions about generalizability of results. 6) Few papers associated polysomnography data with patient-based quality of life measures. 7) Missing data and inconsistent definitions were common. 8) Baseline measures were often biased because the same assessment was inappropriately but routinely used for both screening and baseline. LU SJ. Chang SY., Shiao GM., Comparison between short-term and log-term post-operative evaluation of sleep apnea after Uvulopalatopharyngoplasty. Journal of Laryngology & Otology. 109(4): 308-12 1995 Apr.
Sample 15 OSAS patients who had UPPP with pre-operative, initial post-operative and long-term post-operative polysomnography studies (more than 5 years after surgery). The subjective improvement after operation is not adequately correlated to the PSG results. Suggestion that long- term follow-up for patients after UPPP is necessary. Watson, Robert K., Thompson, A. Siobhan: Treatment Outcome of Sleep Apnea. CONN Med. 56: 125- 129, 1992. 101 patients. Interviewed over 12-24-month period. CPAP most often treatment used with results of improved daytime alertness (84%). Patients with moderate OSA often had surgery which led to 85% improved daytime sleepiness, and patients with mild OSA were treated with sleep position change and weight loss with 64 - 66% improved daytime alertness.

Applicable Codes

PAP Devices –
Considered Medically Necessary when criteria in the applicable policy statements listed above are met

CPT® or HCPC Codes	Description
E0470	Respiratory assist device, bi-level pressure capability, without backup rate feature, used with noninvasive interface, e.g., nasal or facial mask (intermittent assist device with continuous positive airway pressure device)
E0471	Respiratory assist device, bi-level pressure capability, with back-up rate feature, used with noninvasive interface, e.g., nasal or facial mask (intermittent assist device with continuous positive airway pressure device)
E0472	Respiratory assist device, bi-level pressure capability, with backup rate feature, used with invasive interface, e.g., tracheostomy tube (intermittent assist device with continuous positive airway

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	pressure device)
E0601	Continuous positive airway pressure (CPAP) device
D9947	Custom sleep apnea appliance fabrication and placement
D9948	Adjustment of custom sleep apnea appliance
D9949	Repair of custom sleep apnea appliance

Geniohyoid Advancement Myotomy –
Considered Medically Necessary when criteria in the applicable policy statements listed above are met

CPT® or HCPC Codes	Description
21120	Genioplasty; augmentation (autograft, allograft, prosthetic material)
21121	Genioplasty; sliding osteotomy, single piece
21122	Genioplasty; sliding osteotomies, 2 or more osteotomies (eg, wedge excision or bone wedge reversal for asymmetrical chin)
21123	Genioplasty; sliding, augmentation with interpositional bone grafts (includes obtaining autografts)
Does not require medical review	
21125	Augmentation, mandibular body or angle; prosthetic material
21127	Augmentation, mandibular body or angle; with bone graft, onlay or interpositional (includes obtaining autograft)

Maxillo-mandibular Advancement Surgery for Sleep Apnea-
Considered Medically Necessary when criteria in the applicable policy statements listed above are met

CPT® or HCPC Codes	Description
21198	Osteotomy, mandible, segmental;
21199	Osteotomy, mandible, segmental; with genioglossus advancement
21206	Osteotomy, maxilla, segmental (eg, Wassmund or Schuchard)

Hypoglossal Nerve Stimulation-
Effective until June 1st, 2024
Medicare – Considered Medically Necessary when criteria in the applicable policy statements listed above are met
Non-Medicare- Considered not medically necessary

CPT® or HCPC Codes	Description
64582	Open implantation of hypoglossal nerve neurostimulator array, pulse generator, and distal respiratory sensor electrode or electrode array
64583	Revision or replacement of hypoglossal nerve neurostimulator array and distal respiratory sensor electrode or electrode array, including connection to existing pulse generator
64584	Removal of hypoglossal nerve neurostimulator array, pulse generator, and distal respiratory sensor electrode or electrode array
42975	Drug-induced sleep endoscopy, with dynamic evaluation of velum, pharynx, tongue base, and larynx for evaluation of sleep-disordered breathing, flexible, diagnostic

Hypoglossal Nerve Stimulation-
Effective June 1st, 2024
Medicare – Considered Medically Necessary when criteria in the applicable policy statements listed above are met
Non-Medicare- Considered medically necessary when criteria in the applicable policy statements listed above are met

CPT® or HCPC Codes	Description
64582	Open implantation of hypoglossal nerve neurostimulator array, pulse generator, and distal respiratory sensor electrode or electrode array

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64583	Revision or replacement of hypoglossal nerve neurostimulator array and distal respiratory sensor electrode or electrode array, including connection to existing pulse generator
64584	Removal of hypoglossal nerve neurostimulator array, pulse generator, and distal respiratory sensor electrode or electrode array
42975	Drug-induced sleep endoscopy, with dynamic evaluation of velum, pharynx, tongue base, and larynx for evaluation of sleep-disordered breathing, flexible, diagnostic

Nasal Expiratory Positive Airway Pressure- Considered not medically necessary

CPT® or HCPC Codes	Description
No specific codes	

Pillar Implants- Considered not medically necessary

CPT® or HCPC Codes	Description
C9727	Insertion of implants into the soft palate; minimum of three implants

Oral Pressure Therapy- Considered not medically necessary

CPT® or HCPC Codes	Description
No specific codes	

Mandibular Advancement Devices for Treatment of Obstructive Sleep Apnea-
Medicare – Considered Medically Necessary when criteria in the applicable policy statements listed above are met
Non-Medicare - Medical review no longer required

CPT® or HCPC Codes	Description
E0486	Oral device/appliance used to reduce upper airway collapsibility, adjustable or nonadjustable, custom fabricated, includes fitting and adjustment

Uvulopalatopharyngoplasty-
Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
42145	Palatopharyngoplasty (eg, uvulopalatopharyngoplasty, uvulopharyngoplasty)

Laser Treatments of Snoring-
Considered not medically necessary-
Repose

CPT® or HCPC Codes	Description
41512	Tongue base suspension, permanent suture technique

Somnoplasty

CPT® or HCPC Codes	Description
41530	Submucosal ablation of the tongue base, radiofrequency, 1 or more sites, per session

LAUP

CPT® or HCPC	Description

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Codes	
42160	Destruction of lesion, palate or uvula (thermal, cryo or chemical)
42890	Limited pharyngectomy
S2080	Laser-assisted uvulopalatoplasty (LAUP)

CAPSO

CPT® or HCPC Codes	Description
42950	Pharyngoplasty (plastic or reconstructive operation on pharynx)

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Date Created	Dates Reviewed	Date Last Revised
04/01/1998	04/06/2010[MDCRPC], 02/10/2011[MDCRPC], 12/06/2011[MDCRPC], 02/07/2012[MDCRPC], 10/02/2012[MDCRPC], 12/04/2012[MDCRPC],10/01/2013[MPC], 07/01/2014[MPC], 08/05/2014[MPC], 06/02/2015[MPC], 04/05/2016[MPC], 02/07/2017[MPC], 12/05/2017[MPC], 11/06/2018[MPC], 12/04/2018[MPC], 11/05/2019[MPC], 11/03/2020[MPC], 11/02/2021[MPC], 11/01/2022[MPC], 11/07/2023[MPC]	01/09/2024

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
09/08/2015	Revised LCD L34886 and L35008 Non-Covered Services
12/05/2017	Adopted Kaiser Permanente Policy for Mandibular Advancement Surgery for Sleep Apnea for Medicare
08/06/2019	Added MTAC review for Hypoglossal Nerve Stimulation
10/30/2019	Merged Laser Treatments for Snoring and Sleep Apnea criteria
01/07/2020	MPC approved to retain policy of non-coverage for Hypoglossal Nerve Stimulation in accordance with MTAC recommendation
09/09/2020	Added Medicare LCD L38312 and LCA A57949
10/06/2020	MPC approved to adopt MCG A-0973, Hypoglossal Nerve Stimulation.
09/08/2022	Removed deleted codes 0466T, 0467T and 0468T; Added new codes 64582, 64583, 64584 and 42975 under Hypoglossal Nerve Stimulation section.
10/26/2022	Updated applicable codes, including new codes released 01/01/22 and 04/01/22.
11/11/2022	Updated Medicare Links
11/20/2023	Added MTAT Review for eXciteOSA® for Snoring and Mild Obstructive Sleep Apnea (OSA)
12/27/2023	Merged Laser Treatments for Snoring and Uvulopalatopharyngoplasty (UPPP) criteria to *Obstructive Sleep Apnea- Surgical and Non-Surgical*
01/09/2024	MPC approved medical necessity criteria for hypoglossal nerve stimulation and DISE procedure. Requires 60-day notice, effective date June 1st, 2024.

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Clinical Review Criteria

Treatments for Urinary Incontinence

- Biofeedback for the Treatment of Urinary Incontinence
- Extracorporeal Magnetic Innervation for Urinary Incontinence
- Implanted Electrical Stimulator, Sacral Nerve for Fecal and Urinary Incontinence
- Intravaginal Electrical Stimulation
- Radiofrequency Bladder Neck Suspension for the Treatment of Genuine
- SPARC® Sling for Treatment of Urinary Incontinence
- Stress Urinary Incontinence; Transurethral Radiofrequency Energy Tissue Remodeling for Treatment of Stress Urinary Incontinence (TRETRTSUI)
- Urethral Bulking Agents
- Urgent PC Neuromodulation System for Overactive Bladder; Percutaneous Tibial Nerve Stimulation (PTNS)

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Non-Implantable Pelvic Floor Electrical Stimulator (230.8) Incontinence Control Devices (230.10) *(references Mechanical/Hydraulic Incontinence Control Devices and Collagen Implant)* Biofeedback Therapy for the Treatment of Urinary Incontinence (30.1.1) Sacral Nerve Stimulation for Treatment of Urinary Incontinence (230.18) Assessing Patient's Suitability for Electrical Nerve Stimulation Therapy (160.7.1) Bladder Stimulators (Pacemakers) (230.16)
Local Coverage Determinations (LCD)	3/14/2007 Noridian retired ***LCD Biofeedback Therapy Policy (L14443)*.** These services still need to meet medical necessity as outlined in the LCD and will require review. LCDs are retired due to lack of evidence of current problems, or in some cases because the material is addressed by a National Coverage Decision (NCD), a coverage provision in a CMS interpretative manual or an article. Most LCDs are not retired because they are incorrect. Therefore, continue to use LCD L14443 for determining medical necessity.
Local Coverage Article	11/01/2023 Noridian retired Posterior Tibial Nerve Stimulation Coverage (A52965). These services still need to meet medical necessity as outlined in the LCA and will require review. LCAs are retired due to lack of evidence of current problems, or in some cases because the material is addressed by a National Coverage Decision (NCD), a coverage provision in a CMS interpretative manual or an

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	article. Most LCAs are not retired because they are incorrect. Therefore, continue to use LCA 52965 for determining medical necessity.
Botox Injections & Oral Medications for the Treatment of Urinary Incontinence	Covered under the Medicare Part D Pharmacy Benefit, may be subject to medical necessity criteria

For Non-Medicare Members

Treatments for Urinary Incontinence	Criteria Used
Implanted Electrical Stimulator, Sacral Nerve for Fecal and Urinary Incontinence	Kaiser Permanente has elected to use the MCG* Implanted Electrical Stimulator, Sacral Nerve (A-0645) for medical necessity determinations. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access. **If requesting these services, please send the following documentation to support medical necessity:** • Last 6 months of clinical notes from requesting provider &/or specialist.
Extracorporeal Magnetic Innervation Radiofrequency Bladder Neck Suspension Transurethral Radiofrequency Energy Tissue Remodeling for Treatment of Stress Urinary Incontinence (TRETRTSUI) Intravaginal Electrical Stimulation	There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.
Sling Procedures for Urinary Incontinence	**Effective until August 1st, 2024** Medical necessity review is not required for this service. **Effective August 1st, 2024** Kaiser Permanente has elected to use the Sling Procedures for Urinary Incontinence (e.g., mid- urethral and pubovaginal slings) (KP-S-850 08012024) the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.
Urethral Bulking Agents	**Effective until August 1st, 2024** Medical Necessity Review is not required. **Effective August 1st, 2024** Kaiser Permanente has elected to use the Urethral Bulking Agent Injections (KP-A-0268 08012024) the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.
Percutaneous Tibial Nerve Stimulation (PTNS) - Urgent® PC Neuromodulation System for Overactive Bladder	Percutaneous tibial nerve stimulation (PTNS) which consists of a regimen of 30-minute weekly sessions for 12 weeks is medically necessary when **ALL** of the following are present: a. Overactive bladder syndrome b. Symptoms not due to spinal cord injury c. They must meet **ONE** of the following

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Treatments for Urinary Incontinence	Criteria Used
	o They must EITHER fail at least two medications with adequate trial (for example, two anticholinergics or an anticholinergic and a beta-agonist) OR o Have a contraindication to pharmacotherapy. d. Behavioral therapy (eg, bladder training, pelvic floor muscle training) that is of a sufficient duration to fully assess its efficacy. PTNS for any other urinary indication because it is considered experimental, investigational or unproven. More than 12 PTNS treatments are not medically necessary when there is no improvement of OAB symptoms.
Biofeedback for the Treatment of Urinary Incontinence	**Effective until August 1st, 2024** There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies. **Effective August 1st, 2024** **Biofeedback for urinary Incontinence** ***Coverage varies across plans*** *For FEHB plans: See the member's contract for specific coverage details* Medical necessity review is not required.
Botox Injections for the Treatment of Urinary Incontinence	Covered under the Pharmacy Benefit subject to medical necessity criteria
Oral Medications for the Treatment of Urinary Incontinence	Covered under the Pharmacy Benefit (e.g. Vibegron, Mirabegron), may be subject to medical necessity criteria

***The MCG* are proprietary and cannot be published and/or distributed**. However, on an individual member basis, Kaiser Permanente can share a copy of the specific criteria document used to make a utilization management decision. If one of your patients is being reviewed using these criteria, you may request a copy of the criteria by calling the Kaiser Permanente Clinical Review staff at 1-800-289-1363 or access the MCG Guideline Index using the link provided above.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Stress urinary incontinence (SUI) is defined as leakage of urine during activities that cause increased abdominal pressure such as exercise or coughing in the absence of a detrusor contraction. It is the most common form of urinary incontinence in women and is estimated to affect about 6.5 million women in the United States. Current understanding is that urinary continence during stress events requires both intact supportive structures (i.e. endopelvic fascia) and functioning neurological control of the muscles of the pelvic floor and urethra (Agarwala & Liu, 2002).

Treatments for stress urinary incontinence include conservative therapies such as strengthening the pelvic floor muscles with Kegel exercises and devices such as electrical stimulation devices and pessaries. There are also medications such as estrogen and various surgical treatments.

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Evidence and Source Documents

Biofeedback for the Treatment of Urinary Incontinence
Collagen Injections for Stress Urinary Incontinence
Extracorporeal Magnetic Innervation for Urinary Incontinence
Intravaginal Electrical Stimulation for Urinary Incontinence
Radiofrequency Bladder Neck Suspension / Transurethral Radiofrequency Energy Tissue Remodeling for Treatment of Stress Urinary Incontinence (TRETRTSUI)
SPARC® Sling for Treatment of Urinary Incontinence
Urgent PC Neuromodulation System for Overactive Bladder; Percutaneous Tibial Nerve Stimulation (PTNS)
Bladder Pacemaker /Sacral Nerve Stimulation for Treatment of Urinary Incontinence
Sacral Nerve Stimulator for Fecal Incontinence

Medical Technology Assessment Committee (MTAC)

Biofeedback for the Treatment of Urinary Incontinence

BACKGROUND

Urinary incontinence (UI), defined as the involuntary loss of urine, is a common problem affecting many women of all ages, but is more prevalent in the elderly. It is estimated that UI affects 30-60% of middle aged and older women in the community, and up to 80% of nursing home residents (Herderschee 2011, Markland 2011, Goode 2010). The main types of UI are stress incontinence (SUI), urge (or urgency) incontinence (UUI), and mixed stress and urgency incontinence (MUI). Stress urinary incontinence is the most common type and occurs in about half of incontinent women. The next most common is the mixed urinary incontinence (around 30%) followed by the urge or urgency urinary incontinence. Mixed and urge incontinence predominate in older women, while stress incontinence mainly occurs in young and middle-age women (Lipp 2011). SUI is the involuntary leakage of urine with activities that increase intra-abdominal pressure such as coughing, sneezing, lifting, or sport activities. SUI occurs as a result of a combination of intrinsic urethral sphincter muscle weakness and an anatomic defect in the urethral support, leading to insufficient closure pressure in the urethra during physical effort. The etiology of SUI is multifactorial and includes pregnancy, vaginal delivery, pelvic surgery, neurologic causes, active lifestyle, and various comorbidities. UUI is the involuntary leakage of urine accompanied by or immediately preceded by a sensation of urgency, or the sudden compelling desire to pass urine which is difficult to defer. This can be caused by an involuntary bladder contraction that overcomes the sphincter mechanism; or poor bladder compliance due to loss of the viscoelastic features of the bladder. UUI is part of the spectrum of overactive bladder. MUI is the symptom complex of involuntary leakage associate with both urgency and effort and exertion (Lipp 2011, Deng 2011, Markland 2011). Urinary incontinence is not a life-threatening condition but has a profound negative impact on the quality of life. Symptoms of UI interfere with the performance of everyday household and social activities, and may lead to anxiety, frustration, social isolation, and depression. It is reported that UI is associated with a 30% increase in functional decline, a 2-fold increase in the risk of falls, and nursing home placement (Goode 2010, Markland 2011, Mladenovic 2011). Treatment options for urinary incontinence can be divided into conservative measures, pharmacotherapy, and surgical interventions. Conservative treatment is usually the first-line therapy for many patients and is useful for both stress and urge incontinence. Behavioral treatments have been well studied and proved to be effective in reducing leakage by 50-80%, with 10-30% of the patients achieving continence. These interventions improve incontinence by teaching skills and helping patients change their behavior. Behavioral programs comprise multiple individualized components which may include bladder control strategies, self-monitoring (bladder diary), scheduled or prompted voiding, delayed voiding, urge suppression strategies, moderate weight loss, fluid management, caffeine reduction, pelvic floor muscle training, and /or other lifestyle changes. Behavioral treatment is most useful when the person is motivated, wants to be actively involved in therapy, can follow directions, and when there is a readily identifiable and measurable response (Markland 2011, Lipp 2011). Pelvic floor muscle training (PFMT) and exercise, also known as Kegel exercise, is considered a cornerstone in behavioral treatment. PFMT is a program of repeated voluntary pelvic floor muscle contractions taught and supervised by a health care professional. These work by increasing the strength and tone of the pelvic floor muscles, which in turn increases the urethral closure force and prevents stress incontinence during an abrupt increase in intra-abdominal pressure. It is also useful for urge incontinence as the detrusor contractions can be reflexively or voluntarily inhibited by tightening the pelvic floor. The success of PFMT depends on the patient's ability to perform the exercise correctly and the motivation to actually practice it regularly. In clinical practice, PEMT is often combined by some type of feedback or biofeedback to help the woman learn how to contract the muscle, to improve the effectiveness of the contraction through modulating the performance of the learned contraction, and to encourage further exercising (Herderschee 2011, Goode 2010, Deng 2011). Feedback is defined as the return of part of the output of a system to the input in a way that affects its performance. It thus provides information on what was done, rather than what to do, i.e. the bodily sensation felt by the woman performing the contraction gives inherent feedback about the movement. Augmented feedback

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is a feedback with supplementary information provided e.g. verbal feedback from a clinician palpating or observing the contraction. Biofeedback (BF) is a form of augmented feedback that uses monitoring devices to display information about the operation of a bodily function that is not normally consciously controlled, to help the patient learn to control the function consciously. When performed in conjunction with Kegel exercises for the treatment of UI, specialized pressure transducers or sensors are inserted in the vagina or rectum, or placed on the perineum, and biofeedback instruments are used to reinforce correct techniques through visual and auditory cues. BF typically gives the user an auditory or visual record of the contraction or both. This can potentially be helpful and motivating women who find it difficult to identify and isolate their pelvic floor muscles. BF devices vary considerably; many of the devices used in the studies consist of air or water filled balloons that are inserted into the rectum or vagina to measure pressure. Other devices measure electrical activity (electromyography) via surface metal electrodes on vaginal or anal probes. Some devices can only be used in clinical setting because they require a health professional to set up and use the equipment, and others are very simple and portable and are designed for home use (Herderschee 2011). A typical program of biofeedback consists of 10 to 20 training sessions; 30 minutes each. Training sessions are typically performed in a quiet environment, and under the supervision of a physiotherapist or specialized nurse. Patients are instructed to use mental techniques to contract the pelvic muscles and feedback is provided for a successful contraction. This feedback may be signals such as lights, verbal praise, or other auditory or visual stimuli. The Food and Drug Administration have cleared a variety of biofeedback devices for marketing. It defines a biofeedback device as “an instrument that provides a visual or auditory signal corresponding to the status of one or more of a patient's physiological parameters) so that the patient can control voluntarily these physiological parameters.”

04/14/1999: MTAC REVIEW
Biofeedback for the Treatment of Urinary Incontinence
Evidence Conclusion: The published scientific evidence on biofeedback consists of small-randomized trials with typically one-month follow-up. These studies reported that adding biofeedback to a trial of pelvic floor muscle exercises did not produce any incremental benefit. It was noted that there were 3 randomized controlled trials that provided good evidence that biofeedback produces no incremental improvement in urinary incontinence compared to pelvic muscle exercise alone. It was also noted that biofeedback was currently a covered service at Kaiser Permanente Northwest and that this policy may undergo re-evaluation as a result of evaluating the evidence.
Articles: Berghmans, LCM et al, Neurology and Urodynamics, 1996:15:37-52. See Evidence Table. Burns, PA et al, J. Gerontology, 1993;48 M167-M174 See Evidence Table. Burton, JR, et al, J Am Geriatr Soc. 1988; 36:693-698 See Evidence Table. Burgio, KL, et al. Am J Obstet Gynecol, 1986;154:58-64 See Evidence Table.

Biofeedback for the treatment of stress or urge urinary incontinence does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

10/09/2002: MTAC REVIEW
Biofeedback for the Treatment of Urinary Incontinence
Evidence Conclusion*:* The new evidence on the benefit of biofeedback compared to pelvic floor muscle exercise alone consists of one RCT and one meta-analysis, both with threatened validity. Even with their methodological limitations, neither found a significant benefit of adding biofeedback to PFM exercises. There was also an additional RCT that compared PFM exercise with biofeedback to drug treatment (Burgio) and found a greater reduction in incontinent episodes with PFM exercise. Although the Burgio study had reasonably valid methods, it did not include a group receiving PFM exercises without biofeedback, so the additive benefit of using a biofeedback device with an exercise program cannot be determined. The new evidence on biofeedback for the treatment of urinary incontinence is consistent with earlier evidence that biofeedback does not substantially add to the effectiveness of pelvic floor muscle exercise.
Articles: The search yielded 73 articles, many of which were review articles or opinion pieces. There was one meta-analysis of RCTs and two RCTs. One of the RCTs was published prior to 1999 but was not included in the previous review. The two RCTs and the meta-analysis were critically appraised: Weatherall M. Biofeedback or pelvic floor muscle exercises for female genuine stress incontinence: A meta-analysis of trials identified in a systematic review. BJU Internat 1999; 83: 1015-1016. (Some methodological information taken from: Berghmans LCM, Hendriks HJM, Bo K. Conservative treatment of stress urinary incontinence in women: a systematic review of randomized controlled trials. Br J Urol 1998; 82: 181-191. See Evidence Table. Lacock J, Brown J, Cusack C et al. Pelvic floor reeducation for stress incontinence: comparing three methods. Br. J Commun Nurs 2001; 6: 230-237. See Evidence Table. Burgio KL, Locher JL, Goode PS. Behavioral vs. drug treatment for urge urinary incontinence in older women. JAMA 1998; 280: 1995-2000. See Evidence Table.

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The use of biofeedback in the treatment of urinary incontinence does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

10/17/2011: MTAC REVIEW
Biofeedback for the Treatment of Urinary Incontinence
Evidence Conclusion*:* Herderschee and colleagues' (2011) meta-analysis included 24 randomized or quasi randomized trials that compared the use of PFMT program with a form of feedback or biofeedback in women with urinary incontinence. The results of the meta-analysis indicate that women who received biofeedback were significantly more likely to report that their urinary incontinence was improved or cured compared to those who received PFMT alone. The meta-analysis had valid methodology; however, the trials included were small, some were quasi randomized, and all, but one small study, had moderate or high risk of bias. In addition, there were many variations in the regimens of biofeedback added to PFMT and women in the biofeedback or feedback group had more contact with the health providers. The overall results of the meta-analysis show that women in the biofeedback groups had statistically significant higher satisfaction and perception of improvement in symptoms compared to those in the PFMT only groups. However, the number of leak episodes indicates that the addition of biofeedback to PFMT leads to approximately one less leak every eight days. The limitations in the trials included in the analysis make it hard to determine whether the improvement was due to the intervention, bias, more contact with health providers, or other confounding factors.
Articles: The search revealed one recent Cochrane review of trials on feedback and biofeedback for augmenting pelvic floor muscle training in women with urinary incontinence. A number of RCTs that were included in the meta-analysis were also identified. Only the Cochrane's meta-analysis was selected for critical appraisal. Herderschee R, Hay-Smith EJ, Herbison GP, et al. Feedback or biofeedback to augment pelvic floor muscle training for urinary incontinence in women. *Cochrane Database Syst Rev*. 2011;(7):CD009252. See Evidence Table.

The use of biofeedback in the treatment of urinary incontinence does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Collagen Injections for Stress Urinary Incontinence
BACKGROUND
Stress incontinence is one of the two common types of urinary incontinence. The primary symptom is an involuntary loss of urine during physical exertion associated with increased intra-abdominal pressure, such as with coughing, laughing or sneezing. Treatments for stress incontinence include exercises to strengthen the external urethral sphincter, mechanical devices (pessaries) to support the urinary sphincter muscles, medications such as estrogen and phenylpropanolamine (PPA) and surgery. Injection of periurethral bulking agents for stress incontinence was first described by Murless in 1938 who used a sclerosing agent, sodium morrhuate. Injectable materials are usually used for patients with incontinence due to intrinsic sphincter deficiency (ISD). Currently, the most commonly used bulking agent is collagen. Collagen, however, is biodegradable, and therefore any benefit it may provide is short-lived. According to researchers, the ideal injectable substance has not yet been developed but it would be durable yet nonimmunogenic, noncarcinogenic, nonmigratory and produce minimal inflammatory responses (Lightner; Pannek). Collagen used for treating urinary incontinence is a bovine-derived collagen gel manufactured by the Bard Company and injected sub or periurethrally via percutaneous injection. Its mechanism of action is to increase tissue bulk in the area of the urethra until the urethra becomes closed. Multiple injections of up to 30 ml. may be injected in a single patient and up to 5 subsequent collagen treatments may be required to produce clinical improvement. A collagen implant, which is injected into the submucosal tissue of the urethra and/or the bladder neck and into the adjacent tissues of the urethra, is a prosthetic device used in the treatment of stress urinary incontinence resulting from intrinsic sphincter deficiency (ISD). ISD is a cause of stress urinary incontinence in which the urethral sphincter is unable to contract and generate sufficient resistance in the bladder, especially during stress maneuvers. Duraphere is an injectable bulking agent that is composed of pyrolytic carbon-coated beads suspended in a water-based carrier gel. In September 1999 the FDA approved Durasphere. A transurethral or periurethral method of injection can be used. A potential advantage of Durasphere over collagen is that the particle size is relatively large (251 to 300*u*) and particle migration is not believed to occur. Durasphere is also believed to not cause allergic reactions. However, recent studies have refuted that assumption.

1999: MTAC REVIEW
Collagen Injections for Stress Urinary Incontinence
Evidence Review: The published scientific evidence on collagen injection consists mostly of small case series with 1-2 year follow up. Several case series with good follow up in a population of women with stress incontinence reported short term benefit in 25-80% of patients which declines to 25-30% over the course of 3 years. Reported

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complication rates ranged from 10 to 20%. One study report that 9% of women and 25% of men eventually required surgical intervention for their incontinence. The wide range of reported outcomes makes interpretation of the effect of collagen injection difficult. Evidence tables of the relevant published studies are presented below.
Articles: Swami, S et al. Collagen for female genuine stress incontinence after a minimum two-year follow-up. 1997, *British Journal of Urology*, 80, 757-761 See Evidence Table. Stothers, L et al. Complications of periurethral collagen for stress urinary incontinence. 1998, *J. Urol.* 159, 806-807 See Evidence Table.

Collagen Injection for urinary incontinence did not pass the *Kaiser Permanente Medical Technology Assessment Criteria*.

2002: MTAC REVIEW
Collagen Injections for Stress Urinary Incontinence
Evidence Review: The best evidence was an RCT that compared injections with Durasphere to collagen injections among women with stress urinary incontinence due to intrinsic sphincter deficiency (Lightner). The authors did not find a significant difference in effectiveness between the two treatments. In both groups, about 66% of women in the analysis had an improvement of >1 continence grade on the Stamey scale after 12 months of follow-up. There was no placebo comparison and it may be that neither collagen nor Duraphere performs better than placebo. MTAC evaluated collagen injections in 1999 and found that there was insufficient evidence of effectiveness. The validity of the Lightner study was also threatened by the high dropout rate. Only 65% of patients completed the 12-month follow-up and there was no intention to treat analysis. The other article reviewed (Pannek) was a small case series that identified two cases of particle migration three months after Durasphere injections. Additional research is needed to verify the extent of particle migration and determine any possible harms associated with this migration.
Articles: The search yielded 9 articles. There were two empirical articles, one RCT and one case series (n=20). Both articles were reviewed. A case series of this size (n=20) would not normally be reviewed, but this article was included because it dealt with the safety of the technology. *The following articles were critically appraised.* Lightner D, Calvosa C, Andersen R, Klimberg I, Brito CG, Snyder J. et al. A new injectable bulking agent for treatment of stress urinary incontinence: Results of a multicenter, randomized, controlled double-blind study of Durasphere. Urology 2001; 58:12-15. See Evidence Table. Pannek J, Brands FH, Senge T. Particle migration after transurethral injection of carbon coated beads for stress urinary incontinence. J Urol 2001; 166:1350-1353. See Evidence Table.

Durasphere Injection for urinary incontinence did not pass the *Kaiser Permanente Medical Technology Assessment Criteria.*

Extracorporeal Magnetic Innervation for Urinary Incontinence
BACKGROUND
Extra-corporeal magnetic innervation therapy (approved by the FDA in June 1998) is a technology designed to treat stress urinary incontinence. Extra-corporeal magnetic innervation therapy is a technology that has been developed to provide conservative therapy for stress urinary incontinence by creating a magnetic field and the induction of electrical activity to de-polarize the nerves and exercise the muscles of the pelvic floor. The technology provides a potential alternative to surgical treatment for incontinence. It provides an additional option to conservative therapies such as fluid restriction, medical management, timed voiding, Kegel exercises, biofeedback and electrical stimulation. Its promoters state that this technology will prove more attractive to patients than electrical stimulation because patches or probes, skin contact or gel, and undressing for treatment are not necessary. Patients are positioned in a special chair provided with a cushion containing a magnetic field generator which is powered and controlled by an external power unit. The output of the power unit consists of pulses of current at 275 microseconds in duration and which can be adjusted in amplitude by the clinician. Treatment involves approximately ten minutes of intermittent low frequency stimulation (5 Hz) followed by a rest interval of 1-5 minutes and then ten minutes of intermittent high frequency stimulation (50 Hz). Treatments are given twice a week for six weeks. The FDA has approved this as Class II device requiring a physician's prescription and administration.

02/06/2000: MTAC REVIEW
Extracorporeal Magnetic Innervation for Urinary Incontinence
Evidence Conclusion: Although extracorporeal magnetic innervation therapy has FDA approval, there is insufficient scientific evidence to permit conclusions regarding the effects of this technology on health outcomes. This study is a cohort study without a control group and therefore lacks the validity of a randomized control trial.

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Validity of the before and after results are threatened by the drop-out or lack of follow-up of 14 patients in the original group. Validity is also threatened by the likelihood of co-interventions such as advice regarding voiding and fluid management. The possibility of a placebo effect is real.
Observation bias is likely in this study (e.g., the investigators received payment from the manufacturer).
Articles: Four articles were located using Medline (OVID). Articles were sorted on the basis of study type. One case series of seven male patients was rejected because the population was limited to males with spinal cord injury. A second study was eliminated because the 12 patients underwent saline infusion into the bladder followed by magnetic stimulation of S3. A third study was excluded because it reviewed literature dealing with urethral pressure in anesthetized dogs. Gallaway NT, El-Galley RE, Sand PK et al. Extracorporeal magnetic innervation therapy for stress urinary incontinence. *Urology*. 53 (6): 1108-11, 1999 June. See Evidence Table.

The use of extracorporeal magnetic innervation for the treatment of stress urinary incontinence has been approved by the FDA and therefore meets *Kaiser Permanente Medical Technology Assessment Criteria*.

Intravaginal Electrical Stimulation for Urinary Incontinence

BACKGROUND

Urinary incontinence (UI), the accidental release of urine, affects up to 30 million women in the United States. Most symptoms of UI will fall into two different categories. The first, stress incontinence, is characterized by the involuntary loss of urine occurring after exerting some force on the bladder through physical activities such as coughing, sneezing, laughing, exercising or lifting. Urge incontinence, on the other hand, causes urine leakage due to bladder spasms or untimely contractions. Symptoms of both stress and urge incontinence may be experienced at the same time and is most often referred to as mixed incontinence. While some causes of UI can be attributed to medications or urinary tract infection and may improve after treating the cause, in most cases of urinary incontinence, the cause is difficult to target. In any case, urinary incontinence is embarrassing and uncomfortable and can severely disrupt the quality of life. Pelvic floor muscle training (PFMT) is considered first line treatment for UI and is aimed to target the pelvic musculature. It is a noninvasive education and exercise program that involves repeated voluntary contraction of the pelvic floor musculature building strength, endurance and coordination. Biofeedback is often included in PFMT in an effort to promote adherence and efficiency through the contraction and timing of the correct muscles. Biofeedback is also used to assess improvement over time (Berghmans, Hendriks et al. 1998; Domoulin and Hay-Smith 2010). In the same way, intravaginal electrical stimulation (IVES) also targets the pelvic musculature by sending a mild electric current intended to trigger muscle contraction and, consequently, a strengthening effect similar to that of PFMT. It has also been hypothesized that the electrical stimulation encourages growth of nerve cells that cause the muscles to contract (Schreiner, Santos et al. 2013). In any case, the technology is designed to be used at-home for acute and on-going treatment. With a variety of devices on the market, the technology, in its simplest form, consists of a unit with built in surface electrodes that can be temporarily inserted into the vagina. Most of the devices also come with a hand-held controller allowing the regulation of current and duration. Several IVES devices have been approved by the U.S. Food and Drug Administration (FDA) as class II devices under the non-implanted electrical continence device classification.

04/21/2014: MTAC REVIEW

Intravaginal Electrical Stimulation for Urinary Incontinence

Evidence Conclusion: In 1996, Smith randomized 18 women with genuine stress urinary incontinence to either PFMT or IVES. After at least 16 weeks of treatment, 44% of the patients in the PFMT group showed objective improvement with one patient reported as cured, three with improvement and the remaining five with no significant improvement. In the IVES group, however, there was 66% improvement with two cured patients, four with improvement and three failures. Smith concludes that the device is safe, however, there was no discussion or reports of either how safety was measured or if data on adverse events were routinely collected. In addition, Smith concludes that IVES is at least as effective as PFMT, however, the total number of patients in the group was small and not statistically significant (Smith 1996). [Evidence Table 1] In an attempt to assess the effectiveness of physiotherapeutic treatment modalities in women with proven urge urinary incontinence Berghmans and colleagues randomized 68 patients to one of four treatment arms. With one control group of patients receiving no treatment, the remainder of the groups received IVES, PFMT or both. The primary outcome measure, the DAI, is a combined parameter that quantifies bladder over activity using a score between 0 and 1 where ‘0’ represents no activity and ‘1’ represents severe over activity. Ultimately, the investigators concluded that IVES was the only effective treatment for urge urinary incontinence, with a 0.28 difference in DAI score between pre- and post-treatment, but this conclusion is prone to bias as the intended sample size was 80 and only 68 patients were included in the ITT analysis (Berghmans, van Waalwijk van Doorn et al. 2002). [Evidence Table 2]. IVES treatment was compared to PFMT in a trial including 35 women aged 65 or older. The control group was given verbal instruction on how to perform Kegel exercises while the IVES group received maximal IVES for 30

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minutes three times a week. With several objective and subjective outcomes being measured the authors make several conclusions regarding treatment with IVES of one of which claims high physical and emotional cost for the treated individuals. It is unclear how they came to this conclusion as there is no mention of any kind of QoL questionnaires nor was there systematic collection of adverse effects. In terms of the effectiveness of the IVES device, the authors report no significant improvement in objective outcomes and deem it unreasonable to advise elderly women to undertake this treatment (Spruijt, Vierhout et al. 2003). [Evidence Table 3]. Limitations of the reviewed evidence include small study populations which limit the ability to rule out the role of chance as an explanation of findings and short follow-up times, which limit conclusions regarding the durability of any treatment effects. Data on adverse events and outcomes were not systematically collected in any of the selected studies. Any benefit observed in the urge and stress urinary incontinence studies do not appear to be superior to less invasive treatments such as PMFT. In general, the studies are significantly heterogeneous in their methodology and follow up and suffer from variation in stimulation parameters. Ultimately, there is no clear demonstration that IVES results in improved health outcomes in patients in the long run.
Conclusion: There is insufficient evidence to support the treatment of mixed urinary incontinence with IVES. There is insufficient evidence to support the treatment of stress urinary incontinence with IVES. There is insufficient evidence to support the treatment of urge urinary incontinence with IVES. There is insufficient evidence to support the safety of IVES in females with urinary incontinence.
Articles: The search initially revealed over 700 publications related to urinary incontinence. Articles were screened for comparison studies investigating intravaginal electrical stimulation (IVES) treatment for incontinent females after which the literature was narrowed down to 21 randomized controlled trials (RCTs) summarized in tables 1, 2 and 3. The studies varied in the treatment of urinary incontinence ranging from stress urinary incontinence, to urge and mixed urinary incontinence and none were powered to determine equivalence. In addition, IVES treatment was compared to several different treatment options including various nonpharmacologic, pharmacologic and surgical. Studies that compared IVES to PFMT were selected for critical appraisal. The following studies were selected for review: Smith, JJ. Intravaginal stimulation randomized trial. The Journal of Urology. 1996;155:127-130 Evidence Table 1. Berghmans B, van Waalwijk van Doorn E, Nieman F, et al. Efficacy of physical therapeutic modalities in women with proven bladder overactivity. European Urology. 2002;41:581-587 Evidence Table 2. Spruijt J, Vierhout M, Verstraeten R, et al. Vaginal electrical stimulation of the pelvic floor: a randomized feasibility study in urinary incontinent elderly women. Acta Obstet Gynecol Scand. 2003;82:1043-1048 Evidence Table 3.

The use of IVES does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Radiofrequency Bladder Neck Suspension / Transurethral Radiofrequency Energy Tissue Remodeling for Treatment of Stress Urinary Incontinence (TRETRTSUI)

BACKGROUND

Urinary incontinence is a common symptom that affects women of all ages. Stress urinary incontinence is one of the most common types of urinary incontinence and is defined as the involuntary leakage of urine on exertion, sneezing, or coughing. Risk factors for stress urinary incontinence include obesity, pregnancy, and childbirth (Deng 2011, Rogers 2008). Treatment options for stress urinary incontinence include conservative measures, pharmacotherapy, and surgical interventions. Conservation treatments such as weight loss, pelvic floor muscles exercise (also known as Kegel exercises), as well as other behavioral and lifestyle modifications are the first-lines of treatment for stress urinary incontinence. Duloxetine, a combined serotonin and norepinephrine reuptake inhibitor, has shown some efficacy for the treatment of stress urinary incontinence; however, it failed to obtain FDA approval due to concerns for liver toxicity and suicidal events. Currently, there are no FDA approved drug therapies for stress urinary incontinence. Surgical therapy is indicated for patients who have not responded to conservative treatment options. Surgical interventions include retropubic colposuspension (Burch suspension), midurethral or bladder neck slings, injection of urethral bulking agents, and tension-free vaginal tape (Deng 2011, Rogers 2008). Transurethral radiofrequency micro-remodeling has been proposed as a minimally invasive treatment for stress incontinence among women who fail conservative therapies. In this procedure, controlled, low-level radiofrequency energy results in localized collagen denaturation. This leads to reduced regional dynamic tissue compliance without creating stricture or reducing luminal caliber (Appell 2008, Elser 2009).
Another radiofrequency treatment for stress urinary incontinence is transvaginal radiofrequency bladder neck suspension. This approach differs from the transurethral procedure in two ways. First, the transvaginal procedure is a surgical procedure whereas the transurethral procedure is a non-surgical procedure that does not require an incision. Second, higher levels of radiofrequency energy are used in the transvaginal procedure. These higher levels of energy result in higher temperatures which causes tissue necrosis instead of collagen denaturation to reduce involuntary urinary leakage (Appell 2008).

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Radiofrequency Bladder Neck Suspension / Transurethral Radiofrequency Energy Tissue Remodeling for Treatment of Stress Urinary Incontinence (TRETRTSUI)

Evidence Conclusion: The best available evidence on TRETRTSUI is in case series reports, the weakest study design due to the potential for selection and observation bias and lack of a control or comparison group. The case series articles on the SURx laparoscopic and transvaginal systems suggest a substantial decrease in incontinence episodes 12 months after the procedure compared to baseline. In addition to type of study design, these studies are limited by the strong financial links between the authors and the SURx company, which could bias the design, analysis and/or reporting of results.

Articles: The Medline search yielded 4 articles. There were no randomized or non-randomized controlled trials. There was one case series on the SURx Transvaginal system that was critically appraised. In addition, there were two publications using the SURx Laparoscopic system that reported on the same series of patients. These two articles were critically appraised in the same evidence table. No published studies on the Novasys product were identified. SURx Transvaginal study: Dmochowski RR, Avon M, Ross J et al. Transvaginal radiofrequency treatment of the endopelvic fascia: A prospective evaluation for the treatment of genuine stress urinary incontinence. *J Urol* 2003; 169: 1028-1032. See Evidence Table. SURx Laparoscopic study: Fulmer BR, Sakamoto K, Turk TM et al. Acute and long-term outcomes of radiofrequency bladder neck suspension. *J Urol* 2002; 167: 141-145.Ross JW, Galen DI, Abbott K. et al. A prospective multisite study of radiofrequency bipolar energy for treatment of genuine stress incontinence. *J Am Assoc Gynecol Laparosc* 2002; 9: 493-499. See Evidence Table.

The use of Transurethral Radiofrequency Energy Tissue Remodeling in the treatment of Stress Urinary Incontinence does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

06/20/2011: MTAC REVIEW

Radiofrequency Bladder Neck Suspension / Transurethral Radiofrequency Energy Tissue Remodeling for Treatment of Stress Urinary Incontinence (TRETRTSUI)

Evidence Conclusion: A randomized controlled trial that included 173 women evaluated the safety and efficacy of transurethral radiofrequency micro-remodeling for the treatment of female stress urinary incontinence compared to sham treatment. There were two primary outcomes for this study – quality of life and leak pressure point (LPP). An improvement in quality of life was defined as a 10 point or greater increase on the Incontinence Quality of Life (I-QOL) score. After 12 months of follow-up, 48% of subjects in the intervention group and 44% in the control group experienced an improvement in quality of life (P=0.07). However, in patients with moderate to severe stress urinary incontinence (I-QOL score of 0 to 60 points), 74% of subjects in the intervention group compared to 50% in the control group experienced an improvement in quality of life (P=0.03). There was no significant difference in the percent of subjects with mild stress urinary incontinence (I-QOL score of 61 to 90 points) who experienced an improvement in quality of life (intervention=22% vs. control=35%, P=0.02). Women in the intervention group experienced an increase in LPP at 12 months (13.2 ± 39.2 cmH_2O), while women in the control group experienced a decrease in LPP (-2.0 ± 33.8 cmH_2O) (P=0.02). There was no significant difference in adverse events between the two treatment groups. The most commonly reported adverse events were wet overactive bladder and dysuria (Appell 2006). This trial had several methodological limitations: an intent-to-treat analysis was not performed; it is not clear if the investigators were blinded; power was not assessed; and it is not stated if the subgroup analyses were planned. An interim analysis from a prospective case-series that included 139 women with stress urinary incontinence who had failed conservative treatments and had not undergone surgery or bulking agent treatment also evaluated the safety and long-term efficacy of transurethral radiofrequency micro-remodeling for the treatment of female stress urinary incontinence. After 18 months, patients experienced significant reductions in the median number of leaks per day (-0.43, range -34.3 to 18.9, P=0.006) and per week (-3.0 range -240.0 to 132.0, P=0.006) compared to baseline. Additionally, 46.7% of patients had at least 50% fewer leaks (P<0.0001) compared to baseline. With regard to quality of life, 65 patients (47.8%) experienced at least a 10-point improvement in I-QOL score. During the first three days post-treatment, the most common adverse events were dysuria (N=7, 5.2%), urinary retention (N=6, 4.4%), post-procedure pain (N=4, 2.9%), and urinary tract infection (N=4, 2.9%). At 12 months, one patient reported an increase in leakage, which was probably treatment related. Between 12 and 18 months one patient experienced a myocardial infarction, which was determined to be unrelated to the treatment (Elser 2009). Results from this study should be interpreted with caution as this study is a case-series and therefore more prone to bias. Additionally, 73 subjects (53%) discontinued the study for various reasons. *Conclusion*: Transurethral radiofrequency micro-remodeling: Results from a randomized controlled trial with several methodological limitations suggest that transurethral radiofrequency micro-remodeling may be safe and effective for the treatment of female stress urinary incontinence. More studies are needed to address the durability of the effect and whether women who undergo transurethral radiofrequency micro-remodeling can subsequently undergo other procedures such as retropubic colposuspension (Burch suspension) or tension-free vaginal tape without undo complications. Transvaginal

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radiofrequency bladder neck suspension: There is insufficient information to determine the safety and efficacy of transvaginal radiofrequency bladder neck suspension for the treatment of female stress urinary incontinence.
Articles: *Assessment objective* to determine the safety and efficacy of transurethral radiofrequency micro-remodeling for the treatment of stress urinary incontinence. To determine the safety and efficacy of transvaginal radiofrequency bladder neck suspension for the treatment of stress urinary incontinence. Only one randomized controlled trial was identified that evaluated the safety and efficacy of transurethral radiofrequency micro-remodeling for the treatment of stress urinary incontinence. It was selected for review. Since the 2003 MTAC review, two retrospective cohort studies were identified that evaluated transvaginal radiofrequency bladder neck suspension for the treatment of stress urinary incontinence. As both of these studies included less than 25 participants, neither of them was selected for review (Buchsbaum 2007, Ismail 2008). The following study was critically appraised: Appell RA, Juma S, Wells WG, et al. Transurethral radiofrequency energy collagen micro-remodeling for the treatment of female stress urinary incontinence. *Neurourol Urodyn 2006;* 25: 331-336. See Evidence Table.

The use of Transurethral Radiofrequency Energy Tissue Remodeling in the treatment of Stress Urinary Incontinence does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

The use of transvaginal radiofrequency bladder neck suspension in the treatment of Stress Urinary Incontinence does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

SPARC® Sling for Treatment of Urinary Incontinence

BACKGROUND

Stress urinary incontinence (SUI) is defined as leakage of urine during activities that cause increased abdominal pressure such as exercise or coughing in the absence of a detrusor contraction. It is the most common form of urinary incontinence in women and is estimated to affect about 6.5 million women in the United States. Current understanding is that urinary continence during stress events requires both intact supportive structures (i.e. endopelvic fascia) and functioning neurological control of the muscles of the pelvic floor and urethra (Agarwala & Liu, 2002). Treatments for stress urinary incontinence include conservative therapies such as strengthening the pelvic floor muscles with Kegel exercises and devices such as electrical stimulation devices and pessaries. There are also medications such as estrogen and various surgical treatments. Surgical procedures for stress incontinence attempt to provide support to the bladder neck and/or urethra to limit the movement of these structures. Sling procedures are a surgical option for treating common stress urinary incontinence secondary to intrinsic sphincteric deficiency and urethral hypermobility. The sling procedure involves using abdominal fasci, cadaveric fasci or polypropylene mesh as sling material. The piece of muscle fiber or synthetic material is attached under the urethra and bladder neck and secured to the abdominal wall and pelvic bone. When the patient's abdominal fasci is used, an abdominal incision is required. Synthetic slings are generally inserted through a vaginal approach. Newer sling procedures include SPARC and tension-free vaginal tape (TVT). Both procedures place the sling under the urethra without tension that is intended to minimize disruption of normal urethral mobility. In addition, both use a sling made of loosely woven polypropylene mesh, require a relatively short operating time and can be performed under local anesthesia with sedation (Staskin & Plzak, 2002). The SPARC system differs from TVT in the way in which the sling is placed under the urethra. TVT passes the sling anchoring trocars from below, using a rigid catheter guide. In contrast, SPARC uses small diameter needles that are passed from above through two small suprapubic incisions". In addition, unlike TVT, the SPARC mesh has a knotted "tensioning suture" that allows adjustment of the sling (Staskin & Plzak, 2002).

08/13/2003: MTAC REVIEW
SPARC® Sling for Treatment of Urinary Incontinence
Evidence Conclusion: There is insufficient evidence to determine the effectiveness of the SPARC sling for the treatment of stress urinary incontinence in women. The single published empirical study reports only on 4 patients who experienced vaginal erosion after the SPARC procedure.
Articles: The search yielded 27 articles. Most of these were on related procedures such as tension-free vaginal tape. There was one empirical article on SPARC. This was a case series that presented data on 4 patients who experienced vaginal erosion of the mesh after the sling procedure. Due to the small sample size and the lack of data on the patients in the series who did not experience vaginal erosion, this study was not critically appraised.

The use of SPARC Sling in the treatment of urinary incontinence does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Urgent PC Neuromodulation System for Overactive Bladder; Percutaneous Tibial Nerve Stimulation (PTNS)

BACKGROUND

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Overactive bladder (OAB) is defined by the International Continence Society as the presence of urinary urgency with or without urge incontinence that is usually accompanied by frequency and nocturia, in the absence of urinary tract infection or other obvious pathology. Urgency, the hallmark of OAB, is defined as the sudden compelling desire to urinate, a sensation that is difficult to defer. Urinary frequency is defined as voiding 8 or more times in a 24-hour period. Nocturia is defined as the need to wake up one or more times per night to void. The National Overactive Bladder Evaluation (NOBLE) epidemiologic study estimated that 16.9% of adult women in the US had OAB syndrome; 9.3% with incontinence, and 7.6% without incontinence (Abrams 2002, Stewart 2003, Martinson 2013). OAB is not a disease but a symptom complex that is generally not life-threatening but has a significant impact on the quality of life, sleep, work productivity, social relationships, mental health, sexual and physical activity. Treatment options for overactive bladder can be divided into 1. Conservative measures as behavioral interventions and pharmacotherapy, and 2. More invasive procedures. Most treatments may improve patient symptoms but are unlikely to eliminate all symptoms. A successful treatment requires a participant who is motivated and well informed about the variable and chronic course of the condition. The first line treatment of OAB is typically behavioral interventions, which consist of bladder training, bladder control, pelvic floor muscle exercises, fluid management, and weight loss. Behavioral interventions may not eliminate all symptoms but lead to significant reductions of symptoms and improve the quality of life of most patients. Pharmacological therapy may be used in combination with behavioral intervention or as a second line treatment. Antimuscarinic drugs or anticholinergics lead to significant improvement in the patient symptoms but are commonly associated with side effects as dry mouth, blurred vision, urinary retention and infection, dyspepsia, and impaired cognitive function. Patients who fail behavioral and pharmacological therapy, who do not tolerate its side effects, or are not candidates for conservative therapy and still have bothersome symptoms, may be offered alternative invasive measures. These include invasive surgical procedures e.g. bladder denervation, detrusor myomectomy, urinary diversion, bladder augmentation, neobladder construction, and others. Surgical procedures have variable cure rates and adverse events. Other less invasive options include detrusor injection with botulinum toxin (BTX), and pelvic neuromodulation therapy (Ridout 2010, Peters 2009, 2010, 2012, Gormley 2012). Pelvic neuromodulation utilizes electrical stimulation to target specific nerves in the sacral plexus that control the pelvic floor and bladder functions. Neuromodulation is either invasive using implantable sacral nerve stimulation (SNS), or minimally or noninvasive using a removable device such as transvaginal or transanal electrostimulation, magnetic stimulation, or percutaneous tibial nerve stimulation (PTNS). The specific mechanism of action is unknown, but it is thought that neuromodulation may have a direct effect on the bladder or a central effect on the micturition centers in the brain. Neuromodulation of the sacral nerve, also known s pacemaker for the bladder, uses mild electrical pulse to activate or inhibit neural reflexes by continuously stimulating the sacral nerves that innervate the pelvic floor and lower urinary tract. A unilateral lead is implanted in the vicinity of S3 nerve root and attached to a small pacemaker placed within a subdermal pocket in the buttock region. SNS therapy was found to be effective for refractory OAB but is invasive and associated with adverse events related to the implant procedure, the presence of the implant, or due to undesirable stimulation. In addition, SNS requires reoperation to replace the implantable generator due to the limited longevity of the neurostimulator. The SNS technology continues to evolve (Peters 2009, 2010, 2012, Al-Shaiji 2011, Mossdoeff-Steinhauser 2013). PTNS, also known as Stoller afferent nerve stimulation (SANS), developed by Stoller in the late 1990s, is a form of peripheral neuromodulation. It is a minimally invasive, office-based procedure that involves percutaneous insertion of a fine (34-guage) needle at the level of the posterior tibial nerve, slightly above the medial alveolus of the ankle (the insertion point for the needle corresponds with an acupuncture point used for a variety of urinary disorders). The needle is connected to a low voltage (6V) stimulator device with 0-10mA at a fixed frequency of 20Hz. The amplitude is increased until the toes are seen to fan or the big toe to flex. The current is set at the highest tolerated level and the stimulation is continued for 30 minutes. Neuromodulation to the pelvic floor is delivered through the S2-S4 junction of the sacral nerve plexus through the posterior tibial nerve. During the initial therapy, treatment is delivered for 30 minutes and repeated weekly for 12 weeks. OAB is a chronic disease and patients who respond to PTNS may need to receive long-term therapy in order to sustain the benefit of PTNS therapy (Peters 2009, Shaiji 2011, Burton 2012, Martinson 2013, Mossdddorff-Steinhauser 2013).

PTNS was approved by the FDA in 2000 as an office-based therapy for OAB.

10/01/2007: MTAC REVIEW
Urgent PC Neuromodulation System for Overactive Bladder; Percutaneous Tibial Nerve Stimulation (PTNS)
Evidence Conclusion: There is insufficient evidence to determine the safety and efficacy of percutaneous tibial nerve stimulation (PTNS) for treating urinary urgency, urinary frequency and urge incontinence. No published randomized or non-randomized controlled trials were identified. This is particularly problematic because there is known to be a high placebo effect in studies evaluating treatments for urinary incontinence. Only case series were available. A team based in the Netherlands published several case series that used either the Urgent PC

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Neuromodulation System (Uroplasty) or a precursor of this device. The studies were conducted before FDA approval. Results of the case series on the Urgent PC were similar. Vandoninck et al. (2003), for example, reported a substantial reduction in incontinence episodes and voiding frequency at the end of treatment among patients for whom data were available. Two other case series were evaluated. Both of these utilized the PerQ Sans (UroSurge), a device similar to the Urgent PC. It is not known whether the PerQ Sans is currently commercially available in the U.S. The Ruiz (2004) and Govier (2001) case series found significant improvement in urinary incontinence symptoms. One study was conducted in the United States; two of the five authors in the U.S. study reported financial relationships with the device manufacturer. Other limitations of the case series include missing data and lack of long-term follow-up.

Articles: The ideal study is a randomized controlled trial comparing PTNS to a placebo and/or alternative established intervention. No randomized controlled trials or non-randomized comparison studies were identified. The search yielded only case series. Sample sizes ranged from 11 to 132, most were in the range of 35 to 55 patients. Seven out of the 10 case series identified were conducted by the same research group in the Netherlands. The articles differed on the indications for treatment (urge incontinence, overactive bladder syndrome, etc.) and the outcomes reported. The largest case series from the Netherlands team, and two other case series (one conducted in Spain, the other in the U.S.) were critically appraised. The remaining case series was excluded because they did not report clinical outcomes. A news release from Uroplasty in July 2006 stated that the company is initiating a randomized controlled trial comparing Urgent PC to anticholinergic medication for patients with symptoms of urge incontinence and urgency and frequency. The announcement did not report the expected date of study completion. *The studies critically appraised in evidence tables are:*

Vandoninck V, van Balken MR, Agro EF et al. Percutaneous tibial nerve stimulation in the treatment of overactive bladder: Urodynamic data. Neurol Urodynam 2003; 22: 227-232. See Evidence Table. Ruiz BC, Outeirino P, Martinez PC et al. Peripheral afferent nerve stimulation for treatment of urinary tract irritative symptoms. Eur Urol 2004; 45: 65-67. See Evidence Table. Govier FE, Litwiller S, Nitti V et al. Percutaneous afferent neuromodulation for the refractory overactive bladder: Results of a multicenter study. J Urol 2001; 165: 1193-1198. See Evidence Table.

The use of Percutaneous Tibial Nerve Stimulation in the treatment of overactive bladder does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

04/15/2013: MTAC REVIEW

Urgent PC Neuromodulation System for Overactive Bladder; Percutaneous Tibial Nerve Stimulation (PTNS)

Evidence Conclusion: The larger published randomized controlled trials on the use of PTNS for overactive bladder syndrome were mainly supported by the manufacturer of the PTNS system and conducted by the same group of researchers who had financial interest and/or other relationships with the manufacture. PTNS was compared either to sham therapy or to antimuscarinic drugs. No comparisons were made versus behavioral therapy or other methods of neuromodulation as sacral nerve stimulation. There were variations between published studies in the inclusion criteria, gender, severity and duration of symptoms, previous treatments, treatment protocol, number of sessions per week during therapy, and treatment intervals during maintenance therapy. Outcome measures were mainly subjective and based on reported patient diaries. No well-conducted trials with long term follow-up and objective urodynamic outcomes were identified. Definition of response or treatment success varied between studies. Burton et al (2012), meta-analysis of randomized and prospective trials showed that the success rate varied from 37-82%. Two of the published RCTs (ORBIT and SUmiT) were followed by reports on mid-term follow-up (12 months for ORBIT and up to 36 months for SUmiT), but only the responders to PTNS (60-70% of those receiving the PTNS therapy) were included in the follow-up studies. Studies showed that OAB symptoms worsen after discontinuation of treatment, and that maintenance therapy, is needed to avoid recurrence of symptoms.

Comparison of PTNS vs. Sham therapy

Peters and colleagues (2010) compared the efficacy of PTNS to sham therapy in 220 adult men and women with OAB (SUmiT trial, evidence table 1). The results showed a statistically significant improvement in bladder symptoms in the PTNS group compared to sham therapy group, with some non-serious adverse events. However, only just over half the patients (54.5%) who received the PTNS therapy showed moderate or marked response to the therapy, almost two third of the patients still had urinary urge incontinence after 12 weeks of PTNS, and more than half still complained of urinary urgency and frequency.

In another sham-controlled, but small and single-blinded trial, Finazzi-Agro and colleagues (2010) randomized 35 women with OAB who did not respond to antimuscarinic therapy to receive PTNS or a sham therapy for 12 sessions. The sessions were performed for 30 minutes three times weekly. Patients with a 50% or greater

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reduction in urge incontinence episodes were considered responders. The primary outcome was the percent of responders in the two groups. The results of the trial showed that 12/17 (71%) of the patients randomized to PTNS reported a 50% or greater reduction in incontinence episodes compared to none of those in the sham therapy. Improvement in the number of incontinence episodes, number of voids, voided volume, and incontinence quality of life score were statistically significant in the PTNS group but not in the sham therapy group.
Comparison of PTNS vs. active therapy with extended-release tolterodine
In the OrBIT trial (evidence table 2), Peters and colleagues compared the effectiveness of PTNS to extended-release tolterodine (Detrol LA) in reducing OAB symptoms. The trial included 100 adults with OAB symptoms, at least 8 voids/24 hours, and with or without a history of anticholinergic drug use. The primary outcome of the trial was the reduction in frequency of urinary voids /24 hours. The study was randomized and controlled, but it was not blinded, and the outcomes were subjective, which does not allow ruling out the placebo effect of PTNS. The patients in the two arms were observed differently during follow-up (visits were made in person for the PTNS group and by phone for the Detrol La group). The duration of follow- was only 12 weeks, the dropout rate was >15%, and analysis was not based on ITT. The study was supported by the manufacturer, and the authors had financial interest with the industry. The results of the OrBIT trial showed a significantly higher improvement in the Global Response Assessment rate with PTNS compared to Detrol LA when self-reported, but not when assessed by the investigator. There was no significant difference in the OAB symptom improvement between the two treatment groups.
Articles: The literature search for studies published after the 2007 MTAC review of PTNS for the treatment of overactive bladder in adults revealed four randomized controlled trials, two of which were conducted by the same group of authors (SUmiT and OrBIT trials) and two had additional publications with extended follow-up data (2 and 3 years follow-up of SUmiT were published as STEP trial). The search also identified two systematic reviews (one with a meta-analysis) of studies on the effect of PTNS for overactive bladder, and an updated Cochrane review that compared anticholinergic drug vs. non-drug active therapies for OAB in adults. The two larger trials and the meta-analysis on the effectiveness of PTNS for OAB were selected for critical appraisal: Burton C, Sajja A, Latthe PM. Effectiveness of percutaneous posterior tibial nerve stimulation for overactive bladder: a systematic review and meta-analysis. *Neurourol Urodyn.* 2012 ;31 :1206-1216. See Evidence Table. MacDiarmid SA, Peters KM, Shobeiri SA, et al. Long-term durability of percutaneous tibial nerve stimulation for the treatment of overactive bladder. *J Uro*l.2010; 183:234-240. See Evidence Table. Peters KM, Carrico DJ, Perez-Marrro RA, et al. Randomized trial of percutaneous tibial nerve stimulation versus Sham efficacy in the treatment of overactive bladder syndrome: results from the SUmiT trial. *J Uro*l.2010; 183:1438-1443. See Evidence Table. Peters KM, Carrico DJ, *MacDiarmid SA,* et al Sustained therapeutic effects of percutaneous tibial nerve stimulation: 24-month results of the STEP study. *Neurourol Urodyn* 2013; 32:24-29. See Evidence Table. Peters KM, Carrico DJ, Woolridge LS Percutaneous Tibial Nerve Stimulation (PTNS) for the Long-Term Treatment of Overactive Bladder: Three-Year Results of the STEP Study. *J Urol.* 2012*;* Dec. See Evidence Table. Peters KM, MacDiarmid SA, Woolridge LS, et al. Randomized trial of percutaneous tibial nerve stimulation versus extended-release tolterodine: results from the overactive bladder innovative therapy trial. *J Uro*l.2009; 182:1055-1061. See Evidence Table

The use of Percutaneous Tibial Nerve Stimulation in the treatment of overactive bladder does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Bladder Pacemaker /Sacral Nerve Stimulation for Treatment of Urinary Incontinence

BACKGROUND

Urinary incontinence (UI) refers to an involuntary leak of urine. There are several types of UI. Stress UI, the most common form, is an involuntary leak on effort or exertion and urge UI is an involuntary leak accompanied or immediately preceded by a sense of urgency. Mixed UI is a combination of stress and urge UI. A related condition is urinary retention, the inability to completely empty the bladder. Another diagnosis is overactive bladder syndrome (OAB), an urge that occurs with us without a leak of urine, and usually occurs with increased urinary frequency and nocturia. The condition is often categorized as either OAB dry (without incontinence) or OAB wet (with incontinence). The prevalence of urinary incontinence in women is approximately 50% when defined as any urine loss and is 8-36% when limited to bothersome urine loss. About half of all cases are stress incontinence. Urinary incontinence that is severe enough it cannot be easily concealed can have a major impact on quality of life, especially if it includes urinary urgency. Severe urinary incontinence has been found to increase the risk of urinary tract infections in post-menopausal women, and the risk of falls and hip fractures in elderly women (Gray, 2005). Treatments for urge incontinence include the use of absorbent pads, bladder training/pelvic floor muscle exercises, treatment with medications (anti-cholinergic agents, antispasmodics, tricyclic antidepressants), topical estrogen, pelvic floor electrical stimulation, and surgery. The most common treatment for urinary retention is self-catheterization. Sacral nerve stimulation using an implantable device (bladder pacemaker) is proposed as an additional alternative to surgery for patients with urge incontinence, urgency-frequency symptoms or urinary

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retention. (It is not proposed for stress incontinence, the most common form of urinary incontinence). The InterStim Therapy for Urinary Control is an FDA-approved device developed by Medtronic. Consistent with the protocol in clinical trials, patients undergo percutaneous test stimulation in an outpatient setting before implantation. This involves insertion of an electrode into a sacral foramen. An external device produces continuous stimulation. The implantable InterStim system uses an implanted lead stimulating the appropriate sacral nerve root, most commonly S3. The proximal part of the lead is tunneled under the skin and connected to the neurostimulator which is placed in a subcutaneous pocket in the lower abdomen. The physician can use a microprocessor-based console programmer to set stimulation settings. There is also a handheld programmer that patients can use to turn the stimulator on and off, and to adjust the voltage output amplitude. The battery operating the device is expected to last 7 to 9 years. It is challenging to evaluate the efficacy of treatments for urinary incontinence because there is no gold standard for outcome assessment. In addition, there is a high placebo effect in randomized incontinence studies; as many as 30-40% of patients in placebo groups report success. The high placebo effect has been attributed to several factors including the strong subjective component in voiding dysfunction, and potentially therapeutic effects of study design components such as keeping a voiding diary and interacting with study personnel (Dmochowski, 2001). Because of the high placebo effect, in order to show that an intervention is effective, it is necessary to show that it has an impact beyond that of a placebo. Sacral nerve stimulation for urinary incontinence was reviewed by MTAC in February 1999 and February 2001. The technology did not meet MTAC evaluation criteria. An evidence update was conducted outside of MTAC in October 2002. The GHP Urology Department has requested an updated review.

01/2001: MTAC REVIEW
Bladder Pacemaker /Sacral Nerve Stimulation for Treatment of Urinary Incontinence
Evidence Conclusion: The Schmidt et al. study found a significant improvement in urinary incontinence symptoms at 6 months among patients who received an InterStim device compared to patients receiving standard medical treatment. This study has several threats to validity including substantial selective loss to follow-up, self-report data and lack of blinding or intention-to-treat analysis. Moreover, the research team had with financial ties to the manufacturer of the device. Due to the potential biases in this study, the existing data are insufficient to permit conclusions about the effectiveness of this technology.
Articles: Eleven articles were identified. Six articles were not directly relevant, did not include clinical outcomes or were review articles; five articles presented empirical data on clinical outcomes. Articles were selected based on study type. There were three randomized controlled trials (RCTs) and two case series. The three RCTs were done by a single group of investigators. Only one of the 3 RCTs were examining urinary incontinence as the outcome. An evidence table was created for this RCT: Schmidt RA, Jonas U, Oelson KA, Janknegt RA, Hassouna MM, Siegel SW, Kerrebroek for the Sacral Nerve Stimulation Study Group. J Urol 1999; 162: 352-57. See Evidence Table.

The use of sacral nerve stimulation for the treatment of urinary incontinence does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

10/2002: MTAC REVIEW
Bladder Pacemaker /Sacral Nerve Stimulation for Treatment of Urinary Incontinence
Evidence Conclusion: The RCT that generated the three reports was done by the same multinational research team and was funded by Medtronic, the device manufacturer. All of the three first authors had financial relationships with Medtronic. The articles reviewed included the identical intervention for urology patients with different presenting symptoms (urge incontinence, urgency-frequency and non-obstructive urinary retention) and were limited by the same biases. The RCT compared implantation of the Interstim device to standard medical treatment for 6 months, among patients who demonstrated during a 3-7-day testing period that they responded to the Interstim device. All found that sacral nerve stimulation was superior to standard medical care during the 6 months before patients in the control group were offered implantation. Bias was introduced because 1) only patients who were shown to respond to the device were included (about 45% of otherwise eligible patients); 2) Treatment was not blinded and did not allow for a placebo effect of the Interstim device and; 3) The intervention was compared to standard medical treatment, which the patients had already failed. A more valid comparison would be to implant the device in all eligible patients and randomly assign patients to receive active stimulation or no stimulation (this type of placebo control group was used in studies of biventricular pacing).
Articles: The search yielded 17 articles, many of which were review articles, opinion pieces, dealt with technical aspects of the procedures or addressed other, similar treatments. There were three articles on a single randomized controlled trial and five case series. The three RCT articles reported on different patient populations enrolled in the same trial (those with urge incontinence, urgency-frequency and non-obstructive urinary retention) and were all critically appraised. The Schmidt study was included in the February 2001 MTAC review. Evidence tables were created for the following articles: Schmidt RA, Jonas U, Oleson KA et al. Sacral nerve stimulation for
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treatment of refractory urinary urge incontinence. *J Urol* 1999; 162: 352-357. See Evidence Table. Hassouna MM, Siegel SW, Lycklama AAB et al. Sacral neuromodulation in the treatment of urgency-frequency symptoms: A multicenter study on efficacy and safety. *J Urol* 2000; 163: 1849-1854. See Evidence Table. Jonas U, Fowler J, Chancellor B et al. Efficacy of sacral nerve stimulation for urinary retention: Results 18 months after implantation. *J Urol* 2001 165: 15-19. See Evidence Table.

The use of sacral nerve stimulation for the treatment of urinary incontinence does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

10/01/2007: MTAC REVIEW

Bladder Pacemaker /Sacral Nerve Stimulation for Treatment of Urinary Incontinence

Evidence Conclusion: The RCT that generated the three reports was done by the same multinational research team and was funded by Medtronic, the device manufacturer. All of the three first authors had financial relationships with Medtronic. The articles reviewed included the identical intervention for urology patients with different presenting symptoms (urge incontinence, urgency-frequency and non-obstructive urinary retention) and were limited by the same biases. The RCT compared implantation of the InterStim device to standard medical treatment for 6 months, among patients who demonstrated in a 3-7-day testing period that they responded to the device. All found that sacral nerve stimulation was superior to standard medical care during the 6 months before patients in the control group were offered implantation. Bias was introduced because 1) only patients who were shown to respond to the device were included (about 45% of otherwise eligible patients); 2) treatment was not blinded and did not allow for a placebo effect of the InterStim device and; 3) the intervention was compared to standard medical treatment, which the patients had already failed. A more valid comparison would be to implant the device in all eligible patients and randomly assign patients to receive active stimulation or no stimulation (this type of placebo control group was used in studies of biventricular pacing). An alternative study design to evaluate the effectiveness of InterStim among patients who respond to a test trial would be to compare InterStim to a different treatment that patients had not already failed. Especially in a non-blinded study with some subjective outcomes, bias can be introduced if one group perceives that they are receiving a new and innovative treatment and the other group is receiving the same treatment they have already received. There are no new RCTs to supplement the above data.

Articles: The ideal study would be a randomized controlled trial comparing InterStim therapy to a placebo and/or established alternative intervention. At the time of the 2002 evidence review, conducted outside of the MTAC meeting, there were several RCTs by the same group of investigators. The RCTs compared InterStim to standard medical therapy. No new RCTs evaluating the efficacy and/or safety of the InterStim device were identified. There was one additional publication on the original RCT, evaluating psychosocial outcomes in a subset of the study population (Das et al., 2004; Urol). One new RCT was identified on a related topic, comparing two methods for predicting which patients would proceed to device implantation (Borawski et al., 2007). The study did not compare the effectiveness of InterStim treatment compared to placebo or an alternative treatment and was thus not reviewed further. In addition, there were several new case series with sample sizes of approximately 30 patients. Since higher grade evidence has been published, the small case series were not reviewed. *The RCTs on InterStim that have been critically appraised are* Schmidt RA, Jonas U, Oelson KA et al. for the Sacral Nerve Stimulation Study Group. J Urol 1999; 162: 352-57. See Evidence Table. Hassouna MM, Siegel SW, Lycklama AAB et al. Sacral neuromodulation in the treatment of urgency-frequency symptoms: A multicenter study on efficacy and safety. J Urol 2000; 163: 1849-1854. See Evidence Table. Jonas U, Fowler J, Chancellor B et al. Efficacy of sacral nerve stimulation for urinary retention: Results 18 months after implantation. J Urol 2001 165: 15-19. See Evidence Table.

The use of sacral nerve stimulation for the treatment of urinary incontinence does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Sacral Nerve Stimulator

2/11/2013: MTAC REVIEW

Evidence Conclusion: Based on evidence from one randomized controlled trial and several observational studies, the Kaiser Medical Technology Assessment Team found that the evidence on the safety and efficacy of sacral nerve stimulation for treating severe fecal incontinence is of insufficient quality and quantity to determine whether sacral nerve stimulation is medically appropriate for the treatment of fecal incontinence. The best evidence comes from the randomized controlled trial conducted by Tjandra and colleagues (see below) (Kaiser 2011).

Results from a RCT that included 120 patients with severe fecal incontinence suggest that compared to optimal medical therapy patients who were treated with sacral nerve stimulation had significantly fewer incontinence episodes per week, days with incontinence, days with straining, and significantly better quality of life at 12

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These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage.
Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

months. Adverse events included pain at implant site, seroma, and excessive tingling in the vaginal region. All patients in the sacral nerve stimulation group needed the program readjusted. The mean number of readjustments per person was three. Adjustments included changes in the electrode used for stimulation as well as changes in amplitude and rate. This study had several limitations: power was not assessed, results are only applicable to patients with severe incontinence, and patients included in the study were refractory to medical therapy and pelvic floor exercises, which was the control group treatment (Tjandra 2008).
Conclusion: There is limited evidence on the safety and efficacy of sacral nerve stimulation for the treatment of fecal incontinence.
Articles: In February 2011, Kaiser Permanente's Medical Technology Assessment Team reviewed implantable sacral nerve stimulators for fecal incontinence. The randomized controlled trial that was included in the Kaiser technology assessment was also selected for review as this was the highest quality study assessing the effects of sacral nerve stimulation for the treatment of fecal incontinence. Since the Kaiser Technology Assessment, several observational studies were identified that evaluated the effects of sacral nerve stimulation. None of these studies were selected for review as they did not compare sacral nerve stimulation to other treatments.
The following study and technology assessment were selected for review: Kaiser Permanente. Implantable sacral nerve stimulators for severe fecal incontinence. February 2011;
http://pkc.kp.org/national/cpg/intc/topics/03_19_125.html
Accessed November 6, 2012.

The use of Sacral Nerve Stimulation for Fecal Incontinence meets the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
53860	Transurethral radiofrequency micro-remodeling of the female bladder neck and proximal urethra for stress urinary incontinence
64561	Percutaneous implantation of neurostimulator electrode array; sacral nerve (transforaminal placement) including image guidance, if performed
64566	Posterior tibial neurostimulation, percutaneous needle electrode, single treatment, includes programming
64581	Incision for implantation of neurostimulator electrode array; sacral nerve (transforaminal placement)
0587T	Percutaneous implantation or replacement of integrated single device neurostimulation system including electrode array and receiver or pulse generator, including analysis, programming, and imaging guidance when performed, posterior tibial nerve
0588T	Revision or removal of integrated single device neurostimulation system including electrode array and receiver or pulse generator, including analysis, programming, and imaging guidance when performed, posterior tibial nerve
E0740	Nonimplanted pelvic floor electrical stimulator, complete system
E0746	Electromyography (EMG), biofeedback device
L8603	Injectable bulking agent, collagen implant, urinary tract, 2.5 ml syringe, includes shipping and necessary supplies
L8604	Injectable bulking agent, dextranomer/hyaluronic acid copolymer implant, urinary tract, 1 ml, includes shipping and necessary supplies
L8606	Injectable bulking agent, synthetic implant, urinary tract, 1 ml syringe, includes shipping and necessary supplies

Biofeedback:

Effective until August 1, 2024
Non-Medicare—Considered Not Medically Necessary:
Medicare—Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

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CPT® or HCPC Codes	Description
90901	Biofeedback training by any modality
90912	Biofeedback training, perineal muscles, anorectal or urethral sphincter, including EMG and/or manometry, when performed; initial 15 minutes of one-on-one physician or other qualified health care professional contact with the patient
90913	Biofeedback training, perineal muscles, anorectal or urethral sphincter, including EMG and/or manometry, when performed; each additional 15 minutes of one-on-one physician or other qualified health care professional contact with the patient (List separately in addition to code for primary procedure)

Effective August 1, 2024
Non-Medicare—Medical necessity review no longer required:
Medicare—Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
90901	Biofeedback training by any modality
90912	Biofeedback training, perineal muscles, anorectal or urethral sphincter, including EMG and/or manometry, when performed; initial 15 minutes of one-on-one physician or other qualified health care professional contact with the patient
90913	Biofeedback training, perineal muscles, anorectal or urethral sphincter, including EMG and/or manometry, when performed; each additional 15 minutes of one-on-one physician or other qualified health care professional contact with the patient (List separately in addition to code for primary procedure)

Sling Procedures for Urinary Incontinence
Effective until August 1st, 2024
Non-Medicare—Considered Not Medically Necessary
Medicare—Considered Medically Necessary when criteria in the applicable policy statements listed above are met

**Requires review for level of care: Elective Surgical Procedures*

CPT® or HCPC Codes	Description	IP only
51840	Anterior vesicourethropexy, or urethropexy (eg, Marshall-Marchetti-Krantz, Burch); simple	x
51841	Anterior vesicourethropexy, or urethropexy (eg, Marshall-Marchetti-Krantz, Burch); complicated (eg, secondary repair)	x
51845	Abdomino-vaginal vesical neck suspension, with or without endoscopic control (eg, Stamey, Raz, modified Pereyra)	
51990	Laparoscopy, surgical; urethral suspension for stress incontinence	
51992	Laparoscopy, surgical; sling operation for stress incontinence (eg, fascia or synthetic)	
57287*	Removal or revision of sling for stress incontinence (eg, fascia or synthetic)	
57288	Sling operation for stress incontinence (eg, fascia or synthetic)	
57289	Pereyra procedure, including anterior colporrhaphy	
53440*	Sling operation for correction of male urinary incontinence (eg, fascia or synthetic)	
53442*	Removal or revision of sling for male urinary incontinence (eg, fascia or synthetic)	

Effective August 1st, 2024
Non-Medicare— Considered Medically Necessary when criteria in the applicable policy statements listed above are met
Medicare—Considered Medically Necessary when criteria in the applicable policy statements listed above are met

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*Requires review for level of care: Elective Surgical Procedures

CPT® or HCPC Codes	Description	IP only
51840	Anterior vesicourethropexy, or urethropexy (eg, Marshall-Marchetti-Krantz, Burch); simple	x
51841	Anterior vesicourethropexy, or urethropexy (eg, Marshall-Marchetti-Krantz, Burch); complicated (eg, secondary repair)	x
51845	Abdomino-vaginal vesical neck suspension, with or without endoscopic control (eg, Stamey, Raz, modified Pereyra)	
51990	Laparoscopy, surgical; urethral suspension for stress incontinence	
51992	Laparoscopy, surgical; sling operation for stress incontinence (eg, fascia or synthetic)	
57287*	Removal or revision of sling for stress incontinence (eg, fascia or synthetic)	
57288	Sling operation for stress incontinence (eg, fascia or synthetic)	
57289	Pereyra procedure, including anterior colporrhaphy	
53440*	Sling operation for correction of male urinary incontinence (eg, fascia or synthetic)	
53442*	Removal or revision of sling for male urinary incontinence (eg, fascia or synthetic)	

Urethral Bulking Agents

Effective August 1, 2024

Non-Medicare—Considered Not Medically Necessary:

Medicare—Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
51715	Endoscopic injection of implant material into the submucosal tissues of the urethra and/or bladder neck
L8603	Injectable bulking agent, collagen implant, urinary tract, 2.5 ml syringe, includes shipping and necessary supplies
L8604	Injectable bulking agent, dextranomer/hyaluronic acid copolymer implant, urinary tract, 1 ml, includes shipping and necessary supplies
L8606	Injectable bulking agent, synthetic implant, urinary tract, 1 ml syringe, includes shipping and necessary supplies

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed	Date Last Revised
11/1998	08/03/2010[MDCRPC], 04/05/2011[MDCRPC], 05/03/2011[MDCRPC], 12/06/2011[MDCRPC], 10/02/2012[MDCRPC], 06/04/2013[MDCRPC], 08/06/2013[MPC], 11/05/2013[MPC], 09/02/2014[MPC], 07/07/2015[MPC], 05/03/2016[MPC], 03/07/2017[MPC], 01/09/2018[MPC], 12/04/2018[MPC], 12/03/2019[MPC], 12/01/2020[MPC],12/07/2021[MPC],12/06/2022[MPC], 12/09/2023[MPC]	03/15/2024

[MDCRPC] Medical Director Clinical Review and Policy Committee

[MPC] Medical Policy Committee

Revision History	Description
09/08/2015	Revised LCD L35008 and 34886

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06/28/2015	Added coverage article A52965
03/07/2017	MPC approved criteria for PTNS
12/02/2022	Added Retired LCD 14443
11/13/2023	Updated Medicare coverage article link A52965, which has been retired as of 11/1/23.
03/12/2024	MPC approved to discontinue medical necessity review of biofeedback for the treatment of urinary incontinence, effective August 1st, 2024. Requires 60-day notice. MPC approved the revised clinical criteria for sling procedures to treat urinary incontinence, effective August 1st, 2024. Requires 60-day notice. MPC approved the revised clinical criteria for use of urethral bulking agents in commercial members, effective August 1st, 2024. Requires 60-day notice.

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Clinical Review Criteria
Tumor Treatment Field Therapy

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	Tumor Treatment Field Therapy (TTFT) (L34823)
Local Coverage Article	Tumor Treatment Field Therapy (TTFT) (A52711)

For Non-Medicare Members

I. Tumor-treating fields (TTF) to treat primary (not recurrent) supratentorial glioblastoma multiforme (GBM) may be considered medically necessary when **ALL of the following** are met:
   A. Patient is 18 years of age or older; and
   B. Karnofsky Performance Status* is 70% or higher; and
   C. Documentation of histologically confirmed primary glioblastoma multiforme; and
   D. Patient has completed standard concomitant chemoradiation with temozolomide(TMZ); and
   E. Disease did not progress through chemo radiation (possible “pseudo progression” does not exclude patients from receiving TTF) and
   F. TTF will be administered concurrently with TMZ, unless TMZ has been ineffective, not tolerated, or is contraindicated and
   G. TTF must be started no later than 60 days from the end of chemo radiation

II. Continued treatment of TTF can be covered until the second radiological progression (meaning 2 consecutive images showing tumor progression) or clinical deterioration

All authorizations are for 90 days. Re-authorizations require updated clinical notes and imaging.

*Karnofsky Performance Status Scale

Condition	Value (%)	level of Functional Capacity
Able to carry on normal activity and to work; no special care needed	100%	No complaints; no evidence of disease
	90%	Able to carry on normal activity; minor signs or symptoms of disease
	80%	Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed	70%	Cares for self; unable to carry on normal activity or to do active work
	60%	Requires occasional assistance but is able to care for most personal needs

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	50%	Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; diseases may be progressing rapidly	40%	Disabled; requires special care and assistance
	30%	Severely disabled; hospital admission indicated although death not imminent
	20%	Very sick; hospital admission necessary; active supportive treatment necessary
	10%	Moribund; fatal processes progressing rapidly

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Glioblastoma (GBM), an incurable disease, has the highest incidence rate (3.19/100,000 population) amongst the central nervous system (CNS) tumors with an average survival of 15 months (Thakkar et al., 2014). Numerous genetic and environmental risk factors have been investigated but none is associated with a large population of GBM (Wrensch, Minn, Chew, Bondy, & Berger, 2002). The median age of diagnosis is 64 years and GBM is frequently found in the supratentorial region (Adams et al., 2013). GBM is an aggressive malignancy with poor prognosis and low survival. The first year relative survival rate is 35% and this estimate decreases over time (Ostrom et al., 2013) making the long term survival very harsh. Standard treatment consists of resection with combination of radiation and chemotherapy. These therapies, whether combined or utilized alone, do not significantly decrease mortality and do not lack adverse effects. Because GBM infiltrates the brain, it is prone to recurrence. Management of recurrence became challenging and therefore indispensable for better clinical outcomes. Different therapeutic options have been investigated but tumor treating fields (TTFields), a novel treatment, seems comparable to standard chemotherapy including Temozolomide and is less toxic (Roger Stupp et al., 2012).

TTFields, developed by NovoCure Ltd, is a medical device for the treatment of recurrent GBM. It is a portable, non-invasive, battery-operated and wearable device that disrupts the division of cancer cells and proliferation in the supratentorial region by delivering low-intensity and intermediate frequency (200 kHz) alternating electric fields via transducer arrays applied to the scalp by means of hypoallergenic ceramic disks, which are placed on the scalp using Hydrogel (Axelgaard Manufacturing Co, Ltd, Fallbrook, CA) as a conductor; It is believed that TTFields inhibits cytokinesis and microtubule assemble, and therefore inhibiting growth and causing death of cancer cells (Butowski, Wong, Mehta, & Wilson, 2013). The NovoTTF-100A received premarket approval from the Food and Drug Administration (FDA) on April 10, 2011 for treatment in adult patients with confirmed GBM, following confirmed recurrence in an upper region of the brain after receiving chemotherapy. The device is intended to be used independently and as an alternative to standard medical therapy after surgical and radiation options have been exhausted (FDA 2011).

The review of the safety and effectiveness of TTFields Therapy for the treatment of recurrent GBM in adults has been reviewed previously. However, it is being reviewed based on a request from the Clinical Review Unit with a focus on the combination of TTFields plus Temozolomide as maintenance therapy on newly diagnosed GBM. It is also being reviewed for coverage decision support.

Medical Technology Assessment Committee (MTAC)

Tumor Treatment Fields Therapy

08/19/2013: MTAC REVIEW

Evidence Conclusion: The randomized phase III trial sought to compare the overall survival of subjects treated with the NovoTTF-100A alone to subjects treated with the best standard of care (BSC) chemotherapy available for recurrent GBM (Stupp, Wong et al. 2012). In the clinical study, 237 subjects with previously diagnosed GBM who experienced recurrence of their tumor or their condition worsened despite conventional therapy (surgery and

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chemo-radiotherapy followed by chemotherapy) were randomly assigned to receive either NovoTTF-100A stand-alone treatment or the BSC chemotherapy (as determined by the local physician). The primary endpoint for the study was overall survival, as assessed by the log-rank test in the intent-to-treat population. In addition, the study examined the safety and tolerability of NovoTTF-100A treatment based on the incidence and severity of adverse events and toxicities. Secondary endpoints measured in the study included the progression free survival rate at 6 months, time to progression, one-year survival rate, quality of life and radiological response rate. The ITT population includes all subjects who were randomized to the trial. At a median follow up of 39 months 93% of patients had died. The analysis was performed by the treatment group to which the subject was randomized. The study results showed that overall survival with the NovoTTF-100A System was no superior to that seen with active best standard of care chemotherapy. There was a slightly higher incidence of neurological adverse events in the NovoTFF-100A treated group (43.1%) compared to the best standard of care control group (36.3%). Mild to moderate skin irritation beneath the device electrodes was seen in 16% of NovoTFF-100A-treated subjects. NovoTFF-100A treated subjects experienced a lower frequency of the classic adverse events as seen with chemotherapy (such as gastrointestinal, hematological and infectious adverse events) with the best standard of care. Quality of life surveys indicated an improved quality of life in the NovoTFF-100A recurrent GBM subjects compared to the best standard of care recurrent GBM subjects. The trial was generally well designed and conducted with recruitment from 28 different clinics, randomization and minimal loss to follow up. Limitations identified by the authors include the somewhat heterogenous patient population with patients included after progression of one or several lines of prior chemotherapy. The authors also observed that the study could have benefited from a placebo or treatment-free control arm. Some limitations that are not highlighted by the authors include the decreasing number of subjects remaining after 12 months which may limit the ability to reliably estimate the long-term survival outcomes. Furthermore, it is important to note that the primary investigator, as well as a number of other authors had financial and professional ties with the manufacturer of the device Novocure Ltd., Rye Beach, New Hampshire. Although the study failed to show that the NovoTTF-100A treatment is superior to chemotherapy with respect to overall survival the NovoTTF-100A treatment exhibits minimal toxicity, has clinically comparable primary and secondary effectiveness and better quality of life compared to the chemotherapies used in the control arm of the study.

Articles: A literature search was conducted revealing a small pilot trial and one larger pivotal study. The pilot study was an open-label prospective single arm study to assess the safety and effectiveness of TTFields for the treatment of GBM. The pivotal study was prospective, open label, best standard of care randomized control trial to compare the overall survival of subjects treated with NovoTTF-100A alone to subjects treated with the best standard of care chemotherapy available for recurrent GBM. In addition, the search revealed a case study illustrating one patient's success with TTFields therapy and one expert opinion article discussing the concept, evidence and future of TTFields. The clinical study that formed the FDA's basis for determining that the NovoTTF-100A System is safe and effective for its intended use was selected for review: Stupp R, Wong ET, Kanner AA, Steinberg D, Engelhard H, et al. NovoTFF-100A versus physician's choice chemotherapy in recurrent glioblastoma: A randomized phase III trial of a novel treatment modality. *European Journal of Cancer*. 2012;48, 2192-2202. See Evidence Table.

The use of TT Fields Therapy does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Tumor Treating Fields plus Temozolomide as maintenance therapy for Glioblastoma Multiforme (GBM)

03/21/2016: MTAC REVIEW

Evidence Conclusion: The previous review on TTFields, completed in 2013, aimed to determine the safety and efficacy of TTFields therapy compared to standard medical therapy, for the treatment of recurrent GBM for adult patients. The study evaluating NovoTTF-100A versus Physician Choice Chemotherapy in recurrent glioblastoma (Roger Stupp et al., 2012) was reviewed and no improvement in overall survival was identified. The author of the review concluded that there was insufficient evidence to determine the safety and effectiveness of TTFields Therapy. Stupp, R., S. Taillibert, et al. (2015). "Maintenance Therapy With Tumor-treating Fields plus Temozolomide vs Temozolomide Alone for Glioblastoma: A Randomized Clinical Trial." See Evidence Table 1. This randomized phase 3 trial, open label, parallel design, multicenter, (R. Stupp et al., 2015) intended to assess the efficacy and safety of TTFields in combination with temozolomide for treatment of patients with GBM after initial treatment with chemoradiation. After patients were diagnosed, they were initially treated with chemoradiation comprised of Temozolomide and concomitant radiation. Brain MRI was required 2 weeks prior to starting the maintenance treatment (to exclude progression cases). After completion of the initial treatment, patients were randomized at a ratio of 2 to 1 to receive TTFields + Temozolomide (n=466) or Temozolomide alone (n=229).TTFields was initiated within 4-7 weeks from the last dose of concomitant chemoradiotherapy. While Temozolomide was given on a basis of 150-200 mg/m2/d for 5 days every 28 days for 6-12 cycles, TTFields was delivered continuously (>18 hours/day) via 4 transducer arrays placed on the shaved scalp and connected to a portable medical device. The primary outcome was progression-free survival (PFS) in the intent-

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to-treat population (significance level of 0.01) and the secondary outcome was the overall survival (OS) in the per-protocol population (significance level of 0.006). Safety and tolerability were also evaluated. A total of 695 patients were recruited but the trial was terminated after the interim analysis showed a benefit in Progression Free Survival. This interim analysis was conducted after the first 315 randomized patients reached a minimum of 18-month follow-up. Thus, data from 315 patients with 210 patients in the intervention group and 105 patients in the control group were analyzed. Baseline characteristics were nearly similar across the groups with median age of 57 years. The findings were based on the interim analysis. Patients who were treated with TTFields plus Temozolomide had longer PFS [7.1 months (CI, 5.9 – 8.2)] than those who were treated with Temozolomide alone [4 months (95%CI, 3.3 – 5.2)]. Likewise, patients who were treated with TTFields plus Temozolomide had longer OS [20.5 months (16.7 - 25)] than those who were treated with Temozolomide alone [15.6 months (CI, 13.3 – 19.1)]. In addition, no major increases in toxic effects were associated with the intervention. The most common adverse events were thrombocytopenia, mild to moderate skin irritation, and general disorders. In conclusion, the combination of TTFields plus Temozolomide prolonged PFS as well as OS compared to Temozolomide alone for the maintenance treatment of patients with GBM. However, this is an interim analysis with less than 50% of participation with exclusion of patients with early progression decreasing the quality of the evidence. MTAC will re-review the technology once full data are analyzed. Conclusion: The interim analysis with less than 50% participation suggests that TTF plus Temozolomide may prolong progression-free survival and overall survival versus Temozolomide alone. Nevertheless, the study failed to include patients with severe prognosis, therefore results should be interpreted with cautious. Other pitfalls remain in the open-label nature of the RCT leading to placebo effects and variation in the delivery of chemotherapy and radiochemotherapy.
Articles: A literature search was conducted revealing 13 articles (Please refer to appendix B) of which one meets inclusion criteria (studies involving histologically confirmed GBM, standard concomitant chemoradiation with Temozolomide, age >18 years with ≥ 70% on Karnofsky Performance Status (KPS) score and good renal and bone marrow function, received TTFields plus Temozolomide as maintenance therapy). The study on "Maintenance Therapy with tumor-treating fields plus temozolomide vs Temozolomide alone for Glioblastoma: A randomized clinical trial" will be critically appraised.

The use of Tumor Treating Fields (TTFields) plus Temozolomide as maintenance therapy for Glioblastoma multiforme (GBM) does meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
A4555	Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only
E0766	Electrical stimulation device used for cancer treatment, includes all accessories, any type

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed	Date Last Revised
10/01/2013	10/01/2013[MPC], 10/07/2014[MPC], 08/04/2015[MPC], 05/03/2016[MPC], 04/04/2017[MPC], 02/06/2018[MPC], 02/05/2019[MPC], 02/04/2020[MPC], 02/02/2021[MPC], 02/01/2022[MPC], 02/07/2023[MPC], 01/09/2024[MPC]	09/06/2016

[MPC] Medical Policy Committee

Revision History	Description
03/21/2016	Added MTAC Review for of Tumor Treating Fields (TTFields) plus Temozolomide as maintenance therapy for Glioblastoma multiforme (GBM)
05/03/2016	MPC approved GH developed criteria for Tumor Treating Fields (TTFields)

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09/06/2016	Criteria added for continued treatment of TTF
06/28/2017	Added Medical Directors Comments
03/06/2018	MPC approved revised criteria for continued treatment of TTF

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Date Sent: 3/29/24
These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage.
Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

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Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Ultrasound Guided Percutaneous Needle Release of Carpal Tunnel

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article	None
Kaiser Permanente Policy	Due to the absence of a NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Clinical Review Criteria, “Ultrasound Guided Percutaneous Needle Release of Carpal Tunnel” for medical necessity determinations. Use the Non-Medicare criteria below.

For Non-Medicare Members

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies (and/or) provides better long-term outcomes than current standard services/therapies.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Carpal tunnel syndrome (CTS) is a neuromuscular clinical condition caused by compression or irritation of the median nerve where it passes under the transverse carpal ligament in the wrist. Thickening of tendon sheaths or encroachment by other structures lead to a sustained rise in pressure within the canal. The pressure is further increased by flexion or extension of the wrist. The incidence of CTS in the United States has been estimated at 1-3 cases per 1,000 subjects per year, with a prevalence of 50 cases per 1,000 per year. CTS is more common in individuals 45-65 years of age and among females. The etiology of the syndrome is not well known and continues to be debated. It is believed that it may have a hereditary component and that physical occupational activity such as repeated and forceful movement of the hand and wrist or the use of handheld powered vibratory tools can predispose to the condition. Other predisposing causes included rheumatoid arthritis, pregnancy, obesity, and hypothyroidism (Nathan 2005, Verdugo 2008, Bickel 2010, Palmer 2011, Page 2013).

The most common symptoms of carpal tunnel syndrome are pain, tingling, and numbness within the median nerve distribution of the hand (thumb, index and middle, and radial half of the ring finger). Pain may radiate to the arm and is often worse at night and when gripping an object for a long duration of time. In advanced stages, thenar muscle weakness can occur. Based on symptoms alone, the British Society for Surgery of the Hand has classified carpal tunnel syndrome into mild, moderate and severe. In mild carpal tunnel syndrome, there is intermittent paresthesia which may be nocturnal or associated with certain hand positions or conditions such as pregnancy or

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hypothyroidism. In moderate carpal tunnel syndrome, there is constant paresthesia which interferes with activities of daily living and wakes the patients from sleep. It is associated with reversible numbness and/or pain. Severe cases have constant numbness or pain associated with weakness and/or wasting of the thenar muscles, but with small risk of damage to the nerve (McCartan 2012, Page 2013).

Carpal tunnel syndrome may be treated by surgical or non-surgical approaches. Non-surgical treatments are usually offered to patients with intermittent symptoms of mild to moderate CTS. These include the use of wrist splints, local steroid injections, oral steroid therapy, activity modification, ergonomic modification, or therapeutic ultrasound. The more severe or refractory cases may require surgical decompression of the median nerve. Surgery involves complete division of the flexor retinaculum to release the median nerve and can be performed through a number of different techniques as the standard open carpal tunnel release, the mini-open release, and the endoscopic carpal tunnel decompression. Each technique has its advantages and drawbacks (McCartan 2012, Figaro 2012, Page 2013).

The standard open carpal tunnel release (O-CTR), the oldest and most commonly used technique, involves releasing the flexor retinaculum under direct vision to ensure a complete release. The procedure is safe and simple, but is associated with painful and sensitive scars, decrease in grip strength, and long healing time. A less aggressive mini-open release (mini-OCTR) involves division of the retinaculum with limited access through a 1-1.5 cm incision at the distal wrist crease and the use of specially developed instruments. Carpal tunnel release can also be performed endoscopically (E-CTR) using single or double portal techniques to visualize the under surface of the flexor retinaculum and guide the surgeon's knife. The mini-open or endoscopic techniques cause less tissue trauma, have a smaller scar, less postoperative pain, faster recovery, and conserves the grip strength. However, these techniques with their limited approaches are associated with decreased visualization of the median nerve and its terminal branches (thenar muscular branch and palmar branch, vascular structures, and anatomic variations, all of which may increase the risk of neurovascular injury during the procedure. In addition, these techniques may carry the risk of incomplete release of the flexor retinaculum as a result of poor visualization, leading to persistent symptoms. (McCartan 2012, Nakamichi 2010, de la Fuente 2012).

Mini-open carpal tunnel release (Mini-OCTR) and percutaneous carpal tunnel release using ultrasonographic guidance are recently developed surgical techniques that allow combining the advantages of both the O-CTR and mini-OCTR i.e. the direct visualization of all the key anatomic structures including the variants together with the small incision. The size of the incision with percutaneous carpal tunnel release is 0.4-0.6 cm compared to 1-2 cm for the mini, and >4cm for the classic carpal tunnel release. These newly developed techniques may potentially lead to the same neurological and functional outcomes as O-CTR but with less scar sensitivity and pain, and better grip strength. The sonographically guided percutaneous needle technique is office-based and performed under local anesthetic. However, not all patients are legible for the procedure, and the results of hand surgeries performed under ultrasonography depend on the surgeon's experience with ultrasound, which is known to be examiner dependent, and involves a learning curve and interobserver variation in interpretation. In addition, there are many unanswered questions as regards the contraindications to the percutaneous procedure, the release extent at the deepest layer portions, best approach, best location, and best advancing direction of the instrument (Nakamichi 2010, de la Fuente 2012, McShane 2012, Rojo –Manuaute 2013).

Medical Technology Assessment Committee (MTAC)

Ultrasound Guided Percutaneous Needle Release of Carpal Tunnel

08/19/2013: MTAC REVIEW

Evidence Conclusion: There is a lack of published literature on ultrasound-guided percutaneous release of the carpal tunnel for individuals with carpal tunnel syndrome. The larger of two published studies to date, was a small non-randomized observational study that compared the outcomes of percutaneous carpal tunnel release vs. mini-open surgical release performed under ultrasonographic guidance. The technique was not compared to the standard open surgery, and the patients were not randomized to the procedures but were assigned to one versus the other according to the orthopedist's discretion based primarily on the safe zone that varied between the study participants and also on the patient's preference. In conclusion, there is insufficient published evidence to determine the efficacy and safety ultrasound-guided percutaneous release of the carpal tunnel for individuals with carpal tunnel syndrome.

Articles: The published literature on ultrasound-guided percutaneous release of the carpal tunnel is very limited. The search revealed only one nonrandomized study that compared the technique with mini-OCTR both performed under ultrasonographic guidance, and a very small retrospective case series with 17 patients. The following study was selected for critical appraisal: Nakamichi K, Tachibana S, Yamamoto S, et al. Percutaneous carpal tunnel

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release compared with mini-open release using ultrasonographic guidance for both techniques. *J Hand Surg Am*. 2010; 35:437-445. See Evidence Table

Ultrasound Guided Percutaneous Needle Release of Carpal Tunnel did not pass the *Kaiser Permanente Medical Technology Assessment Criteria*.

Applicable Codes

Considered Not Medically Necessary:

CPT® or HCPC Codes	Description
76942	Ultrasonic guidance for needle placement (e.g., biopsy, aspiration, injection, localization device), imaging supervision and interpretation
With Diagnosis Codes	
G56.00	Carpal tunnel syndrome, unspecified upper limb
G56.01	Carpal tunnel syndrome, right upper limb
G56.02	Carpal tunnel syndrome, left upper limb
G56.03	Carpal tunnel syndrome, bilateral upper limbs

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Dates Reviewed	Date Last Revised
10/01/2013	10/01/2013[MPC], 08/05/2014[MPC],06/02/2015[MPC], 04/05/2016[MPC], 02/07/2017[MPC], 12/05/2017[MPC], 11/06/2018[MPC], 11/05/2019[MPC], 11/03/2020[MPC], 11/02/2021[MPC], 11/01/2022[MPC], 11/07/2023[MPC]	11/06/2018

[MPC] Medical Policy Committee

Revision History	Description
09/08/2015	Revised LCD L35008
11/06/2018	Added language to use Kaiser Permanente criteria for Medicare members.

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Clinical Review Criteria
Ultrafiltration for the Treatment of Congestive Heart Failure

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Ultrafiltration, Hemoperfusion and Hemofiltration (110.15)
Local Coverage Determinations (LCD)	None
Local Coverage Article	None

For Non-Medicare Members

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or consulting specialist.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Heart failure (HF) is a major and growing health problem worldwide and is the leading cause of hospitalization in the Western world. In the United States more than 5 million patients suffer from HF, and more than one million are admitted annually to hospitals for acute decompensated heart failure (ADHF). The great majority of patients present with dyspnea and edema from the volume overload and pulmonary congestion driven by sodium and water retention, and many are discharged without clinical evidence of adequate decongestion. The prognosis of patients with ADHF is poor with an approximately 4% in-hospital mortality rate. 25% are readmitted within 30 days, and up to 23% die within 6 months. 25-33% of patients with ADHF develop acute cardiorenal syndrome which is defined as worsening renal function (often defined as an increase in creatinine $\geq$0.3 mg/dL from baseline). This results from a number of contributing factors and is usually associated with poor outcome (Chiong 2010, Giglioli 2011, Bart 2012, Felker 2012).

Standard therapy for decompensated HF consists predominantly of intravenous (IV) loop diuretics and vasodilators. Loop diuretics induce rapid diuresis that reduces lung congestion and edema. Intravenous administration of an effective dose of furosemide (a loop diuretic) typically results in a diuretic effect within 30 minutes and peaks at one hour. Heart failure patients require a higher dose to achieve this same effect. It was reported that in ADHF, renal responsiveness to loop diuretics may be decreased, and that patients with New York Heart Association (NYHA) class II or III HF have one third to one fourth the natriuretic response as compared with normal subjects. This response decreases further as the severity of HF increases, and higher doses are required. The effectiveness of the diuretics also declines with repeated exposure, and resistance to the therapy may

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develop as heart failure progresses. In some patients fluid overload persists despite the higher doses. Investigators described two types of diuretic resistance; short-term resistance, which is a decrease in response to the first administration, and long-term resistance that develops after long-term administration of loop diuretics. Approximately 25%-30% of HF patients develop diuretic resistance which is usually associated with worsened outcomes and higher risk of death. In some cases, the intravenous administration of diuretics to patients with ADHF may directly contribute to worsening of renal function, and its continued use for treating persistent congestion after the onset of worsening renal function, may lead to additional kidney injury. Despite the concerns about these potential harms associated with higher doses of diuretic therapy and the lack of proven survival benefit, diuretics remain the standard therapy for removing the excess extracellular fluid in patients with heart failure. Other therapeutic alternatives include inotropic therapy, IV nitroglycerine and natriuretic peptides. When these pharmacological approaches fail, or are unsuitable, the alternative means for fluid removal are dialysis, phlebotomy, or ultrafiltration (Costanzo 2005, 2007, Chiong 2012, Bart 2012, Felker 2009, 2012)

The concept of extracorporeal removal of fluid with ultrafiltration has been used for decades to treat refractory edema. The pump-driven extracorporeal ultrafiltration (UF) was described in the 1970s and was used for patients with heart failure in the mid-1980s. Ultrafiltration is accomplished by mechanically drawing blood from the patient either through peripheral or central venous access. Plasma is then filtered by means of the negative hydrostatic pressure generated by a second pump, and re-infused back into the patient. The ultrafiltrate is composed of water with electrolytes in the same concentration as in the serum without the cells or proteins which are too large to pass through the filter pores. Unlike dialysis, ultrafiltration operates by convection in eliminating iso-osmolar extracellular fluid resulting in a decrease in ventricular filling pressure without significant changes in the renal function, creatinine, or urea concentration. It is reported that ultrafiltration can improve cardiac hemodynamics by reducing both right and left sided filling pressure, increasing the stroke volume and cardiac output. Researchers also found that it restores diuretic responsiveness and improves natriuresis without changes in the heart rate, systolic blood pressure, intravascular volume, or electrolytes. A potential advantage of UF over loop diuretics is that the ultrafiltrate is isotonic, whereas the urinary output with loop diuretics is hypotonic, thus UF removes more sodium (and less potassium) than diuretics for an equivalent volume loss. Ultrafiltration is not a substitute for dialysis and will not lead to removal of accumulated toxins or potassium in hyperkalemic patients (Bourge 2005, Boyle 2005, Costanzo 2005).

Earlier, ultrafiltration required physician placement of a double-lumen central venous catheter and monitoring by a dialysis technician. Recently a simpler, smaller, and portable ultrafiltration device was introduced (System 100, CHF Solutions, Minneapolis, Minnesota). The device is less invasive and does not require intensive care unit monitoring or central intravenous access. It allows a technician to place the blood withdrawal and infusion catheters in peripheral veins, usually the brachial-cephalic system, with subsequent monitoring by a clinical nurse. The device removes water and non-protein-bound small and medium molecular weight solutes through a semipermeable membrane when hydrostatic pressure generated by blood pressure or external blood pump exceeds oncotic pressure. The fluid removal rate can range from 100 to 500 ml/hour and is set by the treating physician. UF requires systemic anticoagulation with the possibility of excess bleeding. Other potential complications include air embolism, and overly aggressive volume removal (Bourge 2005, Bart 2012).

The ACC/AHA clinical practice guidelines do not recommend the use of UF as a class I therapeutic option but as a class II recommendation (level B evidence) for the relief of fluid overload in patients with refractory congestion not responding to medical therapy.

CHF Solutions received marketing clearance from the FDA for System 100 in June 2002 and for central venous access with the system in December 2003. System 100 is indicated for temporary (up to 8 hours) ultrafiltration treatment of patients with fluid overload. In 2005, System 100 was renamed Aquadex FlexFlow™ and launched with several new features (according to the manufacturer).

Medical Technology Assessment Committee(MTAC)

Ultrafiltration in the Treatment of Congestive Heart Failure

08/07/2006: MTAC REVIEW

Evidence Conclusion: The RAPID-CHF trial (Bart 2005) was a randomized, controlled, non-blinded trial that compared usual care vs. usual care plus ultrafiltration (UF) in 40 patients admitted to hospital with acute decompensated heart failure and fluid overload. Patients randomized to the usual care group received the conventional heart failure therapy. Those in the UF group received an 8 hour UF treatment with a maximum fluid removal rate of 500 cc/hour. Diuretics were administered after the 8 hours of UF, and additional courses of UF were allowed after 24 hours. The results of the trial show that the weight loss (primary endpoint of the trial) was not

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significantly different between the two study groups. The average volume removal of fluid was significantly higher in the UF group at 24 and 48 hours. Patients in the two treatment groups experienced improvement in their symptoms during the treatment period. The improvement observed was significantly greater in the UF group compared to the usual care group at 48 hours but not at 24 hours. The significant difference may be due to the greater fluid removal or due to chance as the trial was small, un-blinded, and the outcome measure was subjective. Costanzo et al (2005) reported their experience with early initiation of UF in 20 selected HF patients admitted to hospital with manifest signs and symptoms of fluid overload. The patients underwent UF which was continued until the acute decompensation heart failure symptoms were resolved. The removal of fluid was aggressive (8,654 + 4,205 ml) and resulted in a mean decrease of 6 kg of weight at discharge, and improvement in the clinical signs of symptoms of fluid overload that seem to have lasted for the 90 days of follow-up. This was only an observational case series with no comparison or control group and subject to selection and observation bias. The results of the UNLOAD (or UltrafiltrationN versus IV diuretics for patients hospitalized for Acute Decompensated congestive heart failure) trial was presented at the 2006 ACC conference in Atlanta, but have not been published in a peer reviewed journal to date. The trial randomized 200 patients from 28 centers to receive the standard intravenous diuretic drug therapy or IV diuretics plus ultrafiltration to treat fluid overload. The study was not blinded, the primary outcomes were weight loss and dyspnea score at 48 hours, and the patients were followed up for 90 days. The unpublished results of the trial indicate that both treatments were associated with significant improvement in the dyspnea score at 48 hours, but with no significant difference between the two treatment groups. Patients in the UF group had significantly greater net fluid and weight loss at 48 hours, and a lower incidence of hypokalemia. The results also show that the hospital readmission rate, during the 3 months of follow-up, was significantly lower in the UF group, vs. the IV diuretic group. All three studies were funded or supported by the manufacturer of the device CHF Solutions, Brooklyn Park, Minnesota, which may introduce bias. In conclusion, there is insufficient evidence to date to determine the efficacy and long-term safety of ultrafiltration versus standard care in acute decompensated heart failure, or to determine who would benefit most from the intervention.

Articles: The search yielded around 280 articles most of which were review articles, opinion pieces, or dealt with the technical aspects of the procedures. There was one RCT, and several small case series, many of which dated back in the 1980s and 1990s. The RCT and the relevant case series using the new UF device (System 100, CHF Solutions, Minneapolis, Minnesota) were selected for critical appraisal: Bart BA, Boyle A, Bank AJ, et al. Ultrafiltration versus usual care for hospitalized patients with heart failure. The Relief for Acutely fluid-overloaded Patients with Decompensated Congestive Heart Failure (RAPID-CHF) trial. J Am Coll Cardiol 2005; 46:2043-2046. **See** Evidence Table. MR, Saltzberg M, O'sollivan J, et al. Early ultrafiltration in patients with decompensated heart failure and diuretic resistance. J Am Coll Cardiol 2005;46:2047-2051. **See** Evidence Table.

The use of ultrafiltration in the treatment of congestive heart failure does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

06/17/2013: MTAC REVIEW

Ultrafiltration in the Treatment of Congestive Heart Failure

Evidence Conclusion: All published trials on the use of ultrafiltration in patients with acute decompensated heart failure with or without renal dysfunction compared UF with IV diuretic-based therapy. No published RCT, to date, examined the efficacy and safety of ultrafiltration in patients with ADHF who refractory to diuretics were. This latter indication of ultrafiltration was only evaluated in a one retrospective study with no control group. Ultrafiltration as a first line therapy The UNLOAD (ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure) trial compared ultrafiltration to diuretic therapy in patients hospitalized for acute decompensated heart failure. The trial examined UF as a first-line early therapy not as a rescue therapy (i.e. patients did not have to fail an initial diuretic therapy to be included in the trial). 200 patients were randomized to receive early UF (within 24 hours of hospitalization) or intravenous diuretic drug therapy. The co-primary outcomes were weight loss and patient self-assessed dyspnea score at 48 hours. The results show that both the UF and IV diuretic therapies were associated with significant improvement in the dyspnea score at 48 hours, with no statistically significant difference between the two treatment groups. Patients in the UF group had significantly greater fluid and weight loss at 48 hours, and a lower incidence of hypokalemia. This however, did not have an impact on the length of the index hospital stay. The rates of rehospitalization and unscheduled visits during the 90 days of follow-up were significantly lower in the UF group, vs. the IV diuretic group. The results also show a higher rise in serum creatinine levels in the UF group vs. the IV diuretic group (twice as many patients in the UF arm experienced an increase in sCr level >0.3 ml/dL during the first 24 hours of therapy) but the difference did not reach a statistically significant level. The authors considered the lack of significant difference between the two groups for this as well as other outcomes, as similar effects when the trial was not designed as equivalent study, and the lack of significant differences could results from insufficient statistical power. The study was a multicenter RCT but had several limitations many of which were acknowledged by the authors. The trial had a relatively small size and short follow-up duration, excluded

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patients with hypotension or hemodynamic instability, and used suboptimal dose and mode of administration of loop diuretics. The dose of the diuretic, duration, and rate of UF were all based on the discretion of the attending physician who was not blinded to the randomization groups and could be a source of bias. In addition, the authors did not present any data on low-salt diet compliance, or criteria for hospitalization. The study was supported by CHF Solution Inc., and the primary author as well as a number of other authors had financial ties to the manufacturer of the device CHF Solutions, Brooklyn Park, Minnesota. The Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF, sponsored by the NHLBI) investigated the role of UF as a treatment for patients with persistent congestion and worsening of kidney function (increase in serum creatinine ≥0.3 mg/dL within 12 weeks before or 10 days after index admission). 188 patients were randomized to undergo ultrafiltration (fluid removal at a rate of 200 ml/hour using Aquadex System 100; CHF Solutions), or to receive stepped pharmacological therapy involving increasing the doses of loop diuretics (with or without metolazone), vasodilators and inotropes (based on an algorithm that aimed at achieving urine output of 3-5 liters/ day). The assigned treatment was continued in the two groups until signs and symptoms of congestion were improved as possible. The primary endpoint was bivariate (simultaneous) change in serum creatinine level and body weight in 96 hours after randomization. The trial was not blinded, and the patients were followed-up for 60 days. Recruitment for the trial was stopped early before reaching the planned size of 200 subjects based on the advice of the data and safety monitoring board due to lack of benefit and excess adverse events with ultrafiltration. The results of CARRESS-HF show that stepped pharmacological therapy was superior to UF when the primary end point was assessed at 96 hours after randomization. There was a statistically significant reduction the serum creatinine (sCr) in the pharmacologic therapy group compared to the UF group. There was no significant difference between the groups in weight loss at 96 hours. At the 60 days of follow-up, there were no statistically significant differences in weight loss, or rate of hospitalization due to heart failure. There was a nonsignificant increase in the all-cause readmission rate in the UF group. UF, was also associated with a significantly higher rate of serious adverse events including kidney failure, bleeding complications, and catheter–related complications. The sixty-day mortality was17% for the UF group and 13% for the pharmacological therapy group with no significant difference between the groups, however, as indicated earlier, a lack of significant difference does not indicate equivalence due to the study design. These results should be interpreted with caution and cannot be generalized to patients with ADHF with better renal function than those included in the trial.

Other published trials Two other very small published RCTs (ULTRADISCO (Giglioli et al 2011), and Hanna and colleagues' trial (2012) also compared ultrafiltration versus intravenous diuretics inpatients hospitalized for ADHF. The trials had intermediate outcomes (hemodynamic variables in the ULTRADISCO trials, and time for pulmonary wedge pressure to be maintained at >18 mmHg for ≥4 consecutive hours in Hanna and colleagues' study). Their overall results showed greater fluid loss with UF vs. diuretic therapy with no significant difference between the groups in the serum creatinine levels. Ultrafiltration as a rescue therapy for patients with ADHF who are refractory to IV diuretic therapy The literature search did not identify any published RCT to date, that examined the efficacy and safety of ultrafiltration in patients with ADHF who were refractory to diuretics. In a retrospective observational study with no comparison group, Patarroyo and colleagues (2012) analyzed data from hospital records for adult patients with ADHF admitted to one heart failure intensive care unit in Cleveland Ohio ((2004-2009) and who required slow continuous ultrafiltration therapy (SCUF). The study population was a highly selected group of 63 adult patients with advanced HF, worsening renal function, and congestion refractory to hemodynamically guided intensive medical therapy. Their median age was 58 years, mean LV ejection fraction 26 ±15%, baseline serum creatinine (sCr) 1.9 ± 0.8 mg/dL and hemodynamics consistent with cardiogenic shock. SCUF was initiated after a mean of 8 days from admission, was performed at a rate of 200ml/hr. and for a mean duration of 8 days. At the initiation of SCUF therapy the sCr level was 2.2 ± 0.9 mg/dL. The mean duration of the UF therapy was 3+2 days, and the primary endpoint of the study was all-cause mortality and the secondary endpoint included number of readmissions for ADHF and dialysis-dependent status at time of discharge. The results of the analysis showed that after 48 hours of SCUF the overall cohort lost weight significantly compared to baseline (mean 4.4 kg). This was associated with significant improvement in hemodynamic variables but with no improvements in sCr levels or blood urea. 37 patients (59%) required conversion to continuous hemodialysis during their hospital stay and 9 (14%) were dependent on hemodialysis at hospital discharge. 34/37 (93%) of these patients were readmitted to the hospital within 60 days form discharge.19/63 patients (30%) died during the index hospitalization, and 4 were discharged to terminal care in hospice. The overall 1-year all-cause mortality was 70% and 2 of the surviving patients underwent heart transplantation. The results of the study should be interpreted with caution due to the study design and its inclusion of severely ill patients. Conclusion: There is insufficient evidence to support the use of ultrafiltration as a first-line treatment in hospitalized ADHF with volume overload. There is insufficient evidence to determine the safety and efficacy of ultrafiltration in patients with ADHF who are refractory to diuretic therapy. Results from UNLOAD trial, suggest, but do not provide good evidence, that ultrafiltration may provide better correction of volume overload than IV diuretics (given at the dose used in the trial) in patients hospitalized ADHF who are not resistant to diuretic therapy. The trial had its limitations and does not provide any evidence on the safest and most effective rates of fluid removal, duration of treatment, or the conditions for termination of ultrafiltration. There is evidence from the CARRESS-HF that IV loop diuretic-based therapy adding distal-acting

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diuretics, IV vasodilator and inotropic agents as needed is superior to ultrafiltration in patients with acute decompensated heart failure and worsening renal function. CARESS-HF results show increased incidence of worsening kidney function in the ultrafiltration group versus the stepped pharmacologic therapy group.
A large ongoing trial (AVOID-HF) (NCT01474200) involving 810 patients in 40 US centers is examining the effect of UF vs. intravenous diuretics in reducing hospitalization in patients with ADHF before worsening renal function.
Articles: UNLOAD trial (Costanzo et al 2007, evidence table 1) See Evidence Table. CARRESS-HF (Bart yet al 2012, evidence table 2) See Evidence Table

The use of ultrafiltration in the treatment of congestive heart failure does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Medicare - Considered Medically Necessary when criteria in the applicable policy statements listed above are met
Non-Medicare - Considered Not Medically Necessary

CPT® or HCPC Codes	Description
0692T	Therapeutic ultrafiltration

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check.**

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Date Created	Date Reviewed	Date Last Revised
08/29/2006	04/04/2011[MDCRPC], 02/07/2012[MDCRPC], 12/04/2012[MDCRPC], 08/06/2013[MPC], 06/03/2014[MPC], 02/03/2015[MPC], 12/01/2015[MPC], 10/04/2016[MPC], 08/01/2017[MPC], 07/10/2018[MPC], 07/09/2019[MPC], 07/07/2020[MPC], 07/06/2021[MPC], 07/05/2022[MPC], 07/11/2023[MPC]	12/08/2022

[MPC] Medical Policy Committee

Revision History	Description
12/08/2022	Added new applicable CPT code to criteria

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KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Myoelectric Upper Limb Prosthesis

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article	None
Kaiser Permanente Medical Policy	Due to the absence of an active NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Clinical Review Criteria, "***Myoelectric Upper Limb Prosthesis***," for medical necessity determinations. Use the Non-Medicare criteria below.

For Non-Medicare Members

1. Myoelectric upper limb prosthetic components may be medically necessary when **ALL of the following** criteria are met:
   - A. The patient has an amputation or missing limb at the wrist or above (forearm, elbow, etc.); AND
   - B. Standard body-powered prosthetic devices cannot be used or are insufficient to meet the functional needs of the individual in performing activities of daily living. The inadequacies of a standard device must be documented in detail by a physical or occupational or physiatrist therapist who is not employed by the vendor or prosthetist; **AND**
   - C. The remaining musculature of the arm(s) contains the minimum microvolt threshold to allow operation of a myoelectric prosthetic device, as demonstrated by functional testing using a physical or computer model prosthesis; **AND**
   - D. The patient has demonstrated sufficient neurological and cognitive function to operate the prosthesis effectively; **AND**
   - E. The patient is free of comorbidities that could interfere with function of the prosthesis (neuromuscular disease, etc.); **AND**
   - F. Functional evaluation by a qualified professional (e.g., prosthetist) indicates that with training, use of a myoelectric prosthesis is likely to meet the functional needs of the individual (e.g., gripping, releasing, holding, and coordinating movement of the prosthesis) when performing activities of daily living. This evaluation should consider the patient's needs for control, durability (maintenance), function (speed, work capability), and usability. **BOTH of the following** criteria must be met:
     - i. The device is necessary for the patient to perform instrumental activities of daily (see B above)
     - ii. The device is not primarily for the purpose of allowing the patient to perform vocational, leisure or recreational activities.
   - G. Patient must be at least 1 year old.

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Prosthesis with individually powered digits, including but not limited to partial hand prosthesis, is considered investigational.

Repair and/or replacement of an external prosthetic device, including an upper limb myoelectric prosthetic device, is covered as follows:

- Repair is covered only when anatomical change or reasonable wear and tear renders the item nonfunctional and the repair will make the equipment usable.
- Replacement is covered only when anatomical change or reasonable wear and tear renders the item nonfunctional and non-repairable.

Repair or replacement of an external prosthetic device, including an upper limb myoelectric prosthetic device, made unusable or nonfunctioning because of individual misuse, abuse or neglect is not covered

If requesting this these services, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

External prosthetic appliances, often referred to as prosthetic devices or prostheses, are devices used to replace the functions of missing body parts. A passive prosthesis is a type of device that must be moved manually, typically by the opposite arm. The standard prosthetic appliance for replacement of an upper extremity, either below or above the elbow, is a body-powered prosthesis with a terminal hook device. This type of prosthetic device is the most durable and requires gross body movement and sufficient strength for adequate use. It is attached to the user's body through a system of harnesses. The patient controls the hand, forearm and elbow by movement of the harness system. Gross body motion is required to pull the harness and thereby move the prosthesis. Usage of a body-powered prosthesis requires adequate space for compensation of movement; the user must be able to place his/her body in front of the object to be manipulated. This type of device allows voluntary closing or opening of the hand, but not both.

The myoelectric device functions by means of electrical impulses. It is a prosthetic device used as an alternative to a passive or conventional body-powered device which enables a patient to adjust the force of his/her grip and both open and closes the hand voluntarily. Myoelectric devices may be recommended for amputees who are unable to use body-powered devices or who require improved grip function/motion for performance of daily activities. Adults or children with above- or below-the-elbow amputations may use the device effectively, although for children there is some controversy regarding use because due to normal growth patterns the prosthesis may require multiple socket replacements over time.

Unlike body-powered prosthetic devices, myoelectric devices move the prosthetic limbs with small, electric, motorized controls, which allow more precise movement. Small electrodes are installed in the socket of the prosthesis. The electrodes sense electrical activity of the muscles, called electromyographic (EMG) signals. When amplified, the EMG signal stimulates the motors in the device to perform a function. The signal is very weak (i.e., 5–200 microvolts); an individual must be able to produce a strong enough EMG signal for the device to record and amplify; that is, the person must possess a minimum microvolt threshold in the remaining musculature of the arm. The user must also be able to isolate muscle contraction, so that if one muscle is contracted (e.g., flexion), the opposing muscle is relaxed (e.g., extension). Contraction of both muscles (co-contraction) would result in signals turning the motor on and off at the same time, causing the device not to function and eliminating its myoelectric capability.

Myoelectric devices operate on rechargeable batteries and require no external cables or harnesses. The myoelectric prosthetic device does not require gross body movements or added space for compensation of movement to provide adequate functional movement; it can be operated in any user position that allows muscle contraction. Instead of a suspension harness, the devices use one of two suspension techniques: skeletal/soft tissue lock or suction.

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Proponents suggest that myoelectric devices have many advantages over conventional ones. When designing prostheses to replace a hand, manufacturers attempt to replicate the grip function, the hand's major function. Other functions that are often replicated are pinch force, wrist rotation and elbow function. Investigators assert that a myoelectric device offers greater grip capabilities and more improved rotational function than conventional devices. Furthermore, because no control cable or harness is associated with the myoelectric device, cosmetic skin can be applied to the device to enhance cosmetic appearance. More recent control systems incorporate programmable microprocessors allowing various ranges of adjustment, performance of multiple functions and sequential operation of elbow, wrist and hand motions. In some cases, a combination of myoelectric and body- powered technology (i.e., hybrid prosthesis) is used to enhance the amputee's overall functionality, depending on the level and location of amputation. Patients with amputations above the transhumoral level may elect a body- powered device to control shoulder and elbow movement and a myoelectric device to control hand and wrist motion, allowing control of two joints at once. There are also devices that are similar to the normal wrist, enabling the terminal device to be rotated, thus allowing more natural movement or placement. More recently, hand devices have become available with five individual powered digits and separately powered prosthetic digits are available for individuals who have lost a part of the hand or finger.

Medical Technology Assessment Committee (MTAC)

Controlled Upper Limb Prosthesis

08/11/2004: MTAC REVIEW

Evidence Conclusion: There is minimal published data on the microprocessor- controlled upper limb prosthesis. These data do not provide evidence on the benefit of using these more sophisticated prostheses in improving health outcomes of the amputees, their impact on their physical and social activities, or to suggest which patients will benefit more with using them.

Articles: The search yielded 35 articles. The majority dealt with the technical aspects and mechanisms of action of the prostheses. The search did not reveal any randomized controlled trials. Only one case series (N=18) that investigated the satisfaction level of young users of myoelectric prosthesis was identified. This was a small case series and did not involve a microprocessor.

Controlled upper limb prosthesis in the treatment of members with missing or amputated upper limb does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPC Codes	Description
L6026	Transcarpal/metacarpal or partial hand disarticulation prosthesis, external power, self-suspended, inner socket with removable forearm section, electrodes and cables, two batteries, charger, myoelectric control of terminal device, excludes terminal device(s)
L6611	Addition to upper extremity prosthesis, external powered, additional switch, any type
L6677	Upper extremity addition, harness, triple control, simultaneous operation of terminal device and elbow
L6715	Terminal device, multiple articulating digit, includes motor(s), initial issue or replacement
L6880	Electric hand, switch or myoelectric controlled, independently articulating digits, any grasp pattern or combination of grasp patterns, includes motor(s)
L6881	Automatic grasp feature, addition to upper limb electric prosthetic terminal device
L6882	Microprocessor control feature, addition to upper limb prosthetic terminal device
L6925	Wrist disarticulation, external power, self-suspended inner socket, removable forearm shell, Otto Bock or equal electrodes, cables, two batteries and one charger, myoelectronic control of terminal device
L6935	Below elbow, external power, self-suspended inner socket, removable forearm shell, Otto Bock or equal electrodes, cables, two batteries and one charger, myoelectronic control of terminal device
L6945	Elbow disarticulation, external power, molded inner socket, removable humeral shell, outside locking hinges, forearm, Otto Bock or equal electrodes, cables, two batteries and one charger, myoelectronic control of terminal device
L6955	Above elbow, external power, molded inner socket, removable humeral shell, internal locking elbow, forearm, Otto Bock or equal electrodes, cables, two batteries and one charger,

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	myoelectronic control of terminal device
L6965	Shoulder disarticulation, external power, molded inner socket, removable shoulder shell, shoulder bulkhead, humeral section, mechanical elbow, forearm, Otto Bock or equal electrodes, cables, two batteries and one charger, myoelectronic control of terminal device
L6975	Interscapular-thoracic, external power, molded inner socket, removable shoulder shell, shoulder bulkhead, humeral section, mechanical elbow, forearm, Otto Bock or equal electrodes, cables, two batteries and one charger, myoelectronic control of terminal device
L7007	Electric hand, switch or myoelectric controlled, adult
L7008	Electric hand, switch or myoelectric, controlled, pediatric
L7009	Electric hook, switch or myoelectric controlled, adult
L7045	Electric hook, switch or myoelectric controlled, pediatric
L7180	Electronic elbow, microprocessor sequential control of elbow and terminal device
L7181	Electronic elbow, microprocessor simultaneous control of elbow and terminal device
L7190	Electronic elbow, adolescent, Variety Village or equal, myoelectronically controlled
L7191	Electronic elbow, child, Variety Village or equal, myoelectronically controlled
L7259	Electronic wrist rotator, any type

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Dates Reviewed	Date Last Revised
08/11/2004	04/04/2011[MDCRPC], 02/07/2012 [MDCRPC], 12/04/2012 [MDCRPC],10/01/2013 [MPC], 08/05/2014 [MPC], 06/02/2015 [MPC], 04/05/2016[MPC], 02/07/2017[MPC], 12/05/2017[MPC], 10/02/2018[MPC], 10/01/2019[MPC], 10/06/2020[MPC] , 10/05/2021[MPC] , 10/04/2022[MPC], 10/03/2023[MPC], 01/09/2024[MPC]	08/28/2020

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
04/05/2016	Developed criteria to expand coverage for service
02/07/2017	Medicare is silent; MPC approved to adopt KPWA criteria for Medicare members
08/28/2020	Removed deleted HCPC code L6025; Added HCPC codes L6026, L6925 and L7259

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KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria

UroVysion FISH Test

- AssayTests for the Diagnosis of Bladder Cancer

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	Bladder/Urothelial Tumor Markers (L36680)
Local Coverage Article	Billing and Coding: Lab: Bladder/Urothelial Tumor Markers (A55029)

For Non-Medicare Members

UroVysion FISH test is covered for members with a suspected new diagnosis of bladder cancer or known prior history of bladder cancer, who have an atypical cytology in spite of normal cystoscopy and upper tract imaging.

A negative test will preclude further evaluation and a positive test either increases the frequency of surveillance or prompts urothelial biopsy.

The FISH test is not covered when used for all other indications, such as, screening for bladder cancer or for the evaluation of hematuria. The tests below are not covered for any indication:

- BTA Stat test
- NMP22 test
- Aura-Tek FDP test

If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

In 2012, cancer of the urinary bladder accounted for 73,510 new cases and 14,880 deaths in the USA, making it the sixth most common and tenth most lethal malignancy in the country (Siegel, Naishadham et al. 2012). Most patients present with superficial low-grade transitional cell carcinoma which is readily resectable and, in some cases, requires additional chemotherapy or immunotherapy (Rouprêt, Babjuk et al. 2013). Although these tumors have a high recurrence, they usually do not invade the bladder wall or metastasize. One third of incident bladder cancers, however, progress into invasive cancer presenting as solid, nonpapillary tumors with a high propensity for metastasis

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requiring radical therapy. The five year survival rate for these tumors is only 30-50% (Arentsen, de la Rosette et al. 2006). Thus, patients with a history of bladder cancer are routinely monitored for recurrence

At present, the diagnosis of both primary and recurrent bladder tumors relies upon both cystoscopy and cytology, of which, neither is completely accurate (Mian, Lodde et al. 2003). Cystoscopy is an efficient method; however, it is invasive, causes patient discomfort, may be associated with a risk of urethral and bladder neck stricture and might not detect flat tumors or carcinoma in situ (false negative rate of 30%) (Daniltchenko, Riedl et al. 2005; Denzinger, Burger et al. 2007). Cytology, often used as an adjunct to cystoscopy, has a poor sensitivity for low grade tumors and frequently the results are inconclusive for malignancy (Nabi, Greene et al. 2004). In addition, patients with atypical cytology pose a challenging problem due to uncertainty about the presence of cancer.
Options for management of this predicament include observation with the possibility of missing a diagnosis or biopsying every patient.

Due to the limitations of cytology, molecular-based detection techniques represent potentially attractive strategies for noninvasive detection of aggressive bladder cancer using urine as the specimen source. Among these is the UroVysion™ Kit, a multi-target, multicolor FISH assay designed to detect aneuploidy for chromosomes 3, 7, 17 or the loss of the 9p21 locus (Sarosdy, Schellhammer et al. 2002). Better performance has been reported in detecting carcinoma in situ and high-grade tumors (Lokeshwar, Habuchi et al. 2005).

UroVysion (Abott-Vysis, Wiesbaden, Germany) was approved by the FDA in January 2005 for the cytologic detection of cancer cells in voided urine specimens.

Medical Technology Assessment Committee (MTAC)

UroVysion FISH Test

10/13/2004: MTAC REVIEW

Evidence Conclusion: The studies reviewed compared the performance of the UroVysion FISH test to the other noninvasive tests used to detect new or recurrent urinary bladder carcinoma, using voided urine specimens. Cystoscopic evaluation (or bladder resection) with histopathologic studies for the suspicious cases was used as gold standard. All studies were conducted among patients referred to cystoscopy for a history of bladder carcinoma, or urinary signs/symptoms. Sarosdy's study only included patients with a history of transitional cell carcinoma, and Halling as well as Placer included patients with either a history of urothelial carcinoma or other genitourinary symptoms and signs. The ages of the study subjects ranged from 28 to 98 years, and the majority were men. Patient characteristics and inclusion criteria provided were insufficient, exclusion criteria were not discussed, and except for one study with consecutive patients, the authors do not explain how the subjects were selected for the studies. None of the studies evaluated the test as a screening tool, and none evaluated its role in improving the management of urothelial carcinomas. Overall, the studies reviewed showed that FISH test was more sensitive than urine cytology in detecting new or recurrent bladder carcinomas among the patients studied. The specificity of the two tests was similar. Compared to the gold standard of cystoscopy/histopathologic evaluation, the overall sensitivity of FISH assays ranged from 71% to 81%, and the overall specificity ranged from 66% in Sarosdy et al's study to 96% in Halling et al's study. The test appears to be more sensitive in detecting later stages, and higher grades of the disease however; the numbers of patients in the subgroups were too small.
Articles: The search yielded 29 articles. There were 14 studies that compared the FISH test with cytologic analysis and/or other tests. In five of these studies the urine specimens were obtained from bladder washings during cystoscopy. These studies were excluded as this review deals specifically with the noninvasive UroVysion FISH test using voided urine specimens. Nine studies on UroVysion FISH test in voided urine were identified. Sensitivity and/or specificity of the test was/were not reported in three of the studies. Four of the remaining studies that had a gold standard, and reported sensitivity and specificity were critically appraised. Selection of these studies for critical review was based on the sample size and validity of the study methodology. *The following articles were critically appraised*:*Sarosdy MF, Schellhammer P, Bokinsky, et al. Clinical evaluation of a multi-target fluorescent in situ hybridization assay for the detection of bladder cancer. *J Urol* 2002; 168:1950-1954. See Evidence Table Halling KC, King W, Sokolova I, et al. A comparison of cytology and fluorescence in situ hybridization for the detection of urothelial carcinoma. *J Urol* 2000; 164:1768-1775. See Evidence Table Halling KC, King W, Sokolova I, et al. A comparison of BTA stat, hemoglobin dipstick, telomerase and Vysis assays for the detection of urothelial carcinoma in urine. *J Urol* 2002; 167:2001-2006. See Evidence Table Placer J, Espinet B, Salido M, et al. Clinical utility of a multiprobe FISH assay in voided urine specimens for the detection of bladder cancer and its recurrence, compared with urinary cytology. *Eur Urol* 2002; 42:547-552. See Evidence Table

The use of UroVysion FISH test in the evaluation of new or recurrent urinary bladder carcinoma does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

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UroVysion FISH Test

6/17/2013: MTAC REVIEW

Evidence Conclusion: The accuracy of the UroVysion FISH assay for the diagnosis of bladder cancer in patients with atypical cells has two major components, validity and precision. In this context, the validity of the UroVysion FISH assay refers to the degree to which it does what it is designed to do (i.e. detect urothelial carcinoma of the bladder) and the precision refers to its reliability or it's consistency from one application to the next. In both of the selected studies, the validity of the FISH assay was measured by testing every patient who underwent cystoscopy and cytology with atypical cells within a certain time frame and then reviewing the clinical and pathological data on each patient for congruence. The end result, in both studies, was sensitivity and specificity which allows us to measure how well the test classifies people with the cancer as sick and those without cancer as healthy. In addition, two other measures, positive and negative predictive values, were determined to measure how well the test performed in the given population. Both of the selected studies employed similar methodologic techniques. The UroVysion test was performed on all patients presenting with atypical cytology, both with and without cancer history, within a certain time frame. Results were reviewed comprehensively to evaluate the clinical and pathological data on each patient. Clinical stage was assigned by the operative surgeon and all cytology results were interpreted by an experienced cytopathologist, who was blinded to clinical findings. Cytology results were considered atypical if it was not unequivocally positive or negative. The results of both studies show that the use of the UroVysion test is beneficial in patients with equivocal and negative cystoscopy. Lotan and colleagues found in patients with no cancer history the sensitivity was 77.8% and the specificity was 100% and in patients with cancer history the sensitivity and specificity were both 100%. These findings were validated by Schlomer and colleagues results which show that in patients with cystoscopically visualized lesions UroVysion had a positive predictive value of 100% but there were false negative results. In patients with equivocal cystoscopy and a history of cancer all four high grade tumors were detected and there were no false negative findings. In patients with equivocal cystoscopy and no prior cancer the positive predictive value was 100% and there were no false negative results. In patients with negative cystoscopy the UroVysion test detected all cancers but the positive predictive value was 10% and 29% in patients with and without a history of cancer, respectively. Although these prospective studies indicate that the use of UroVysion in patients with atypical cytology is beneficial in identifying cancer in patients with atypical results they come with limitations. First and foremost, both studies are working with relatively small samples threatening the generalizability of the study. In addition to the small samples, both studies yielded and excluded uninformative UroVysion results. Furthermore, both studies employed more than one diagnostic technique which leads to potential bias. It should also be noted that the UroVysion FISH assay has been approved by the FDA as a noninvasive tool for the detection of cancer cells through voided urine. A portion of the sample collections described in the two prospective studies included specimens that were obtained via bladder washings during cystoscopy which makes comparison difficult with studies that solely used voided urinary samples.

Articles: Lotan Y, Bensalah, Ruddell T, Shariat S, Sagalowsky A, Ashfaq R. Prospective evaluation of the clinical usefulness of reflex fluorescence in situ hybridization assay in patients with atypical cytology for the detection of urothelial carcinoma of the bladder. The Journal of Urology 2008; 179:2164-2169. See Evidence Table Schlomer BJ, Ho R, Sagalowsky A, Ashfaq R, Lotan Y. Prospective Validation of the clinical usefulness of reflex fluorescence in situ hybridization assay in patients with atypical cytology for the detection of urothelial carcinoma of the bladder. The Journal of Urology 2010; 183:62-67. See Evidence Table

The use of UroVysion FISH test in the evaluation of new or recurrent urinary bladder carcinoma does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® Codes	Description
88120	Cytopathology, in situ hybridization (eg, FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; manual
88121	Cytopathology, in situ hybridization (eg, FISH), urinary tract specimen with morphometric analysis, 3-5 molecular probes, each specimen; using computer-assisted technology

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****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed	Date Last Revised
10/13/2004	04/04/2011 MDCRPC, 02/07/2012 MDCRPC, 12/04/2012 MDCRPC, 08/06/2013MPC, 09/03/2013 MPC, 07/01/2014MPC, 05/05/2015MPC, 03/01/2016MPC, 11/07/2017MPC, 09/04/2018MPC, 09/03/2019MPC, 09/01/2020MPC, 09/07/2021MPC, 09/06/2022MPC, 09/05/2023MPC	09/01/2020

MPC Medical Policy Committee

Revision History	Description
09/08/2015	Revised LCD L34067
09/01/2020	Removed CPT code 88271

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KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Vertebral Axial Decompression (VAX-D System)

- Internal Disc Decompression (IDD)
- Spinal System Therapy
- Traction, Spine

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	National Coverage Determination (NCD) for Vertebral Axial Decompression (VAX-D) (160.16) *This service is not covered per Medicare criteria.*
Local Coverage Determinations (LCD)	None
Local Coverage Article	None

For Non-Medicare Members

Kaiser Permanente has elected to use the Traction, Spine (A-0345) MCG* for medical necessity determinations. This service is not covered per MCG guidelines. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.

***The MCG manuals are proprietary and cannot be published and/or distributed**. However, on an individual member basis, Kaiser Permanente can share a copy of the specific criteria document used to make a utilization management decision. If one of your patients is being reviewed using these criteria, you may request a copy of the criteria by calling the Kaiser Permanente Clinical Review staff at 1-800-289-1363 or access the MCG Guideline Index using the link provided above.

If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Chronic lower back pain is a major health problem and cause of disability in Western countries. The cause of the persistent pain is not well understood for the majority of patients. It generally occurs without specific damage or signs that can be revealed by imaging or other neurophysiological techniques. It is believed that the pain starts as acute pain of muscle and connective tissue and persists among approximately one third of the patients (Rittweger 2002). Mechanical low back pain may have various causes including degenerative disc disease, degenerative spondylosis, disc herniation, facet arthropathy, and others. Patients with low back pain may also experience reduced lumbar flexibility, reduced flexion-relaxation and static balance. The pain is aggravated by sitting, standing and lifting, which increase axial loading on the spine. Walking may relieve some of the pain, but patients experience more relief by lying down as it unloads the spine and reduces intradiscal pressure (Gose 1998).

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Conservative medical care for chronic back pain includes bed rest, steroid injection, anti-inflammatory drugs, muscle relaxants, conventional physiotherapy, exercises, stretching, manipulative techniques, ultrasound treatments, electric stimulation techniques and others. These measures ease the pain for some patients but are ineffective, intolerable, or unsuitable for others. Patients not responding to conservative therapy may be offered conventional or percutaneous surgical procedures such as disc space decompression, epidural blocks, and spinal instrumentation. These interventions play an important role in treating patients with low back pain due to herniated disc and degenerative disc problems. However, surgery may not relieve all the pain, and could permanently disrupt the biomechanical and physiological function of the disc. Moreover, not all patients are candidates for surgery.

Some researchers have found that lumbar traction, if adequately applied, may alleviate many of the conditions that cause low back pain. Conventional traction involves simple mechanical stretch which when applied continuously, or by certain techniques, may lead to paravertebral muscle recruitment and increase the intradiscal pressure (Ramos 1994). This observation led to the continuous development of devices and equipment that would achieve decompression of the lumbar discs at a force that the patients can tolerate without stimulating the reactive reflexes of the lumbar musculature (Gose 1998), i.e. without an increase in the resistance to the applied force.

Several systems for vertebral axial decompression have been introduced including the VAX-D equipment, and the Decompression Reduction Stabilization (DRS) System later developed to the Spina System then the Accu-spina Logic System. According the manufacturer's web site, the latter system provides lumbar decompression, cervical decompression, and high-tension oscillation all in one machine, which is also certified to administer IDD therapy treatments.

The VAX-D applies distraction tensions to the patient's lumbar spine in order to non-surgically decompress the spine and intervertebral discs. The patient lies prone on the VAX table that has a split design and is restrained by holding on to adjustable handgrips with the arms extended above the head to stabilize the shoulder girdle and upper body. Patients are allowed to release the handgrips at any time during the treatment. The upper body lies over a stationary portion, and a special harness designed to apply forces to the lateral pelvic alae is fitted and tightened around the patient and connected to a tensionometer at the caudal end of the table. The distraction- relaxation cycles are automated, and continuous feedback from the tensionometer is captured on a chart printout, which allows the operator to constantly monitor the patient. The therapy consists of an average of 20 sessions comprising 15 cycles of decompression and relaxation. The cycles are characterized by one minute of distraction and one minute of relaxation. The therapeutic range of tension is 50-95 pounds, which is reduced by 10-15 pounds when the patients are asymptomatic, or the symptoms have reached a plateau. The investigators of this technology indicate it for patients with low-back pain associated with herniated discs, or degenerative disc disease, and contraindicate it for patients with cauda equine syndrome, infection, tumor severe osteoporosis, fractures, bilateral pars defect, spondylolisthesis Grade 2, and the presence of surgical hardware (Ramos 2004).

The Spina IDD System is also a non-invasive procedure that provides static intermittent and cyclic distraction forces to relieve the pressure on structures causing chronic neck or lower back pain. The system consists of a table split into two cushions, and a controller unit. The patient is anchored by means of a pelvic harness to the traction connector for the prescribed period of time. The therapy is provided in 20 treatment sessions over a period of 35 days. Each session lasts for approximately 30 minutes.

Both the VAX-D System and the Spina System were cleared by the FDA as Class II Medical devices 510 (k). The technology is being reviewed based on requests for coverage of the Internal Disc Compression Therapy.

Medical Technology Assessment Committee (MTAC)

Internal Disc Decompression Therapy in the Treatment of Pain from Spinal Disc Problems

06/09/1999: MTAC REVIEW

Evidence Conclusion: The published scientific evidence reporting clinical outcomes from VaxD treatment consists of a case series of 778 patients diagnosed with herniated or degenerated lumbar discs or facet syndrome. This study reports improvements in pain, mobility, activity and satisfaction following treatment. The validity of these results are uninterpretable however because no statistical analysis was reported and no information on the length and completeness of patient follow up was presented. Another small retrospective case series of 17 patients reports some changes in sensory nerve function as measured by a Current Perception Threshold neurometer following VaxD but the relationship between these changes and clinical improvement is unclear. The published evidence is not sufficient to determine if the benefits of Vax-D outweigh the harms of treatment. No studies which compare benefits and harms of Vax-D to the natural history of disc related low back pain have been published. Data from the large case series was obtained from 22 medical centers in the US. However, a lack of statistical analysis of this data

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does not permit conclusions to be made regarding the effect of Vax-D on back pain. The best published evidence is insufficient to demonstrate that Vax-D is effective and therefore Vax-D does not represent an efficient use of healthcare resources.
Articles: Gose, EA, et al, Neurological Research, 1998, 20:186-190 See Evidence Table.

The use of internal disc decompression therapy in the treatment of pain from spinal disc problems does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

02/06/2006: MTAC REVIEW
Internal Disc Decompression Therapy in the Treatment of Pain from Spinal Disc Problems
Evidence Conclusion: The literature search did not reveal any published studies on the IDD Therapy or the Spina System. The latter received FDA Clearance, in July 2000 based on its equivalence to the vertebral axial decompression device (VAX-D). There was one randomized trial and few case series published on the VAX-D. The RCT and a large series were critically reviewed. Sherry et al randomized 44 patients, 18-65 years old, with chronic low-back pain to receive either vertebral axial decompression (VAX-D) or transcutaneous electrical nerve stimulation (TENS) therapy. The primary outcome was the difference in proportion of successfully treated patients in the two treatment groups. Success of treatment was defined as 50% decrease in pain on the visual analogue scale and improvement in disability. The trial was small, poorly randomized, un-blinded, and had a high dropout rate. The authors did not conduct an intention to treat analysis but calculated their results on data for patients who completed therapy and follow-up, and concluded that VAX-D therapy was associated with a significant reduction in pain and disability. They compared the therapy to TENS, which seems to have a negative effect. A recent Cochrane Systematic Review (Khadilkar 2005) of published RCTs evaluating the effect of TENS on lower back pain, showed that the efficacy of TENS therapy was limited and inconsistent. Gose et al, reported the results of 778 patients with low back pain who had received at least 10 sessions of VAX-D therapy in 22 centers in the USA. The primary outcome was reduction in pain, improvement in mobility, ability to walk and sit, and patient satisfaction with the treatment. The study was only observational and had no control or comparison group. Moreover, all outcomes were subjective, and apparently there was no extended follow-up after the end of treatment. Overall, the results show that the treatment was successful among 71% of cases, with treatment success defined as a reduction in pain to 0 or 1 on a 0-5 scale. In conclusion, the current literature does not provide sufficient evidence to recommend the use of the VAX-D therapy, or the Spina System for the management of chronic low back pain. Larger, multi-center randomized controlled trials are needed to determine the effectiveness and long-term net health outcomes of the therapy. The published scientific evidence reporting clinical outcomes from VaxD treatment consists of a case series of 778 patients diagnosed with herniated or degenerated lumbar discs or facet syndrome. This study reports improvements in pain, mobility, activity and satisfaction following treatment. The validity of these results is uninterpretable however because no statistical analysis was reported and no information on the length and completeness of patient follow up was presented. Another small retrospective case series of 17 patients reports some changes in sensory nerve function as measured by a Current Perception Threshold neurometer following VaxD but the relationship between these changes and clinical improvement is unclear.
Articles: The search yielded 20 articles several of which were not related to the devices. Four studies on the vertebral axial decompression therapy using the VAX-D device were identified. One was an RCT comparing it to TENS, and the other three were case series with patient sizes varying from 5 to 778 patients. The RCT and the largest case series were selected for critical appraisal. No articles on the Spina System were identified. *The following articles were critically appraised:* Sherry E, Kitchener P, and Smart R. A prospective randomized controlled study of VAX-D and TENS for the treatment of chronic low back pain. Neurol Res 2001; 53:780-784. See Evidence Table. Gose EE, Naguszewski WK, and Naguszewski RK. Vertebral axis decompression therapy for pain associated with herniated or degenerated discs or facet syndrome: An outcome study. Neurol Res 1998; 20:186-190. See Evidence Table.

The use of internal disc decompression therapy in the treatment of pain from spinal disc problems does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Applicable Codes

Considered Not Medically Necessary:

CPT® or HCPC Codes	Description
S9090	Vertebral axial decompression, per session

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***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
12/1998	04/04/2011[MDCRPC], 02/07/2012[MDCRPC], 12/04/2012[MDCRPC], 10/01/2013[MPC], 08/05/2014[MPC], 06/02/2015[MPC], 04/05/2016[MPC], 02/07/2017[MPC], 12/05/2017[MPC], 11/06/2018[MPC], 11/05/2019[MPC], 11/03/2020[MPC], 11/02/2021[MPC], 11/01/2022[MPC], 11/07/2023[MPC], 02/13/2024[MPC]	08/05/2014

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description

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Clinical Review Criteria
Vectra DA (Multiple Biomarker Disease Activity [MBDA])

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article	9/17/2021 Noridian retired: *Billing and Coding: MolDX: Vectra™ DA (A54505)*. These services still need to meet medical necessity as outlined in the coverage article and will require review. Coverage articles are retired due to lack of evidence of current problems, or in some cases because the material is addressed by a National Coverage Decision (NCD), a coverage provision in a CMS interpretative manual or an article. Most LCDs are not retired because they are incorrect. Therefore, continue to use LCD A54505 for determining medical necessity.

For Non-Medicare Members

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or consulting specialist.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder that primarily involves synovial joints. It is debilitating disease that if uncontrolled, may lead to joint destruction, functional disability, and premature death. It is thus important to detect RA early, and to control the disease as soon as possible after diagnosis to delay its progression and preserve physical function.

Treatment of RA has shifted from symptom management, to reducing the disease activity and delaying its progression. Recent guidelines recommend treating RA promptly and aggressively aiming for remission as a therapeutic target (tight control or treatment-to-target strategy). Tight control may be defined as a treatment

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strategy tailored to the disease activity in individual patients with RA with the aim of achieving a predefined level of low disease activity, or preferably remission within a reasonable period of time. The availability of an increasing number of biologic and non-biologic effective disease-modifying anti-rheumatic drugs (DMARDs) has allowed the achievement of this treatment goal, but requires close monitoring of the disease activity, which is the cornerstone of tight control (Bakker 2007, Anderson 2012, Curtis 2012, Peabody 2013, Segurado 2014, Michaud 2015).

There are a number of composite tools available for assessing RA disease activity, six of which have been recommended by the American College of Rheumatology (ACR): Clinical Disease Activity Index (CDAI), Disease Activity Score with 28-joint counts (DAS28), Patient Activity Scale (PAS), PAS-II, Routine Assessment of Patient Index Data with 3 measures (RAPID-3), and Simplified Disease Activity Index (SDAI). These indices are based on information obtained from clinical, laboratory, and physical measures that include quantitative joint counts, patient reported outcomes, physician examination, and laboratory test including erythrocyte sedimentation rate (ESR) and C- reactive protein (CRP). These composite measurements are of great importance, but are complicated, may have intra- and inter-observer variability, are unable detect subclinical synovial damage, and may be influenced by cumulative damage and other conditions unrelated to RA (Anderson 2012, Curtis 2012, Owens 2015).

More recently, researchers have been investigating biomarkers to complement the clinical assessment of RA and improve the evaluation of disease activity. No single biomarker has been found to accurately assess RA activity, and it is hypothesized that a combination of biomarkers that measure diverse pathways to RA may have the potential of providing objective information on disease activity (Curtis 2012, Hirata 2013).

Vectra DA (Crescendo Bioscience, South San Francisco, CA), is a commercially available blood test that measures the serum concentration of 12 biomarkers and combines them into an algorithm to generate a multibiomarker disease activity (MBDA) score. The biomarkers included in Vectra DA test are: VCAM-1 (vascular cell adhesion molecule-1), EGF (epidermal growth factor), VEGF-A (vascular endothelial growth factor A), IL-6 (interleukin-6), TNF-RI (tumor necrosis factor receptor, type 1), MMP-1 (matrix metalloproteinase-1 or collagenase-1), MMP-3 (matrix metalloproteinase-3 or stromelysin-1), YKL-40, SAA (serum amyloid), CRP (C-reactive protein), leptin, and resistin. The score generated by the test is believed to represent the level of RA disease activity on a scale of 1 (lowest activity) to 100 (greatest activity). According to the manufacturer a score between 45 and 100 indicates high level of disease activity; 30 to 44 indicates moderate disease activity; and 1 to 29 indicates a low level of disease activity. Vectra DA test is not intended or validated to diagnose RA, but as an aid in the assessment of disease activity in adults RA patients when used in conjunction with standard clinical assessment (Curtis, 2012, Peabody 2013, Michaud 2015, Vectra.com).

Medical Technology Assessment Committee(MTAC)

12/21/2015: MTAC REVIEW

Vectra DA Test for Rheumatoid Arthritis

Evidence Conclusion: *Analytic validity* **-** Eastman and colleagues (2012), evaluated the analytical performance of each of the individual biomarker assays that comprise the MBDA test and the generated MBDA score. The investigators quantified the 12 serum biomarkers and found that all 12 individual assays exhibit a high level of precision with minimal cross-reactivity and interference by substances commonly seen in RA patients. The total MBDA score had good reproducibility over time with a median coefficient of variation of <2% across the score range. The same MBDA score was observed in different subjects with different biomarker profiles (Eastman 2012). *Clinical validity* **-** The published literature on the clinical validity of the MBDA Vectra DA test consists of observational cohort studies and posthoc analyses of randomized controlled trials performed for other reasons and among patients for whom serum samples were available to retrospectively evaluate the Vectra DA test. The studies correlated the MBDA score with other validated measures used for disease activity (mainly DAS28-CRP), radiographic joint progression, or response to therapy, and had no long-term follow-up to determine the test ability to predict clinical outcomes. Curtis and colleagues (2012), prospective cohort study (Evidence table 1): The authors used blood samples for 371 patients from 3 diverse RA cohorts in North America and Europe to validate the MBDA scores against DAS28-CRP (Disease Activity Score in 28 joints using the C-reactive protein level) as the reference measure for disease activity. The analysis of the results showed that MBDA score was positively, but moderately correlated with DAS28-CRP in both seropositive and seronegative patients (correlation coefficient r=56 and 43 respectively). The area under the receiver operating characteristic curve (AUROC) for discriminating low disease activity from moderate disease activity was 0.77 for seropositive patients and 0.70 for seronegative patients. The analysis also showed that changes in the MBDA scores at 6-12 weeks were significantly correlated with the corresponding changes in DAS28-CRP (Spearman's correlation coefficient r_s = 0.51). The study did not adjust for confounding factors, and did not evaluate the ability of the test to predict long-term outcomes of RA. In addition, it was partially supported by Crescendo Bioscience, the company manufacturing the laboratory test, and the authors had financial ties to the company. Bakker, et al (2012), Posthoc analysis of a completed randomized controlled trial (Evidence table 2): The investigators evaluated the performance of individual biomarkers and a

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MBDA (Vectra DA) test score in a subset of RA patient population enrolled in the Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA) tight control study. Only patients with available serum samples were included in the study evaluating the performance MBDA test (72 patients out of the 299 enrolled in CAMERA trial). There were significant differences between the patients with available samples versus those without. Blood samples were obtained from 72 patients at baseline and from 46 patients after treatment. MBDA scores were calculated and the performance of the Vectra DA test was evaluated relative to DAS28-CRP. The analysis showed that MBDA score had a significant correlation with DAS28-CRP (r=0.72; p<0.001) and an area under the receiver operating characteristic curve for distinguishing remission/low from moderate/high disease activity of 0.86 (p<0.001) using a DAS28-CRP cut-off of 2.7. The agreement of MBDA score with DAS28-CRP for classifying disease activity was fair (kappa score =0.34, 95% CI 0.19-0.49). The results also showed that MBDA score decreased from 53±18 at baseline to 39 ±16 at 6 months in response to study therapy (p<0.0001). Neither MBDA score nor DAS28-CRP was predictive of radiographic progression. The study was based on posthoc analysis of data from a completed trial, did not adjust for confounding factors, and did not evaluate the ability of the test to predict long-term outcomes of RA. The study was supported by Crescendo Bioscience, and the authors had financial ties to the company. Hirata and colleagues (2013) evaluated MBDA score in 125 patients with RA from the Behandel Strategieën (BeSt) study. Data and serum samples were available from 179 visits (91 at baseline and 88 at year 1). The results showed that the MBDA scores was significantly correlated with DAS28-ESR (Spearman's rank correlation coefficient r_s=0.66). It was also correlated with simplified disease activity index (SDAI), clinical disease activity index (CDAI). Changes in MBDA between baseline and year 1 were also correlated with changes in DAS28-ESR (assessed in a subgroup of 54 patients, r_s=0.55). The study was also a posthoc analysis of patients enrolled in BeSt study, was supported by Crescendo Bioscience, Inc., and the authors had financial ties to the company. *Prediction of radiographic joint progression* - Posthoc analyses of two RCTs: SWEFOT (Hambardzumyan et al, 2015) and BeSt [Markusse et al, 2014) suggest that MBDA scores may predict radiographic damage progression in patients with RA. These analyses had their limitations including, but not limited to the use of data obtained from RCTs designed primarily to compare different RA therapies, the patients included in the trials do not represent all RA patients as those with low DAS28 were excluded, patients were not randomized to therapy based on their MBDA scores, these scores were only available at baseline, and after 1 year (in one trial). In addition, patients in SWEFOT trial switched from one drug to another during the trial, which could affect radiographic outcomes, and the treatment-to-target strategy in BeSt trial suppressed inflammation and progression of radiographic joint damage in the majority of patients. A more recently published retrospective observational study (Li, 2015) with its limitations also suggest that MBDA score may enhance the ability to predict radiographic progression in patients with RA treated with non-biologic DMARDs. In conclusion, the published studies on the relationship between MBDA and radiographic joint damage had their limitations and do not provide sufficient evidence to determine the value of MBDA in predicting progression of radiographic joint damage in patients with rheumatoid arthritis. *Clinical utility*- There are no published RCTs, to date, that that compared a management strategy using the MBDA score versus another established measure of disease activity, and reported clinical outcomes such as disease progression, functional statue, or quality of life. The studies that evaluated the impact of Vectra DA test on clinical-decision making used simulated cases or physician surveys and did not report outcome data. Li and colleagues (2013), assessed the impact of MBDA, Vectra DA blood test on RA treatment decisions in 101 patients with RA. The health care providers (HCP) completed surveys before and after viewing the MBDA test result, recorded the dosage and frequency for all planned RA medications and the physician global assessment of disease activity. Frequency and types of change in treatment plan that resulted from viewing the MBDA test result were determined. The results of the study showed that, after reviewing MBDA test results treatment decisions were changed in 38 cases (38%), of which 18 involved starting, discontinuing, or switching a biologic or non-biologic DMARD. Other changes involved drug dosage, frequency or route of administration. The total frequency of use of the major classes of drug therapy changed by <5%. Treatment plans changed 63% of the time when the MBDA test result was perceived as being not consistent or somewhat consistent with the HCP assessment of disease activity. The study had its limitations including the small sample size, lack of a control group, and absence of follow-up to determine the impact on patient outcomes. Rech and colleagues (2015) analyzed the role of MBDA score in predicting disease relapse in patients with RA in sustained remission with tapered disease modifying antirheumatic drug (DMARD) therapy in RETRO trial. This was a RCT that evaluated the possibility of tapering or stopping DMARDs in patients fulfilling classification criteria for RA. The participants were randomized to 3 arms: 1. continuing DMARDs for 12 months, 2. Tapering the treatment by 50%, or 3. Reducing the dose by 50% for the first 6 months before entirely discontinuing the treatment. MBDA scores were calculated from the analysis of baseline serum samples of 94 patients participating in the RETRO trial. Retrospective analysis of data showed that baseline MBDA levels were significantly higher in patients experiencing a relapse vs. those in sustained remission. The analysis was retrospective and does not provide sufficient evidence to determine utility of MBDA in predicting the disease relapse and tapering or discontinuing the use of DMARDs accordingly. Conclusion There is insufficient evidence to determine whether MBDA is as good as or better than other established indices used to measure RA disease activity. The published studies show a

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moderate correlation between Vectra DA and DAS28-CRP in classifying patients into low vs. moderate to high disease. There is insufficient evidence to determine the clinical validity of Vectra DA test and its ability to predict outcomes. There is insufficient evidence to determine that Vectra DA test results have an impact on the management of patients with rheumatoid arthritis and/or improve their health outcomes.

Articles: The literature search revealed a study on the analytic validity of MBDA test score, four studies on the clinical validity of the MBDA Vectra Da test, and few small simulating studies or surveys on the clinical utility of the test. The following two studies on the clinical validity of MBDA test studies were selected for critical appraisal: Bakker MF, Cavet G, Jacobs JW, et al. Performance of a multi-biomarker score measuring rheumatoid arthritis disease activity in the CAMERA tight control study. *Ann Rheum Dis.* 2012 Oct; 71(10):1692-1697. See Evidence Table 1. Curtis JR, van der Helm-van Mil AH, Knevel R, et al. Validation of a novel multibiomarker test to assess rheumatoid arthritis disease activity. *Arthritis Care Res (Hoboken).* 2012 Dec; 64(12):1794-1803. See Evidence Table 2.

The use of Vectra DA (Multiple Biomarker Disease Activity [MBDA]) test for monitoring disease activity in patients with rheumatoid arthritis does not meet the *Kaiser Permanente Technology Assessment Criteria.*

Applicable Codes

Medicare - Considered Medically Necessary when criteria in the applicable policy statements listed above are met
Non-Medicare - Considered Not Medically Necessary

CPT® Codes	Description
81490	Autoimmune (rheumatoid arthritis), analysis of 12 biomarkers using immunoassays, utilizing serum, prognostic algorithm reported as a disease activity score

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
01/06/2016	01/05/2016[MPC], 11/01/2016[MPC], 09/05/2017[MPC], 07/10/2018[MPC], 07/09/2019[MPC], 07/07/2020[MPC], 07/06/2021[MPC], 07/05/2022[MPC], 07/11/2023[MPC]	01/06/2016

[MPC] Medical Policy Committee

Revision History	Description

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KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Treatment of Varicose Veins

- Radiofrequency Catheter Closure
- Sclerotherapy
- Surgical Stripping
- Trivex System for Outpatient Varicose Vein Surgery
- VenaSeal Closure System
- VNUS Closure Device

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	Treatment of Varicose Veins of the Lower Extremities (L34010)
Local Coverage Article	Billing and Coding: Treatment of Varicose Veins of the Lower Extremities (A57707)

For Non-Medicare Members

I. For great saphenous vein or small saphenous vein ligation, stab phlebectomy, division, stripping, radiofrequency endovenous occlusion (VNUS procedure), Endovenous Radiofrequency Ablation Treatment (ERFA) and endovenous laser ablation of the saphenous vein (ELAS) (also known as endovenous laser treatment (EVLT) **ALL of the following** criteria must be met:

A. The patient is symptomatic and has one or more of the following:
   1. Pain or burning in the extremity
   2. Recurrent episodes of superficial phlebitis
   3. Non-healing skin ulceration
   4. Bleeding from a varicosity
   5. Stasis dermatitis
   6. Refractory dependent edema

B. Vein size is 4.5 mm or greater in diameter (not valve diameter at junction) or with exception of short saphenous vein 3.5 mm or greater can be ablated

C. Pre-operative doppler demonstrates reflux (reflux duration of 500 milliseconds (ms) or greater in the vein to be treated).

D. In addition, all of the following are true for ERFA and laser ablation:
   1. Absence of aneurysm in the target segment.
   2. Maximum vein diameter of 12 mm for ERFA or 20 mm for laser ablation.
   3. Absence of thrombosis or vein tortuosity, which would impair catheter advancement.
   4. The absence of significant peripheral arterial diseases.

E. Microfoam sclerotherapy (e.g. Varithena) can be used if patient meets criteria B (above) when laser ablation is not an option, per criteria D3 (above).

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II. Sclerotherapy is covered for up to 6 months after a covered stab phlebectomy, endovenous ablation or a vein stripping. Sclerotherapy can be approved at these same venous sites if symptoms persist associated with persistent varicosities. Also, sclerotherapy can be approved for 4.0 mm or greater superficial varicosities associated with spontaneous bleeding or a poorly healing ulcer.
III. VenaSeal Closure System
Can be covered if all criteria above are met.

No evidence to support coverage for:
A. Treatment of reticular veins, spider veins or superficial telangiectasias by any technique (considered cosmetic)
B. Procedures with devices not FDA-approved

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Superficial venous reflux occurs when the valves that keep blood flowing out of the veins in the leg become damaged or diseased. Primary symptoms are pain, swelling and varicose veins. The basic treatment is to re-route blood flow through other healthy veins. This can be done using several techniques: stripping the greater damaged vein, using radiofrequency energy to heat and occlude the vein, and using irritant solution to obliterate the vein.

The conventional treatment is stripping of the greater damaged vein. This procedure has favorable clinical outcomes (REF), but is associated with substantial post-operative morbidity, particularly pain and bruising. Recurrent reflux is possible with the existing treatments and the risk of recurrence increases over time.

Rather than vein stripping, radiofrequency (RF) energy to heat and occlude the damaged vein. RF energy is delivered via collapsible catheter electrodes that are introduced into the vein lumen. The operator sets the target temperature, usually 85°C. The temperature is monitored using a microprocessor-controlled bipolar generator. The procedure is performed on an outpatient basis, using either local or regional anesthesia.

Sclerotherapy is the treatment of veins that are distended, lengthened and tortuous (i.e. varicose veins) by the injection of an irritant solution to encourage obliteration of the veins by thrombosis and subsequent scarring.

The treatment of varicose veins and spider veins can be for either cosmetic purposes or for the improvement of clinical symptoms related to these conditions. In order to identify when the care will be covered a common set of clinical appropriateness criteria were developed.

Evidence and Source Documents

Radiofrequency Catheter Closure
Trivex
VenaSeal Closure System

Medical Technology Assessment Committee(MTAC)

Radiofrequency Catheter Closure in the treatment of varicose veins

BACKGROUND
Superficial venous reflux occurs when the valves that keep blood flowing out of the veins in the leg become damaged or diseased. Primary symptoms are pain, swelling and varicose veins. The basic treatment is to re-route blood flow through other healthy veins. The conventional treatment is stripping of the greater damaged vein. This procedure has favorable clinical outcomes (REF), but is associated with substantial post-operative morbidity, particularly pain and bruising. Recurrent reflux is possible with the existing treatments and the risk of recurrence increases over time. The VNUS Closure System was proposed as a minimally invasive treatment for superficial venous reflux. Rather than vein stripping, the Closure system uses radiofrequency (RF) energy to heat and occlude the damaged vein. RF energy is delivered via collapsible catheter electrodes that are introduced into the vein lumen. The operator sets the target temperature, usually 85o C. The temperature is monitored using a microprocessor-controlled bipolar generator. The procedure is performed on an outpatient basis, using either local or regional anesthesia. The VNUS Closure System received FDA approval March 1999.

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08/13/2003: MTAC REVIEW

Radiofrequency Catheter Closure in the treatment of varicose veins

Evidence Conclusion: The best, published evidence on the VNUS Closure system is a small RCT with n=33 (Rautio et al., 2002). This study found that patients had less pain and fewer sick days a mean of 50 days after the Closure procedure than patients who received the stripping operation. There was no significant difference in quality of life variables. Potential sources of bias in the Rautio RCT include lack of blinding, lack of intention to treat analysis and potential confounding. In addition, the RCT did not have long-term follow-up and did not address the issue of recurrent reflux. Also available are case series data from a multi-center registry (Merchant et al., 2002). 93% of patients had complete the use of Radiofrequency Catheter Closure in the treatment of varicose veins does not meet the Kaiser Permanente Medical Technology Assessment Criteria. Occlusion after the VNUS Closure procedure. Twelve months after treatment, among the patients with data available, 94% of those with complete occlusion had varicose veins absent and 100% had reflux absent. These findings could be biased because data were missing on 20% of the patients at 12 months. Although the Rautio study suggests short-term benefit of the Closure system compared to the stripping procedure, there is insufficient evidence on long-term effectiveness.

Articles: The search yielded 12 articles. The best evidence was a recent case series taken from a multi-center registry and a small randomized controlled trial. The following studies were critically appraised: Rautio T, Ohinmaa A, Perala J. et al. Endovenous obliteration versus conventional stripping operation in the treatment of primary varicose veins: A randomized controlled trial with comparison of the costs. *J Vasc Surg* 2002;35: 958-65. See Evidence Table. Merchant RF, DePalma RG, Kabnick LS. Endovascular obliteration of saphenous reflux: A multicenter study. *J Vasc Surg* 2002;35: 1190-1196. See Evidence Table.

The use of Radiofrequency Catheter Closure in the treatment of varicose veins does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

TriVex System for Outpatient Varicose Vein Surgery

BACKGROUND

Because there are no published studies on the TriVex transluminated powered phlebectomy for outpatient varicose vein surgery, this was documented. Transilluminated phlebectomy is a minimally invasive surgical technique for removing varicose veins. The TriVex system was introduced by Smith & Nephew in 2000. The TriVex resector and TriVex illuminator are placed under the skin through small 2mm vertical incisions on either side of the varicosity. According to Smith & Nephew, “one of the key features of the TriVex system is its ability to light the area beneath the skin. For the first time, the vein is clearly visible, allowing the surgeon to quickly and accurately remove it using a powered resector and then visually confirm its complete extraction.”

08/08/2001: MTAC REVIEW

TriVex System for Outpatient Varicose Vein Surgery

Evidence Conclusion: There are no published studies on the TriVex System Transilluminated Powered Phlebectomy for outpatient varicose vein surgery. We were not given any unpublished data of sufficient quality to review as evidence. In conclusion, there is no evidence on which to base conclusions about the effect of this technology on health outcomes.

Articles: No published articles were found. Literature from the manufacturer included conference abstracts that cannot be evaluated as evidence. Conclusion: There is no evidence on which to base conclusions about the effect of this technology on health outcomes.

The use of TriVex in the treatment of Varicose Veins does not meet the Kaiser Permanente *Medical Technology Assessment Criteria*.

VenaSeal Closure System for Varicose Veins

BACKGROUND

Chronic venous disorders of the lower limb affect approximately 30 million adults or 35% of screened adults in the United States (McLafferty et al., 2008) and manifest most frequently like varicose veins. The mechanism underlying varicose veins can be explained by a defective valve inside the veins. The valves of the superficial veins and those of the Great Saphenous Vein (GSV) transferring blood toward the heart are dysfunctional leading to venous dilation and stasis. The accumulation of blood in the vein causes the swelling, pain, chronic skin changes, spontaneous hemorrhage, leg ulcers and fatigue. Evolution of the condition is marked by a reduction of quality of life (QoL) (Nick Morrison et al., 2015).

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The management of varicose veins has undergone a shift and several treatment options have been described. These include surgery and minimal invasive therapies. Surgery which is represented by ligation, stripping and various other techniques are described and involve saphenous vein inversion and removal, high ligation of the saphenous vein, ambulatory phlebectomy, trans illuminated phlebectomy, conservative venous ligation (CHIVA), and perforator ligation. Although surgery improves symptoms and leads to patient satisfaction (Baker, Turnbull, Pearson, & Makin, 1995; MacKenzie et al., 2002; Nelzén & Fransson, 2013; Smith, Garratt, Guest, Greenhalgh, & Davies, 1999), it can be complicated by hematoma, paresthesia and high recurrence rate (Ostler, Holdstock, Harrison, Price, & Whiteley, 2015). Other treatments encompass thermal-based techniques including endovenous thermal ablation (EVTA) by radiofrequency ablation (RFA) or laser ablation. These techniques are believed to have long-term success (vein closure) rates of 78 to 84% (Carroll et al., 2014; Nesbitt, Bedenis, Bhattacharya, & Stansby, 2014; Pan, Zhao, Mei, Shao, & Zhang, 2014) and necessitate tumescent anesthesia. In contrast, new technique such as venaseal closure system (VSCS) does not seem to require tumescent anesthesia, and has recently been approved for treatment of the incompetent GSV in the European Union, Hong Kong, and Canada (Nick Morrison et al., 2015).

The VenaSeal Closure System (VSCS) treats symptomatic varicose veins of the legs by closing the affected superficial veins with a cyanoacrylate-based adhesive. The VenaSeal System is composed of a catheter, guidewire, dispenser gun, dispenser tips, and syringes. A catheter is introduced through the skin into the varicose vein and a clear liquid (adhesive) is also injected. The insertion of the catheter and the delivery of adhesive are performed under ultrasound guidance. After the delivery of the adhesive, manual compression of the affected area begins and the adhesive changes into a solid to seal the varicose vein. The system is used for patients with venous reflux disease and it seals superficial varicose veins of the legs. Treating the diseased veins generally relieves symptoms. The VenaSeal System should not be used in patients with a known hypersensitivity to the VenaSeal adhesive or cyanoacrylates, patients who have acute inflammation of the veins due to blood clots and patients with acute whole-body infection (FDA, 2015).

06/20/2016: MTAC REVIEW
VenaSeal Closure System
Evidence Conclusion:
Conclusion:

- Based on low quality evidence, manufacturer sponsored trial, cyanoacrylate embolization (CAE) performed with the VSCS was non-inferior to radiofrequency ablation (RFA).
- There is a lack of evidence to determine whether the VenaSeal Closure System (VSCS) for varicose veins treatment is effective and safe compared to other alternative treatments.

Articles: The following article was selected for critical appraisal: Randomized trial comparing cyanoacrylate embolization and radiofrequency ablation for incompetent great saphenous veins (VeClose) See Evidence Table 1.

The use of VenaSeal Closure System of Varicose Veins does not meet the Kaiser Permanente *Medical Technology Assessment Criteria*.

01/04/2019: MTAC REVIEW
VenaSeal Closure System
Evidence Conclusion: Moderate evidence shows that VenaSeal is non-inferior and comparable to RFA in patients with moderate to severe varicosities and incompetence of the great saphenous vein on the short-term and long-term (36 months).
Articles: PubMed was searched from May 2016 through June 6, 2018 with the search terms venaseal OR venaseal closure system OR venaseal system. The search was limited to English language publications and human populations. The reference lists of relevant studies were reviewed to identify additional publications. The search yielded 18 articles. After screening, 12 articles were retained and assessed. See Evidence Tables.

The use of VenaSeal Closure System of Varicose Veins does meet the Kaiser Permanente *Medical Technology Assessment Criteria*.

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are

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met:

Endovenous Laser Ablation

CPT® or HCPC Codes	Description
36478	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, laser; first vein treated
36479	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, laser; subsequent vein(s) treated in a single extremity, each through separate access sites (List separately in addition to code for primary procedure)

Ligation and Excision

CPT® or HCPC Codes	Description
37700	Ligation and division of long saphenous vein at saphenofemoral junction, or distal interruptions
37718	Ligation, division, and stripping, short saphenous vein
37722	Ligation, division, and stripping, long (greater) saphenous veins from saphenofemoral junction to knee or below
37735	Ligation and division and complete stripping of long or short saphenous veins with radical excision of ulcer and skin graft and/or interruption of communicating veins of lower leg, with excision of deep fascia
37780	Ligation and division of short saphenous vein at saphenopopliteal junction (separate procedure)
37785	Ligation, division, and/or excision of varicose vein cluster(s), 1 leg

Sclerotherapy Telangiectasias

CPT® or HCPC Codes	Description
36468	Injection(s) of sclerosant for spider veins (telangiectasia), limb or trunk

Radiofrequency Ablation

CPT® or HCPC Codes	Description
36475	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, radiofrequency; first vein treated
36476	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, radiofrequency; subsequent vein(s) treated in a single extremity, each through separate access sites (List separately in addition to code for primary procedure)

Laser Ablation

CPT® or HCPC Codes	Description
36478	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, laser; first vein treated
36479	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, laser; subsequent vein(s) treated in a single extremity, each through separate access sites (List separately in addition to code for primary procedure)

Sclerotherapy

CPT® or HCPC Codes	Description
36465	Injection of non-compounded foam sclerosant with ultrasound compression maneuvers to guide dispersion of the injectate, inclusive of all imaging guidance and monitoring; single incompetent extremity truncal vein (eg, great saphenous vein, accessory saphenous vein)

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36466	Injection of non-compounded foam sclerosant with ultrasound compression maneuvers to guide dispersion of the injectate, inclusive of all imaging guidance and monitoring; multiple incompetent truncal veins (eg, great saphenous vein, accessory saphenous vein), same leg
36470	Injection of sclerosant; single incompetent vein (other than telangiectasia)
36471	Injection of sclerosant; multiple incompetent veins (other than telangiectasia), same leg
36473	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, mechanochemical; first vein treated
36474	Endovenous ablation therapy of incompetent vein, extremity, inclusive of all imaging guidance and monitoring, percutaneous, mechanochemical; subsequent vein(s) treated in a single extremity, each through separate access sites (List separately in addition to code for primary procedure)
S2202	Echosclerotherapy

Stab Phlebectomy

CPT® or HCPC Codes	Description
37765	Stab phlebectomy of varicose veins, 1 extremity; 10-20 stab incisions
37766	Stab phlebectomy of varicose veins, 1 extremity; more than 20 incisions

Subfascial Endoscopic Perforator Surgery (SEPS)

CPT® or HCPC Codes	Description
37500	Vascular endoscopy, surgical, with ligation of perforator veins, subfascial (SEPS)
37760	Ligation of perforator veins, subfascial, radical (Linton type), including skin graft, when performed, open,1 leg
37761	Ligation of perforator vein(s), subfascial, open, including ultrasound guidance, when performed, 1 leg

VenaSeal (chemical adhesive)

CPT® or HCPC Codes	Description
36482	Endovenous ablation therapy of incompetent vein, extremity, by transcatheter delivery of a chemical adhesive (eg, cyanoacrylate) remote from the access site, inclusive of all imaging guidance and monitoring, percutaneous; first vein treated
36483	Endovenous ablation therapy of incompetent vein, extremity, by transcatheter delivery of a chemical adhesive (eg, cyanoacrylate) remote from the access site, inclusive of all imaging guidance and monitoring, percutaneous; subsequent vein(s) treated in a single extremity, each through separate access sites (List separately in addition to code for primary procedure)

Varithena

CPT® or HCPC Codes	Description
36465	Injection of non-compounded foam sclerosant with ultrasound compression maneuvers to guide dispersion of the injectate, inclusive of all imaging guidance and monitoring; single incompetent extremity truncal vein (eg, great saphenous vein, accessory saphenous vein)
36466	Injection of non-compounded foam sclerosant with ultrasound compression maneuvers to guide dispersion of the injectate, inclusive of all imaging guidance and monitoring; multiple incompetent truncal veins (eg, great saphenous vein, accessory saphenous vein), same leg

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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1992	05/04/2010 MDCRPC, 03/01/2011 MDCRPC, 01/03/2012MDCRPC, 11/06/2012MDCRPC, 09/03/2013MPC, 01/07/2014MPC, 07/01/2014MPC, 06/02/2015MPC, 05/03/2016MPC, 03/07/2017MPC, 01/09/2018MPC, 12/04/2018MPC, 12/03/2019MPC, 12/01/2020MPC,12/07/2021MPC,12/06/2022MPC, 12/09/2023MPC	10/01/2019

MDCRPC Medical Director Clinical Review and Policy Committee

Revision History	Description
09/08/2015	Revised LCD L34010
01/13/2016	Added CPT codes and stab phlebectomy language
06/20/2016	Added VenaSeal Closure System MTAC review
04/03/2018	MPC approved to adopt the revised indication for varicose veins: *Vein size is 4.5 mm or grater in diameter (not valve diameter) & Sclerotherapy can be approved for 4.0 mm or greater superficial varicosities associated with spontaneous bleeding or a poorly healing ulcer.*
02/05/2019	MPC approved to adopt coverage criteria for VenaSeal Closure System; added 01/2019 MTAC review
10/01/2019	MPC approved to add coverage for Varithena

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Clinical Review Criteria
Vertebral Artery Angioplasty / Stenting

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Percutaneous Transluminal Angioplasty (20.7)
Local Coverage Determinations (LCD)	None
Local Coverage Article	None

For Non-Medicare Members

Kaiser Permanente has elected to use the Vertebral Artery Angioplasty, with or without Stent Placement (A-0233) MCG* for medical necessity determinations. This service is not covered per MCG. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.

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The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Vertebral artery angioplasty for stroke prevention, with or without stenting (also called endovascular intervention), has had high technical success for patients sustaining recurrent vertebrobasilar transient ischemic attacks or strokes; however, long-term outcome data are limited. (per MCG)

Applicable Codes

Considered not medically necessary:

CPT® or HCPC Codes	Description
0075T	Transcatheter placement of extracranial vertebral artery stent(s), including radiologic supervision and interpretation, open or percutaneous; initial vessel
0076T	Transcatheter placement of extracranial vertebral artery stent(s), including radiologic supervision and interpretation, open or percutaneous; each additional vessel (List separately in addition to code for primary procedure)

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Date Sent: 3/29/24

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[MPC] Medical Policy Committee

Revision History	Description

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Date Sent: 3/29/24
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Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

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Clinical Review Criteria
Virtual Colonoscopy or CT Colonography

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Colorectal Cancer Screening Tests (210.3)
Decision Memo	Decision Memo for Screening Computed Tomography Colonography (CTC) for Colorectal Cancer (CAG-00396N)*
Local Coverage Determinations (LCD)	None
KPWA Medical Policy	**Screening** Per Medicare, for Virtual Colonoscopy or CT Colonography: The evidence is inadequate to conclude that CT colonography is an appropriate colorectal cancer screening test under §1861(pp) (1) of the Social Security Act. However, for Kaiser Permanente Medicare Advantage members, virtual colonoscopy or CT colonography for colorectal cancer screening after a positive fecal immunochemical (FIT) or fecal occult blood test (FOBT) may be considered medically necessary if the patient meets the non-Medicare criteria below. **Diagnostic** Virtual Colonoscopy or CT Colonography: Due to the absence of a NCD, LCD, or other coverage guidance, KPWA has chosen to use their own Clinical Review Criteria, ***Virtual Colonoscopy or CT Colonography*** for medical necessity determinations. Use the non-Medicare criteria below.

For Non-Medicare Members

Computed tomographic (CT) colonography, also known as virtual colonoscopy, utilizes helical computed tomography of the abdomen and pelvis to visualize the colon lumen, along with 2D or 3D reconstruction. The test requires colonic preparation similar to that required for fiberoptic colonoscopy, and air insufflation to achieve colonic distention.

CT colonography is indicated only in patients having **ONE of the following** qualifying conditions:

1. Instrument colonoscopy of the entire colon is incomplete and/or contraindicated due to colon obstruction;
2. A coagulation disorder known to increase bleeding risk;
3. Lifetime anticoagulation or long-term anticoagulation therapy with increased patient risk if discontinued;
4. Significant medical or surgical complications from previous standard colonoscopy;
5. Medical condition that places the patient at increased risk with use of conscious sedation;
6. CT colonography is not a covered service when utilized in preoperative cancer staging, and in this clinical situation as standard CT or MRI is the preferred imaging study, or for screening or diagnostic evaluation in the absence of one of the indications 1-5 above.

Patient personal preference or patient refusal to undergo colonoscopy, in the absence of one of the qualifying

conditions noted above, even if signs or symptoms of colon disease are present, is not a covered indication for CT colonography. *Per the USPSTF, upon a patient request virtual colonoscopy can be covered for *"screening purposes"* (not diagnostic).

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Background

Colorectal cancer is the third most common cancer and the second leading cause of cancer-related deaths in the United States. A majority of cases can be prevented with colonoscopic removal of the precursor adenomatous polyp. With early detection, patients with cancer limited to the colonic wall will have a corrected 5-year survival of around 90%, whereas for those with lymphatic spread this figure drops to 30%. Although standard colonoscopy is a total colonic examination that allows lesion biopsy and resection, it is an invasive procedure, may fail to demonstrate the entire colon in up to 5% of cases examined by an experienced gastroenterologist, and could miss up to 20% of all adenomas. (Yee J, 2001).

Computed tomography colonography, commonly referred to as virtual colonoscopy, is a new method of imaging the colon. It uses data from thin sections helical computed tomography of the clean, air-distended colon, combined with advanced imaging software to create two-dimensional and three-dimensional images of the colon that simulate the endoluminal view seen at endoscopy. Since first introduced by Vining and colleagues in 1994, its performance has improved due to the development of fast helical CT scanners, and advances in the computer software for image reconstruction.
A variety of techniques have been described, but all share the same basic principles: Full bowel cleaning, air distension of the colon using a rectal enema tube, taking thin-section images of the colon in the supine and prone positions, and image interpretation using a combination of axial and multiplanar or endoluminal reconstructions.

The concept of virtual colonoscopy is appealing and appears to many as a potentially attractive method of screening for colorectal cancer. Compared to the standard optical colonoscopy, virtual colonoscopy is less invasive, does not require sedation, analgesia, or recovery time, and allows the entire colon to be visualized in the majority of patients. It might also provide additional information by evaluating colonic wall thickness and imaging abdominal structures outside the colon and may be more acceptable to patients.

However there are a number of potential limitations to this procedure. First of all, it requires a complete and thorough colon cleansing. Poor colonic preparation or distension limits the accuracy of CT colonography. Colonic lavage preparation often results in excess residual fluid or stools in the colon, that may simulate or cover the presence of a lesion. Another significant limitation is that virtual colonoscopy may be less effective at detecting smaller polyps and flat adenomas. In addition, unlike conventional colonoscopy, virtual colonoscopy is only a diagnostic test; the detected polyps cannot be resected during the procedure. If suspicious lesions are detected, the patient undergoes further testing, usually by conventional colonoscopy. (Hawes 2002).

The original MTAC review in June 2001 evaluated virtual colonoscopy as a screening tool, and for evaluation of high-risk patients. The second review in October 2002 focused on virtual colonoscopy for detecting of colorectal polyps among high risk, elderly or frail patients. At both meetings, virtual colonoscopy failed MTAC diagnostic test criteria. The current review is on virtual colonoscopy as a screening method for average risk asymptomatic individuals and was initiated in response to the publication of the Pickhardt study on virtual colonoscopy in a screening population.

Medical Technology Assessment Committee (MTAC)

Virtual Colonoscopy

06/13/2001: MTAC REVIEW

Evidence Conclusion: The available evidence suggests that virtual colonoscopy is not yet as effective as conventional colonoscopy at identifying colorectal polyps and carcinomas. Virtual colonoscopy may be relatively effective at identifying lesions ≥ 10 mm in size, but further study is needed to verify this. No studies to date have examined the use of virtual colonoscopy for general screening or compared the acceptability of virtual compared to conventional colonoscopy.
Articles: The literature search yielded 57 articles. Articles that were opinion pieces, reviews, dealt with technical

aspects of virtual colonoscopy, or had small sample sizes were excluded. There were 4 empirical studies with sample sizes ≥ 50. The two studies with the strongest methodologies were reviewed. Fenlon HM, Nunes DP, Schroy PC, Barish MA, Clarke PD, Ferrucci JT. A comparison of virtual and conventional colonoscopy for the detection of colorectal polyps. N Engl J Med 1999; 341: 1496-503. See Evidence Table. Spinzi G, Belloni G, Martegani A, Sangiovanni A, Del Favero C, Minoli G. Computed tomographic colonography and conventional colonoscopy for colon diseases: A prospective, blinded study. Am J Gastroenterol 2001; 96: 394-400. See Evidence Table.

The use of Virtual Colonoscopy for colon cancer screening failed Kaiser Permanente *Medical Technology Assessment Criteria*

10/09/2002: MTAC REVIEW
Virtual Colonoscopy
Evidence Conclusion: Previously, virtual colonoscopy did not meet GHC Medical Technology Assessment Committee as a screening tool for colorectal polyps and carcinomas. The purpose of the current re-review is to evaluate the use of the technology among high-risk patients, the frail, and the elderly. The available literature does not provide evidence for the use of virtual colonoscopy for the elderly and frail patients. The study (Laghi 2002) currently reviewed, as well as the Fenlon study reviewed for MTAC in June 2001, show that the sensitivity of virtual colonoscopy was good for colorectal carcinomas and large colorectal polyps in the selected symptomatic or high-risk patients. The two studies were appropriate for comparison of diagnostic tests and measured the performance of CT colonography relative to conventional colonoscopy. Virtual colonography was able to detect 100% of the colorectal carcinomas identified by conventional colonoscopy in the two studies. In Laghi's study the sensitivity was 92% for the detection of polyps 10 mm diameter or larger, 82% for those 6-9 mm, but as low as 50% for those less than 5 mm diameter, with an overall sensitivity of 78%. The corresponding values in Fenlon's study were almost similar with a slightly less overall sensitivity most probably because of the higher rate of the smaller polyps in the population studied. The sensitivity in Fenlon's study was (91%, 82%, 50% and 71% respectively). In bothstudies the sensitivity of virtual colonoscopy dropped considerably for polyps with a diameter of 5 mm or less. There is no clear consensus as to the importance of identifying and removing such tiny polyps. The per-patient specificity was 97% in Laghi's study and 84% in Fenlon's study. These high-risk patients with detected lesions may still need to undergo conventional colonoscopy for biopsy or removal of lesions. Neither study examined the impact of CTC on colorectal cancer morbidity, mortality or patient management. The inter-observer variability was not examined or discussed.
Articles: The literature search yielded 84 articles. The majority were opinion pieces, reviews, or dealing with technical aspects of virtual colonoscopy. There were 5 empirical studies, one had a very small sample size and poor methodology, and two were conducted in the same center by the same researchers but one included more patients. The study with the larger size was selected for critical appraisal. The remaining two were retrospective studies conducted on frail or elderly patients, one used non-helical CT scan, and the other was conducted to evaluate the accuracy of CT scans in detecting caecal carcinomas using oral contrast media and minimal preparation. *The study critically appraised is:* Laghi A, Iannaccone R, Carbone I, et al. Detection of colorectal lesions with virtual computed colonography. *Am J Surg* 2002; 183:124-131. See Evidence Table.

The use of virtual colonoscopy in colorectal screening for the frail elderly does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

02/11/2004: MTAC REVIEW
Virtual Colonoscopy
Evidence Conclusion: The two best new studies were evaluated. Pickhardt found a higher sensitivity and specificity of virtual colonoscopy than Johnson. Both included asymptomatic populations, but individuals in the Johnson study were at higher than average risk of colorectal neoplasia (i.e. personal or strong family history of colorectal neoplasia). The difference in the study population does not explain the lower sensitivity in Johnson because any bias introduced by having a higher risk sample would tend to increase, not decrease the sensitivity. The populations in the Pickhardt and Johnson studies may actually have been quite similar. The prevalence of adenomatous polyps ≥1 cm was 4% in Pickhardt and 5% in Johnson. The better performance of virtual colonoscopy in the Pickhardt study may be due in part to the routine use of 3-D CT images by Pickhardt. Johnson generally used 2-D images, and 3-D images were used for regions with suspected abnormalities. In addition, Johnson used conventional colonoscopy as the reference standard whereas Pickhardt used a reference standard developed for the study—conventional colonoscopy enhanced by information from the virtual colonoscopy. Neither of the new studies included polyps < 5mm which many experts believe are not clinically significant. Previous studies of virtual colonoscopy evaluated by MTAC have found low sensitivity for these smaller polyps. In summary, the Pickhardt study is the first to suggest that virtual colonoscopy has comparable sensitivity and specificity to conventional colonoscopy in asymptomatic individuals. The Johnson study suggests that the sensitivity of virtual

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage.
Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

colonoscopy is relatively low and that interobserver variability is high. Replication of the findings obtained in the Pickhardt study would strengthen the evidence.

Articles: The search yielded 103 articles, many of which were reviews, opinion pieces or dealt with technical aspects of the procedure. There were five prospective blinded studies comparing the diagnostic accuracy of virtual colonoscopy to conventional colonoscopy in asymptomatic populations. The two largest studies, each of which had samples larger than 700 individuals, were critically appraised. The others had sample sizes of 205, 158 and 80. The following articles were reviewed: Johnson CD, Harmsen WS, Wilson LA. Prospective blinded evaluation of computed tomographic colonography for screen detection of colorectal polyps. *Gastroenterol* 2003; 125: 311-319. See Evidence Table. Pickhardt PJ, Choi JR, Hwang I. et al. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. *N Engl J Med* 2003; 349: 2191-2000. See Evidence Table.

The use of virtual colonoscopy in colorectal screening does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

06/18/2009: MTAC REVIEW

Virtual Colonoscopy

Evidence Conclusion: Diagnostic accuracy in the Regge et al., 2009 study is not dramatically different than previous studies, particularly when considering that it was conducted in a population at increased risk of CRC. There is still no high-grade evidence on the impact of screening with CT colonography on CRC mortality. Although it is not invasive like colonoscopy, CT colonography requires the same colonic preparation and involves exposure to radiation, and patients who test positive still require a colonoscopy for polyp removal.

Articles: Regge D, Laudi C, Galatola G et al. Diagnostic accuracy of computed tomographic colonography for the detection of advanced neoplasia in individuals at increased risk of colorectal cancer. JAMA 2009; 301: 2453-2461. See Evidence Table 6 and Evidence Table 7.

Update of evidence but the evidence does not change the previous review.

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
74261	Computed tomographic (CT) colonography, diagnostic, including image postprocessing; without contrast material
74262	Computed tomographic (CT) colonography, diagnostic, including image postprocessing; with contrast material(s) including non-contrast images, if performed
74263	Computed tomographic (CT) colonography, screening, including image postprocessing

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check.**

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Date Created	Date Reviewed	Date Last Revised
06/13/2001	05/04/2010[MDCRPC],03/01/2011[MDCRPC], 01/03/2012[MDCRPC], 11/06/2012[MDCRPC], 09/03/2013[MPC], 02/04/2014[MPC], 12/02/2014[MPC], 10/06/2015[MPC], 08/02/2016[MPC], 06/06/2017[MPC], 04/03/2018[MPC], 03/05/2019[MPC], 03/03/2020[MPC], 03/02/2021[MPC], 03/01/2022[MPC],03/07/2023[MPC]	12/05/2022

[MPC] Medical Policy Committee

Revision History	Description
07/25/2016	Changed NCD to (210.0)
06/06/2017	Adopted KPWA policy for Medicare members

09/25/2017	Added Decision Memo language
08/31/2021	Added NCD 210.3. Effective January 1, 2022, virtual colonoscopy or CT colonography for colorectal cancer screening after a positive fecal immunochemical (FIT) or fecal occult blood test (FOBT) may be considered medically necessary for Medicare members when the patient meets the non-Medicare clinical review criteria.
12/05/2022	Clarified USPSTF language with Director of Clinical Knowledge & Implementation.

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Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Vitrectomy Chair or Support Face Down Positioning Device

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Durable Medical Equipment Reference List (280.1)
Local Coverage Determinations (LCD)	None
Local Coverage Article	None
Joint DME MAC Publication	Correct Coding – Face Down Positioning Devices **This device is noncovered per Medicare*

For Non-Medicare Members

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

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Background

The macula is the small area of the retina that provides the sharp central vision that is needed for reading, driving, and seeing fine details. A macular hole is a small break in the macula, which can cause blurred and distorted central vision. Macular holes are related to aging; fifty percent of macular holes occur in patients 65-74 years old. Only three percent were found to occur in patient under the age of fifty-five. The majority of holes are idiopathic; however, they can occur from eye disorders, such as high myopia (nearsightedness), macular pucker, and retinal detachment; eye diseases, such as retinopathy and Best's disease; and trauma to the eye (Solebo 2010; American Academy of Ophthalmology 2008).

The pathogenesis of idiopathic macular holes is not fully understood; however, recent histopathological and high resolution imaging studies have increased current understanding of the natural history of this condition. One theory of macular hole formation suggests that as we age, the vitreous, a gel-like substance that fills about 80 percent of the eye, shrinks and pulls away from the retinal surface creating tractional forces on the retinal and leading to macular holes (Solebo 2010). If left untreated, approximately three percent to eleven percent of macular holes close spontaneously (American Academy of Ophthalmology 2008). The treatment for macular hole is vitrectomy, which involves the surgical removal of the vitreous gel from the middle of the eye and is thought to relieve vitreofoveal traction and reactivate reparative healing mechanisms (Gupta 2009). Some surgeons instruct their patients to postoperatively maintain a face-down position from one day to three weeks to tamponade the macular hole. However, a recent study demonstrated that approximately 77% percent of macular holes close as soon as twenty-four hours after surgery (Solebo 2010). Research is lacking regarding the appropriate duration of postoperative face-down posturing and as to whether face-down positioning is needed at all.

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Medical Technology Assessment Committee (MTAC)

Vitrectomy Chair

04/19/2010: MTAC REVIEW

Evidence Conclusion: There is limited evidence regarding the effect of duration of face-down posturing on macular hole closure. The best available evidence was provided by the Tatham and Banerjee (2009) meta- analysis of five studies. This meta-analysis attempted to determine whether decreasing or eliminating face-down position time would affects surgical outcomes. Posturing for 5 to 10 days was compared to posturing for 24 hours or less. The results from the analysis suggest that there is a 34% increased risk of anatomical failure (macular hole non-closure) when face-down posturing is reduced from 5 to 10 days to less than 24 hours. However, this difference was not statistically significant. Within the studies that comprise the meta-analysis there is diversity of study design, surgical technique used, follow-up periods, and patient characteristics. This diversity reduced the validity of the meta-analysis. Additionally, non-randomized studies were included in the analysis making it more prone to bias. Conclusion: There is insufficient evidence to determine whether the duration of face-down posturing after macular hole surgery affects macular hole closure rates. There is insufficient evidence to determine whether a vitrectomy chair will improve outcomes after surgery.

Articles: The literature search yielded over 100 articles. The majority of the articles were unrelated to the current review. There was only one meta-analysis regarding face-down posturing. This article was selected for critical appraisal. The search did not reveal any evidence pertaining to the use of a vitrectomy chair after surgery.

Tatham A., Banerjee S. Face-down posturing after macular hole surgery: A meta-analysis. British Journal of Ophthalmology 2009. Advance online publication. doi:0.1136/bjo.2009.163741 See Evidence Table.

The use of a Vitrectomy Chair for the treatment of post-operative recovery from macular surgery does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Considered Not Medically Necessary:

CPT® or HCPC Codes	Description
No specific codes	

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
05/10/2010	05/04/2010 MDCRPC, 04/05/2011 MDCRPC, 02/07/2012 MDCRPC, 12/04/2012 MDCRPC, 10/01/2013 MDCRPC, 08/05/2014 MPC, 06/02/2015 MPC, 04/05/2016 MPC, 02/07/2017 MPC,12/052017 MPC, 11/06/2018 MPC, 11/05/2019 MPC, 11/03/2020 MPC,11/02/2021 MPC, 11/01/2022 MPC, 11/07/2023 MPC, 02/13/2024MPC	11/03/2020

MDCRPC Medical Director Clinical Review and Policy Committee

MPC Medical Policy Committee

Revision History	Description
11/03/2020	Added Correct Coding reference from Noridian

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Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Vagus Nerve Stimulation

- Adjunctive Treatment for Partial Onset Epileptic Seizures
- Medical Diagnoses
- Treatment Resistant Depression
- gammaCore Sapphire non-invasive vagus nerve stimulator

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Vagus Nerve Stimulation (VNS) (160.18)
Local Coverage Determinations (LCD)	None
Local Coverage Article	None

For Non-Medicare Members

I. Implantable Vagus Nerve Stimulator
   A. Adjunctive Treatment for Epilepsy
      - No medical necessity review is required for this service
   B. Mental Health Diagnoses
      - MCG* B-821-T, Vagus Nerve Stimulation, Implantable: Behavioral Health Care. This service is not covered per MCG Guidelines. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.
   C. All other non-Mental Health Diagnoses

II. MCG* A-0424, Vagus Nerve Stimulation - Implantable. This service is not covered for any diagnoses besides epilepsy per MCG guidelines. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.

III. Non-Invasive Vagus Nerve Stimulator
   A. gammaCore Sapphire
      - MCG* A-0998, Vagus Nerve Stimulation- Transcutaneous. This service is not covered per MCG guidelines. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.

MCG* manuals are proprietary and cannot be published and/or distributed. However, on an individual member basis, Kaiser Permanente can share a copy of the specific criteria document used to make a utilization management decision. If one of your patients is being reviewed using these criteria, you may request a copy of the criteria by calling the Kaiser Permanente Clinical Review staff at 1-800-289-1363 or access the MCG Guideline Index using the link provided above.

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Background

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The Cyberonics Vagus Nerve Stimulator (VNS) Therapy System is a device similar in design and function to a cardiac pacemaker. It consists of a constant current pulse generator implanted in the anterior chest wall and a bipolar stimulating electrode that is wrapped around the left vagal nerve in the neck. A magnet controlled by the patient can turn off the device.

In 1985, there were initial animal studies to test VNS, and devices were implanted in humans beginning in 1988. The first clinical application was to treat epilepsy. Research on epilepsy treatment suggested that VNS might reduce dysphoria in some patients. Moreover, VNS has been found to increase levels of a metabolite of serotonin in epilepsy patients, an effect similar to that seen after successful treatment of depression. These findings led to an interest in using VNS for patients with treatment-resistant depression (Goodnick et al., 2001).

In July 1997, the FDA granted pre-market approval for the Cyberonics VNS device to be used as an adjunctive treatment for medically refractory partial onset seizures in patients over 12 years of age. In July 2005, the FDA approved the device for patients 18 and older with treatment-resistant depression who failed to respond to at least 4 courses of adequate medication or electroconvulsive therapy (ECT).

Evidence and Source Documents

Adjunctive Treatment for Partial Onset Epileptic Seizures Vagus Nerve Stimulation for Treatment-Resistant Depression

Medical Technology Assessment Committee (MTAC)

Vagal Nerve Stimulation (VNS) as an Adjunctive Treatment for Partial Onset Epileptic Seizures

BACKGROUND

Repetitive stimulation of the vagal nerve has been shown to reduce the frequency of seizures in various animal models of epilepsy. Epilepsy is typically treated with anti-epileptic medications and in some cases surgical resection of the epileptic focus. Despite the efficacy of these treatments, 25-50% of patients with epilepsy continue to experience seizures and/or suffer harms from continued use of anti-epileptic medications. The NeuroCybernetics Prosthesis (NCP) Vagal Nerve Stimulator (VNS) is a device (similar in design and function to a cardiac pacemaker) which consists of a constant current pulse generator implanted subcutaneously in the anterior chest wall and a bipolar stimulating electrode which is wrapped around the left vagal nerve in the neck. A magnet controlled by the patient can initiate stimulation (when the patient senses the onset of a seizure) or can turn off the device depending on how it is placed against the device. The mechanism by which the VNS reduces epileptic seizures is still unknown, however it has been shown that stimulation of the vagal nerve has the ability to affect brain wave activity.

02/10/1999: MTAC REVIEW

Vagal Nerve Stimulation (VNS) as an Adjunctive Treatment for Partial Onset Epileptic Seizures

Evidence Conclusion: Recently published evidence from a large, well designed, multicenter trial of 254 patients randomized to high or low Vagal nerve stimulation demonstrates that the use of VNS in the treatment of medically refractory patients reduces seizure frequency by approximately 28% compared to baseline and 13% compared to an active control group receiving low stimulation. This translates into an average reduction of 3 seizures per week. Adverse events such as voice alteration, cough and pharyngitis during stimulation are reported to occur in 25-60 percent of subjects but are generally well tolerated. Patients receiving high VNS also reported significant improvement in their perception of well-being. A randomized controlled trial of 114 patients reports a similar beneficial effect of VNS. Data from an open extension trial of the first 67 patients exiting the RCT demonstrates that all patients chose to either continue high stimulation or switch from low to high stimulation for up to 15 months. Four out of five patients in this group demonstrated continuing clinically significant reductions in seizure frequency over 15 months with 5 drop-outs (8%) due to lack of efficacy and no drop-outs due to side effects from stimulation. **Articles**: Handforth, A et al. Vagus Nerve Stimulation Therapy for Partial Onset Seizures: A Randomized Active- Control Trial. Ne*urology*1998; 5:48-55 See Evidence Table**.** The Vagus Nerve Stimulation Group, A Randomized Controlled Trial of Chronic Vagus Nerve Stimulation for Treatment of Medically Intractable Seizures. *Neurology, 1995; 45:224-230.* See Evidence Table**.** Vagus Nerve Stimulation for Treatment of Partial Seizures: 3. Long-Term Follow-Up on First 67 patients exiting a Controlled Study. *Epilepsia, 1994;35:637-643.* See Evidence Table.

The use of the NeuroCybernetics Prosthesis (NCP) Vagal Nerve Stimulator (VNS) for treating patients with medically refractory partial onset seizures has been approved by the FDA and therefore meets *Kaiser Permanente Medical Technology Assessment Criteria*.

Vagus Nerve Stimulation for Treatment-Resistant Depression

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BACKGROUND

The Cyberonics Vagus Nerve Stimulator (VNS) Therapy System is a device similar in design and function to a cardiac pacemaker. It consists of a constant current pulse generator implanted in the anterior chest wall and a bipolar stimulating electrode that is wrapped around the left vagal nerve in the neck. A magnet controlled by the patient can turn off the device.

In 1985, there were initial animal studies to test VNS, and devices were implanted in humans beginning in 1988. The first clinical application was to treat epilepsy. Research on epilepsy treatment suggested that VNS might reduce dysphoria in some patients. Moreover, VNS has been found to increase levels of a metabolite of serotonin in epilepsy patients, an effect similar to that seen after successful treatment of depression. These findings led to an interest in using VNS for patients with treatment-resistant depression (Goodnick et al., 2001).

In July 1997, the FDA granted pre-market approval for the Cyberonics VNS device to be used as an adjunctive treatment for medically refractory partial onset seizures in patients over 12 years of age. In July 2005, the FDA approved the device for patients 18 and older with treatment-resistant depression who failed to respond to at least 4 courses of adequate medication or electroconvulsive therapy (ECT). VNS passed MTAC evaluation criteria in 1999 for epilepsy. In 2005, it was reviewed for treatment-resistant depression and failed MTAC evaluation criteria. At that time, all of the major studies were conducted by the same group of researchers (A. John Rush and colleagues) with links to the device manufacturer. There was one published RCT (Rush et al., 2005), with negative findings. A post-hoc sub-group analysis of the Rush RCT with a historical control group (George et al., 2005), a design subject to bias, found a benefit of the treatment for a selected group of patients. FDA approval of the VNS device for depression remains controversial. Citing a lack of efficacy data and concerns about safety, an FDA review team decided not to approve the new indication for the Cyberonics device. Instead, the team recommended additional data from RCTs. The Director of the FDA's Center for Devices and Radiological Health (CDRH) overruled the team and granted pre-market approval. The Director agreed with Cyberonics researchers that it would be unethical to conduct a blinded treatment study with patients with major depression.

The FDA approval in 2005 included a request to Cyberonics for additional post-marketing controlled studies (Shuchman, 2007).

12/05/2005: MTAC REVIEW

Vagus Nerve Stimulation for Treatment-Resistant Depression

Evidence Conclusion: There is insufficient evidence that VNS is effective therapy for treatment-resistant depression. All of the major studies were conducted by the same group of researchers. This research team has close financial links with the device manufacturer which could bias study methodology, analysis and/or results reporting. The single published RCT (Rush et al., 2005) had negative findings. There was not a statistically significant between-group difference in the primary outcome, 3-month HAM-D response, between groups receiving active and placebo VNS therapy. A subsequent non-randomized study (George et al., 2005) followed-up a portion of the RCT study patients, and compared findings to a group of depressed patients who were participating in a different study. The George study found a significant difference in the primary outcome, change in the Inventory of Depressive Symptomatology (IDS) score, favoring the VNS therapy group. The study is subject to selection bias due to the use of different patient populations, and the exclusion of patients who responded to sham treatment in the RCT. It is also subject to observation biases because patients did not receive a consistent intervention e.g. those in the VNS group had different lengths of treatment, and possible bias in the selection of the primary outcome (IDS score was the only significant efficacy outcome in the RCT). A limitation of all of the published studies was that the eligibility for participation did not match the FDA definition of treatment-resistant depression. The studies required patients to have failed a minimum of 2 courses of medication whereas the FDA approved VNS therapy for depressed patients who have failed at least 4 treatments.

Articles: The published empirical studies on VNS therapy for depression were conducted by a single research group with close links to the manufacturer, A. John Rush and colleagues. As described in the recent BlueCross BlueShield review (2005), these studies were: D01: Case series with n=50 patients, D02: 3-month randomized controlled trial with n=233, D02 extension arm. 12 month follow-up of selected patients who participated in study D02, D04: Case series of patients not receiving VNS. This study was used to form a comparison group to the 12- month extension of study D02. *Articles critically appraised were:* Publication reporting the results of the RCT, D02: Rush AJ, Marangell LB, Sackeim HA et al. Vagus nerve stimulation for treatment-resistant depression: A Publication comparing 12-month outcomes in the D02 extension and the D04 comparison group: George MS, Rush AJ, Marangell LB et al. A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. Biol Psychiatry 2005; 58: 364-373. See Evidence Table

The use of Vagus nerve Stimulation in the treatment of treatment-resistant depression does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

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06/01/2009: MTAC REVIEW
Vagus Nerve Stimulation for Treatment-Resistant Depression
Evidence Conclusion: Conclusions of the 2005 MTAC review were as follows: There is insufficient evidence that VNS is an effective therapy for treatment-resistant depression. All of the major studies were conducted by the same group of researchers that had close financial links with the device manufacturer. The single published RCT (Rush et al., 2005) had negative findings. There was not a statistically significant between-group difference in the primary outcome, 3-month HAM-D response, between groups receiving active and placebo VNS therapy. A subsequent non-randomized study (George et al., 2005) followed-up a portion of the RCT study patients and compared findings to a group of depressed patients who were participating in a different study. The George study, which was subject to selection and observation biases, found a significant difference in the primary outcome, change in the Inventory of Depressive Symptomatology (IDS) score, favoring the VNS therapy group. As of May 2009, there is still insufficient evidence to determine whether VNS is effective for depressed patients who have failed antidepressant treatment. There were no additional RCTs or non-randomized comparative studies. A new case series (Schlaepfer) with 74 patients recruited from 9 sites in Europe found a 34% response rate at 3 months (end of active treatment period), which increased to 47% at the 12 month follow-up. The Schlaepfer case series represents a low grade of evidence. There was no comparison group, so response with a different treatment or no treatment is not known. Also, patients were not blinded, and they had regular clinic visits, both of which could affect responses to a subjective outcome measure like the HAMD.
Articles: The Pubmed search yielded 13 articles. Only 9 of these were actually on depression (the rest addressed epilepsy, Alzheimer's disease or rapid-cycling bipolar disorder). Of the 9 articles on depression, 3 were reviews or opinion pieces, 3 were basic research on brain changes during VNS and 3 were empirical studies. Two of the 3 empirical studies were subanalyses of the Rush et al. (2005) RCT. On closer inspection, neither of these analyses was eligible for MTAC review. The Nierenberg et al. (2008) study did not compare outcomes associated with active vs. sham VNS; instead the investigators compared the effects of VNS on bipolar vs. unipolar depressed participants within the Rush RCT. The other sub-analysis, Burke et al. (2006) evaluated the effect of concomitant VNS and electroconvulsive therapy (ECT) in the 14 participants in the Rush RCT who received both treatments. This was a descriptive analysis of a small number of individuals and does not aid our understanding of the effectiveness of VNS. The third new empirical study was a case series (n=74) conducted in Europe. This study was critically appraised. A Blue Cross Blue Shield technology assessment report, used for the first MTAC review, has not been updated since August 2006. No additional published articles were identified on the Cyberonics website. The citation for the new European study is as follows:
Schlaepfer TE, Frick C, Zobel A et al. Vagus nerve stimulation for depression: efficacy and safety in a European study. Psychol Med 2008; 38: 651-661. See Evidence Table.

The use of Vagus Nerve Stimulation in the treatment of treatment-resistant depression does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

10/12/2020: MTAC REVIEW
gammaCore Sapphire non-invasive vagus nerve stimulator
Evidence Conclusion:

- Cluster headache
  - Although results are promising, there is insufficient evidence to determine the efficacy of nVNS for the acute treatment of patients with cluster headache.
  - Results are promising from one RCT. More studies are needed. There is insufficient evidence to determine the efficacy of nVNS as prophylactic treatment for the prevention of episodic or chronic cluster headache.
- Migraine
  - Acute treatment of migraine: A randomized controlled trial with moderate quality shows that nVNS was effective for aborting migraine attacks at 30 and 60 minutes after treatment and for relieving pain 2 hours after treatment. More studies are warranted to confirm these findings.
  - Prevention of migraine: there is insufficient evidence to determine the efficacy of nVNS in preventing migraine with or without aura.

Articles: PubMed was searched through August 2020 with the search terms (gammaCore Sapphire OR non-invasive vagus nerve stimulator) AND (cluster headache OR episodic cluster headache OR chronic cluster headache OR migraine) with variations. The search was limited to English language publications and human populations. The reference lists of relevant studies were reviewed to identify additional publications. Only RCTs were included in the search. Studies with no comparison group were not reviewed. Key trials were selected and reviewed.

Applicable Codes

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Vagus Nerve Stimulation, Implantable- Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
61885	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array
61886	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to 2 or more electrode arrays
61888	Revision or removal of cranial neurostimulator pulse generator or rec
64553	Percutaneous implantation of neurostimulator electrode array; cranial nerve
64568	Incision for implantation of cranial nerve (eg, vagus nerve) neurostimulator electrode array and pulse generator
64569	Revision or replacement of cranial nerve (eg, vagus nerve) neurostimulator electrode array, including connection to existing pulse generator

Vagus Nerve Stimulation, Transcutaneous (gammaCore Sapphire non-invasive vagus nerve stimulator): Considered Not Medically Necessary:

CPT® or HCPC Codes	Description
E1399	Durable medical equipment, miscellaneous

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed	Date Last Revised
10/08/1999	07/06/2010[MDCRPC], 05/03/2011[MDCRPC], 03/06/2012[MDCRPC], 01/08/2013[MDCRPC], 11/05/2013[MPC], 09/02/2014[MPC], 07/07/2015[MPC], 05/03/2016[MPC], 03/07/2017[MPC], 01/09/2018[MPC], 11/06/2018[MPC], 11/05/2019[MPC], 11/05/2019[MPC], 11/03/2020[MPC], 11/02/2021[MPC], 11/01/2022[MPC], 11/01/2022[MPC], 11/07/2023[MPC]	11/02/2021

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
11/03/2020	Added MTAC review for gammaCore Sapphire non-invasive vagus nerve stimulator
11/02/2021	MPC approved to adopt MCG* B-821-T criteria for medical necessity determinations for VNS for Mental Health Diagnoses. Requires 60-day notice, effective 04/01/2022.

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KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria

Left Atrial Appendage (LAA) Closure Therapy

- Watchman, Amplatzer Amulet (percutaneous)
- AtriClip (non-percutaneous, used during surgical procedures)

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Criteria

**Please send all cases to Medical Director for review.*

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Percutaneous Left Atrial Appendage Closure (LAAC) (20.34)
Local Coverage Determinations (LCD)	None
Local Coverage Article	Decision Memo for Percutaneous Left Atrial Appendage (LAA) Closure Therapy (CAG-00445N)
KPWA Policy	Due to the absence of an active NCD, LCD, or other coverage guidance for non-percutaneous left atrial appendage closure devices, Kaiser Permanente has chosen to use their own Clinical Review Criteria, ***Left Atrial Appendage (LAA) Closure Therapy***, for medical necessity determinations. Refer to the Non-Medicare criteria **II.B.** below regarding **non-percutaneous** closure.

For Non-Medicare Members

I. Percutaneous LAA appendage closure using a device approved by the FDA (e.g., the Watchman or Amplatzer Amulet) is approved for patients with atrial fibrillation who meet **ALL of the following criteria**:

- A CHA2DS2-VASc score ≥ 3
- Patient is suitable for short-term warfarin but deemed unable to take long term oral anticoagulation (neither Warfarin nor DOACs) following the conclusion of shared decision making, as LAAC is only covered as a second line therapy to oral anticoagulants.
- The patient is formally evaluated by a multidisciplinary Heart Team of medical professionals who document a collaborative recommendation for LAA occlusion.
- The procedure must be furnished in a hospital with established cardiac surgery, structural heart disease, and electrophysiology (EP) programs.
- A formal shared decision-making interaction with an independent non-interventional cardiologist (not part of procedural treatment team) using an evidence-based decision tool on oral anticoagulation in patients with NVAF prior to LAAC. Additionally, the shared decision-making interaction must be documented in the medical record.
- The procedure must be performed by an interventional cardiologist(s), electrophysiologist(s) or cardiovascular surgeon(s) that meets accepted CMS criteria for training/implantation (see Medicare NCD)
- The patient is enrolled in, and the MDT and hospital must participate in a prospective, national, audited registry.

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II. The use of any other left atrial appendage devices are considered investigational, including but not limited to any of the following:

- Devices not approved by the FDA for percutaneous LAA closure (e.g., LARIAT or PLAATO devices).
- Devices used during surgical procedures (**non-percutaneous**) to occlude the LAA (e.g., AtriClip is not medically necessary).

If requesting these services, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist
- Last 6 months of radiology notes if applicable

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting more than 5.5 million individuals in the US, and its prevalence is increasing with the aging population. AF leads to loss of organized atrial contractions, which results in blood stasis in the atrium and thrombus formation with the potential for embolization leading to stroke. It is reported that the risk of ischemic stroke is up to 5 times higher in patients with AF. This risk of cardioembolic stroke varies from one individual to the other based on other risk factors and comorbidities, but overall it increases considerably with age from 1.5% in patients 50-59 years of age to 23.5% for those 80-89 years of age. Stroke prophylaxis is thus an important component in managing patients with non-valvular AF (Holmes 2009, Reddy 2013, Bode 2015).

Antiarrhythmic drugs, and catheter ablation of AF may provide relief of symptoms, but do not sufficiently prevent the occurrence of thromboembolic events. Long-term oral anticoagulant therapy is the standard of care for effective stroke prevention in AF patients at high risk for thromboembolism according to clinical risk scores such as the CHADS2 and the CHA2DS2-VASc models. Warfarin is highly effective in reducing stroke in at-risk patients with AF, but is often not well tolerated by all patients, has a very narrow therapeutic range, and is associated with a high risk of bleeding. In addition, its effectiveness may vary due to its interactions with some foods and medications resulting in the need for frequent monitoring and dose adjustments. It is reported that 50% of the patients' blood test results are outside the therapeutic range. These limitations as well as intolerance or contraindications to warfarin in some patients have led to the non-use or discontinuation of the drug in a large proportion of AF patients, particularly the older patients who are at an increased risk of stroke. The more recently developed oral anticoagulant agents (NOACs) have overcome many of warfarin's limitations, but also need lifelong use and carry the potential risk of bleeding at similar or lower rates than warfarin, depending on the agent used (Sick 2007, Holmes 2009, Alli 2013, Reddy 2013, Price 2014).

Researchers have been investigating non-pharmacological alternatives for patients with intolerance or contraindication to anticoagulant therapy. It is believed (based on echocardiography and autopsy studies) that more than 90% of the atrial thrombi in patients with non-valvular AF, originate in the left atrial appendage (LAA), which is an embryonic remnant of the original embryonic left atrium. LAA is a long tubular trabeculated structure continuous with the atrial cavity. The location and the discrete nature of the LAA have led to the development of a number of techniques for excluding it from the systemic circulation. These include its surgical excision or obliteration by surgical ligation, or by the use of implantable devices via mini thoracotomy or percutaneously.
These devices include the St Jude Amplatzer® cardiac plug, Coherex WaveCrest® LAA occlusion system, LARIAT® device, the PLAATO system, and the WATCHMANTM LAA system. The latter is the focus of the current review (McCabe 2009, Holmes 2009, Alli 2014).

The WATCHMANTM (WM) left atrial appendage closure (LAAC) system (Boston Scientific Corp., Maple Grove, Minnesota) is the most intensely studied for LAA occlusion. It is a 3-part system consisting of a trans-septal access sheath, a delivery catheter, and an implantable nitinol (nickel titanium) device. The system is designed to facilitate the device placement through femoral venous access via transseptal route into the LAA. The implantable device is parachute-shaped and comprises a self-expanding nitinol frame structure with fixation barbs to secure it in the LAA, and a permeable polyester membrane that covers the atrial facing surface of the device. The WM

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implant is available in 5 sizes (21, 24, 27, 30, and 33 mm) and is typically chosen 10-20% larger than the LAA body to have sufficient compression for stable positioning to minimize the risk of device embolization. The procedure is performed in the cardiac catheterization laboratory under general anesthesia. Transseptal access is obtained using standard techniques guided by fluoroscopic or transesophageal echocardiography (TEE). Once access is gained into the left atrium (LA), a variety of approached can be used to place the guidance sheath. A pigtail angiographic catheter is then inserted into the sheath which is advanced into the distal portion of the LAA. Once this catheter is placed, the sheath is advanced over it into the LAA. Positioning of the sheath is of critical importance as the LAA is thin-walled and fragile and may be damaged or perforated. Anticoagulation is necessary and it is also important to avoid the potential for air embolism during the procedure. WM is permeable to blood and thus the patients require post-procedure warfarin therapy for 45 days with INR between 2.0 and 3.0 for those who are legible for warfarin or other equivalent. A TEE is performed for device assessment at 45 days after which a decision is made to discontinue warfarin. After warfarin is discontinued, the patient is treated with clopidogrel 75 mg and aspirin 81-325 mg for 6 months following the implantation, after which the clopidogrel is discontinued and aspirin is used indefinitely (Sick 2007, Alli 2014, Holmes 2015).

As with other invasive procedures, the techniques and devices used for LAA closure including WATCHMANTM have potential complications including pericardial effusion, procedure-related stroke, device thrombosis, device embolization, bleeding, arrhythmia, access site complications, arteriovenous fistula, and pseudoaneurysm formation (Alli 2014). More recently on April 23, 2015, the FDA recalled the TigerPaw II (Maquet, Rastatt, Germany) LAA closure device following reports that the device could cause tearing of the left atrial wall and bleeding.

The WATCHMANTM device received FDA approval in 2015 as an alternative to commonly-used blood thinners to prevent stroke in patients with atrial fibrillation who are at an increased risk of stroke and systemic embolism based on CHADS2 or CHA2DS2-VASc and are recommended for anticoagulation therapy; are deemed by their physicians to be suitable for warfarin; and have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin. The FDA had initially declined the approval of the device twice before the final approval due of concerns about its safety and effectiveness, including the complications while implanting the device.

Medical Technology Assessment Committee (MTAC)

Watchman

08/17/2015: MTAC REVIEW

Evidence Conclusion: The published evidence does not support the use of Watchman LAA occlusion device for the prevention of stroke in in patients with nonvalvular atrial fibrillation. Ideally a new therapy or intervention would be at least equivalent or noninferior (if not superior), to the gold standard treatment with regard to safety, efficacy, and long term outcomes. To date, LAAC closure with Watchman system in patients with nonvalvular atrial fibrillation has not fulfilled the safety requirement in the two pivotal trials, nor the efficacy requirement in the PREVAIL trial. The PROTECT AF trial showed that occluding the LAA with the Watchman device is feasible and with noninferior efficacy than warfarin in reducing the composite risk of stroke, cardiac death, or systemic embolism as primary prevention therapy in patients with CHADS2 >1. In the PREVAIL trial that included higher risk patients, the device did not reach the noninferiority level for the primary efficacy composite endpoint of ischemic or hemorrhagic stroke, cardiovascular or unexplained death, or systemic embolism. More recent long-term follow-up data from PROTECT AF show that the device remained noninferior to warfarin use as regards its efficacy but not its safety. More recent long-term follow-up data from PREVAIL trial show that the 2 first primary endpoints of the trial do not meet the prespecified noninferiority end point of the study. There is evidence from the published RCTs that the occlusion of the LAA with the Watchman device is associated with high risk of procedure-related ischemic stroke and device embolism, as well as other adverse events including serious pericardial effusion and major bleeding. There is insufficient evidence from well-designed RCTs to determine the efficacy and safety of Watchman in patients with a contraindication or intolerance to warfarin or other blood thinners.
There is insufficient published evidence from well-designed RCTs to determine the efficacy and safety of Watchman device to other LAA occluding devices or surgical interventions in patients with nonvalvular atrial fibrillation. There is no published study to date, that compared the efficacy and safely LAA occlusion to any of the NOACs, that demonstrated (from large RCTs) to be either noninferior or superior to warfarin in reducing stroke or systemic embolism with similar or lower rates of major hemorrhage. There are currently 11 ongoing trials on LAA occlusion/excision that may add more information on the safest and most effective intervention for the prevention of stroke in patients with non-valvular atrial fibrillation. WATCHMAN LAA closure device was reviewed by the Kaiser Interregional New Technologies Committee (INTC) in June 1st, 2015. The Committee used the Blue Cross Blue Shield TEC Assessment Program as their primary evidence source and updated the review with new

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evidence that would change the TEC results or conclusions. Both TEC and INTC concluded that the evidence was insufficient to determine that WATCHMAN LAAC is medically appropriate for stroke prevention for patients with nonvalvular atrial fibrillation.

Articles: The literature search identified two randomized controlled trials (PROTECT AF and PREVAIL), a nonrandomized prospective study, and a pilot observational study on Watchman LAA occlusion system. All studies were conducted mainly by the same group of principal investigators. The literature search also identified a more recent meta-analysis of the two RCTs also conducted by the same investigators, and another meta-analysis of observational studies (with no control groups) that examined different devices used in the percutaneous occlusion of the left atrial appendage. The two RCTs on Watchman LAA closure device and the meta-analysis pooling their results were selected for critical appraisal. Holmes DR, Reddy VY, Turi ZG, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomized non-inferiority trial. Lancet. 2009; 374 (9689):534-542. See Evidence Table 1. Holmes DR Jr, Kar S, Price M, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. J Am Coll Cardiol. 2014 Jul 8; 64 (1):1-12. See Evidence Table 2. Holmes DR Jr, Doshi SK, Kar S, et Al. Left Atrial Appendage Closure as an Alternative to Warfarin for Stroke Prevention in Atrial Fibrillation: A Patient-Level Meta-Analysis. J Am Coll Cardiol. 2015 Jun 23; 65(24):2614-23. See Evidence Table 3. Bode WD, Patel N, Gehi AK. Left atrial appendage occlusion for prevention of stroke in nonvalvular atrial fibrillation: a meta-analysis. J Interv Card Electrophysiol. 2015 June; 43:79-89.

The use of the Watchman does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
33340	Percutaneous transcatheter closure of the left atrial appendage with endocardial implant, including fluoroscopy, transseptal puncture, catheter placement(s), left atrial angiography, left atrial appendage angiography, when performed, and radiological supervision and interpretation

Considered not medically necessary:

CPT® or HCPC Codes	Description
33267	Exclusion of left atrial appendage, open, any method (eg, excision, isolation via stapling, oversewing, ligation, plication, clip)
33268	Exclusion of left atrial appendage, open, performed at the time of other sternotomy or thoracotomy procedure(s), any method (eg, excision, isolation via stapling, oversewing, ligation, plication, clip) (List separately in addition to code for primary procedure)
33269	Exclusion of left atrial appendage, thoracoscopic, any method (eg, excision, isolation via stapling, oversewing, ligation, plication, clip)

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check.**

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Creation Date	Review Dates	Date Last Revised
08/17/2015	09/01/2015[MPC], 06/07/2016[MPC], 04/04/2017[MPC], 02/06/2018[MPC], 01/08/2019[MPC], 01/07/2020[MPC], 01/05/2021[MPC], 01/04/2022[MPC], 01/10/2023[MPC]	02/01/2022

[MPC] Medical Policy Committee

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Revision History	Description
02/07/2017	MPC approved to adopt criteria for commercial members
03/14/2017	Added AtriClip
04/02/2019	MPC approved to update criteria to include Warfarin and DOACs
01/18/2022	Updated applicable coding with new codes effective 1/1/22 (33267, 33268, 33269) for non-percutaneous left atrial appendage exclusion/closure.
02/01/2022	MPC approved to update criteria to clarify that only FDA approved percutaneous devices such as the Watchman or Amplatzer Ampule are covered. Any other LAA devices are considered not medically necessary, and no device inserted during an open procedure are currently covered. Requires 60-day notice, effective date 07/01/2022.

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Date Sent: 3/29/24
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Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

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Clinical Review Criteria
Wearable Automatic Defibrillators

- Automated External Defibrillators (AED) for Home Use by Pediatric Patients
- Heartstream FR2 AED for Home Use by Adult Patients

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Criteria

For Medicare Members

Medical necessity review is no longer required.

For Non-Medicare Members

Medical necessity review is no longer required.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Sudden cardiac death (SCD) is a major cause of mortality in industrialized countries and is thought to account for 50% of deaths related to heart disease. In the majority of cases cardiac arrest caused by a ventricular tachyarrhythmia precedes sudden cardiac death (Reek 2003).

The implantable cardioverter defibrillator (ICD) introduced in the 1980s, proved to improve survival of patients with a history of a previous episode of sudden cardiac arrest, left ventricular dysfunction, and/or ventricular tachyarrhythmia induced by electrophysiological testing (Feldman 2004). The aim of the device is to continuously monitor the heart, identify malignant ventricular tachyarrhythmias, and deliver an electric counter shock to restore normal rhythm. It was reported that most patients experiencing cardiac arrest have no history of severe cardiac disease, and sudden cardiac death is frequently the first manifestation of a cardiovascular disease. Many others with considerable risk of SCD or those with temporary increased risk may not meet the current guidelines for ICD implantation. This has led to the development of automated external cardioverter defibrillators (AEDs) for individual use.

There are two types of AEDs: 1) The automated external defibrillator with integrated electrocardiogram analysis. This is similar to the manual defibrillator except that it detects and analyzes heart rhythms automatically. This AED requires an operator to initiate the delivery of shock, and 2) The wearable cardioverter defibrillator (WCD) which is also an external defibrillator with integrated electrocardiogram analysis, but in a garment type.

The WCD has defibrillation features similar to the ICD and does not require an operator to defibrillate. It consists of a vest-like device worn under the patient's clothing and is sized to accommodate the chest size and weight of the patient. The device holds a monitor, electrodes, battery and a small alarm module. The monitor is designed to automatically sense abnormal heart rhythms and deliver a series of shocks through the electrodes. When arrhythmia is detected, the device displays a message to the patient to press and hold two response buttons to prevent unnecessary shocks. If the device continues to detect the abnormal rhythm and the patient loses consciousness, he / she involuntarily releases the response buttons and an electrical shock therapy is

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automatically delivered to restore the heart rhythm. Non-wearable components of the device include a battery charger, a computer modem, modem cable, computer cable, WCNET, and the diagnostic test. The WCNET is a web based data storage and retrieval system that allows the physician to access the patient's ECG data stored in the WCD monitor. The WCD has the advantage of allowing the patient to ambulate freely, and does not require assistance from a bystander when the life threatening arrhythmic event occurs (Reek 2003). It may have limited use among patients who are unable to wear the WCD vest due to obesity, or due to skin irritation from wearing the electrode 24 hours per day.

The LIFECOR Wearable Cardioverter Defibrillator (WCD ®)2000 system, is FDA approved for its use 24 hours a day by patients at risk of a sudden cardiac arrest, and an implantable defibrillator is not wanted or not practical. It should not be used if the patient has or needs an implantable ICD, is under 18 years of age, pregnant or breast feeding, has a vision or hearing problem or taking medications that would interfere with pushing the response button on the alarm module, is unwilling or unable to wear the device continuously, is of childbearing age and not attempting to prevent pregnancy, or is exposed to excessive electromagnetic interference (FDA Web page).

Medical Technology Assessment Committee(MTAC)

Wearable Automatic Defibrillators

02/05/2007: MTAC REVIEW

Evidence Conclusion: The literature search on the wearable cardioverter defibrillators revealed only small observational studies with no control or comparison groups. Two small studies (Auricchio et al, 1998, and Reek et al, 2003) tested the efficacy of the device in the electrophysiology lab among very small numbers of patients (N=15, and 12 respectively). The largest study (N=289) published by Feldman et al 2004, combined the results of two case series (WEARIT and BIROAD). They were begun as separate studies but were combined at the request of the FDA. The authors did not indicate at what stage they were grouped, but noted that they tracked the results of each group as a subpopulation. The two studies had different inclusion criteria, and different population characteristics with different implications. The WEARIT participants were patients with NYHA class III or IV heart failure and an ejection fraction <30% while BIROAD included a more heterogeneous group of patients considered at high risk after an MI or CABG surgery or were candidates of an ICD but refused the implant. The BIROAD population used the wearable defibrillator (WCD) for 4 months after which they discontinued therapy or received an ICD. The WEARIT population continued in the study until they developed a terminal heart failure requiring bed confinement, became unable to interact with the device, or experienced a definitive event as ICD implant, heart transplantation, or hospitalization for terminal heart failure. Patients in both groups could discontinue participation at any time during therapy. The follow-up duration with a mean of 3.1 months was too short, as only 8 defibrillation attempts were made, six of which were successful, 2 in the WEARIT population occurring the same patient, and four in the BIROAD population and again two occurred in the same patient. Six sudden deaths occurred in patients who were not wearing the device at the time of the event or were improperly wearing it despite the training they received and the 24-hour support they had. Over one fifth of the participants withdrew prematurely from the study, mainly due to discomfort and life style issues or due to receiving an ICD implant. In conclusion the published studies do not provide sufficient evidence to determine the efficacy and safety of the wearable cardioverter defibrillator for patients at high risk for sudden cardiac death.

Articles: The search yielded 95 articles on the automated external defibrillators. The majority were reviews, opinion pieces, studies on the non-wearable AEDs, and other articles not directly related to the current review. Three studies on the wearable cardioverter defibrillators were identified. All were observational, and two were very small (N=12-15). The largest study by Feldman and colleagues was selected for critical appraisal. Feldman AM, Klein H, Tchou P, et al. Use of wearable defibrillator in terminating tachyarrhythmias in patients at high risk for sudden death: results of WEARIT/BIROAD. Pacing Clin Electrophysiol 2004; 27:4-9. See Evidence Table.

The use of Wearable Automatic Defibrillators in the prevention of sudden cardiac death does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Automated External Defibrillators (AED) for Home Use by Pediatric Patients

BACKGROUND

Approximately half of the deaths from cardiovascular disease in the United States are sudden and unexpected. Defibrillation immediately after a witnessed ventricular fibrillation (VF) has been shown to increase survival rates from cardiac arrest. Each minute of delaying defibrillation is associated with about a 10% reduction in survival and survival rates after 10 minutes of VF are low (Marenco et al., 2001) The use of automated external defibrillators (AEDs) by lay people can reduce the time to defibrillation compared to waiting for the arrival of emergency medical personnel. AEDs, which were first introduced in 1979, are portable devices designed both to analyze cardiac

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rhythms via a heart rhythm analysis algorithm and to deliver shocks. Shock treatment is appropriate when the patient is in ventricular fibrillation. The devices indicate to the operator via text and/or voice prompts whether shock treatment is recommended. AEDs were first approved by the FDA for use in adults. In May, 2001, the FDA approved the Heartstream FR2 with attenuated defibrillation pads (Agilent Technologies, Seattle, WA) for use in infants and children with ventricular fibrillation. The Heartstream FR2 is specifically designed for children who are 8 years old or younger, weigh 55 pounds or less, and are not responsive and not breathing. The attenuated pads deliver a shock that is about one-third the strength delivered to adults FDA Web site).
There is interest in having the Heartstream FR2 available at home at school for children with known heart disease. In order to be effective, the pediatric AED device must accurately detect shockable and non-shockable rhythms and must deliver an appropriate level of shock. Moreover, the device must be able to be used properly by parents and school personnel. In addition, AEDs are only applicable when patients are in ventricular fibrillation. Children in cardiac arrest may be less likely than adults to be in VF, although data are few and conflicting. The largest study, an analysis of 10,992 non-traumatic cardiac arrests in Seattle/King County between 1976 and 1992 (Appleton et al., 1995), found that VF was the first recorded rhythm in only 12/412 (3%) of patients 0-7 years old. In adults 30 years or older, the rate of VF was 42%. In another report of Seattle/King County data (Mogayzel et al., 1995), VF was the initial rhythm in 12 out of the 24 emergency medical services patients under 20 years old whose arrest was due to a cardiac cause and 2 out of 8 patients with congenital heart disease. Evidence on the technical accuracy of the Heartstream FR2 and the ability of AEDs to reduce mortality in practice will be reviewed.

12/11/2002: MTAC REVIEW
Automated External Defibrillators (AED) for Home Use by Pediatric Patients
Evidence Conclusion: The findings from a study by Cecchin et al suggest that the Heartstream FR2 AED can effectively distinguish between shockable and non-shockable rhythms in children. Limitations of this study are possible bias in selecting children for inclusion, variability in data collection and the first author being a consultant to the device manufacturer. Shocks were not actually delivered in the Cecchin study, so the appropriateness of the intensity of shock could not be examined. No evidence was available on the effectiveness of the device at reducing mortality in practice.
Articles: The search yielded 28 articles. Many of the articles were reviews, dealt with technical issues or addressed the use of AEDs in public places. There were no articles on clinical outcomes (e.g. mortality) of pediatric patients or on the actual use of AEDs for pediatric patients at home or at school. There was one article on the ability of the Heartstream FR2 to accurately detect arrhythmias in children (Cecchin et al., 2001) and no articles on the appropriateness of the shock delivered by the device to pediatric patients. The Cecchin article was critically appraised: Ceccin F, Jorgenson DB, Berul CI et al. Is arrhythmia detection by automatic external defibrillator accurate for children? *Circulation* 2001; 103: 2483-2488. See Evidence Table.

The use of AED in the prevention of sudden death in the home from ventricular fibrillation does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Applicable Codes

Medical Necessity Review not required:

CPT® or HCPC Codes	Description
E0617	External defibrillator with integrated electrocardiogram analysis
K0606	Automatic external defibrillator, with integrated electrocardiogram analysis, garment type
K0607	Replacement battery for automated external defibrillator, garment type only, each
K0608	Replacement garment for use with automated external defibrillator, each
K0609	Replacement electrodes for use with automated external defibrillator, garment type only, each

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check.**

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Date Created	Date Reviewed	Date Last Revised
04/19/2007	9/7/2010[MDCRPC], 7/5/2011[MDCRPC], 5/1/2012[MDCRPC], 3/5/2013[MDCRPC], 1/7/2014[MDCRPC], 11/04/2014[MPC], 09/01/2015[MPC], 07/05/2016[MPC], 05/02/2017[MPC], 03/06/2018[MPC], 02/05/2019[MPC], 02/04/2020[MPC], 02/02/2021[MPC], 02/02/2021[MPC] , 02/01/2022[MPC], 02/07/2023[MPC], 01/09/2024[MPC]	07/19/2018

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
07/19/2018	No medical necessity review was added for Medicare members.

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KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Mobility Assistive Devices

- Associated Special Parts
- Manual Wheelchairs
- Power Wheelchairs
- Scooters

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Mobility Assistive Equipment (280.3) Seat Elevation Equipment (Power Operated) on Power Wheelchairs (280.16) **Includes CPT E2300 which is now covered when billed for a complex rehabilitative power-driven wheelchair (effective 5/16/23)* INDEPENDENCE iBOT 4000 Mobility System (280.15)
National Coverage Analysis (NCA) – Decision Memo	Seat Elevation Systems as an Accessory to Power Wheelchairs (Group 3) CAG-00461N **Includes CPT E2300 which is now covered when billed for a complex rehabilitative power-driven wheelchair (effective 5/16/23)*
Local Coverage Determinations (LCD)	Manual Wheelchair Bases L33788 Power Mobility Devices L33789 Wheelchair Seating L33312 Wheelchair Options/Accessories L33792
Local Coverage Articles	Manual Wheelchair Bases A52497 Power Mobility Devices A52498 Wheelchair Seating A52505 Wheelchair Options/Accessories A52504

For Non-Medicare Members

Wheelchair, 2-Gear (aka MAGICWHEELS® 2-Gear Wheelchair Drive)

There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

Documentation Requirements:

See 45 Day Visit Documentation Requirements

MANUAL WHEELCHAIRS (new or replacement)

Kaiser Permanente has elected to use the Manual Wheelchair (KP-0354) MCG* for medical necessity determinations. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.

***MCG Manuals are proprietary and cannot be published and/or distributed**. However, on an individual member basis, Kaiser

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Permanente can share a copy of the specific criteria document used to make a utilization management decision. If one of your patients is being reviewed using these criteria, you may request a copy of the criteria by calling the Kaiser Permanente Clinical Review staff at 1-800-289-1363 or access the MCG Guideline Index using the link provided above.

If requesting this service, please send the following documentation to support medical necessity:

- Most recent note from requesting provider
- Most recent Physical Therapy mobility assessment (for a patient 18 and under, therapy evaluation cannot be solely done by a school-based therapist. Wheelchairs are only covered for use inside the home and the therapist must complete an onsite visit in the home to determine accessibility requirements.)
- If recent discharge from SNF/IPR, include therapy notes
- Specialty evaluation as indicated in the criteria above
- Vendor assessment and itemized codes if applicable

POWER OPERATIVE VEHICLES (POV)/SCOOTERS (new or replacement)

Kaiser Permanente has elected to use the Scooter (KP-0352) (MCG)* for medical necessity determinations. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.

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If requesting this service, please send the following documentation to support medical necessity:

- Most recent comprehensive note from requesting provider in which the power mobility device is discussed. The note should provide pertinent information about the following elements but may include other details. Each element would not have to be addressed in every evaluation.
  - History of the present condition(s) and past medical history that is relevant to mobility needs
    - Symptoms that limit ambulation
    - Diagnoses that are responsible for these symptoms
    - Medications or other treatment for these symptoms
    - Progression of ambulation difficulty over time
    - Other diagnoses that may relate to ambulatory problems
    - How far the beneficiary can walk without stopping
    - Pace of ambulation
    - What ambulatory assistance (cane, walker, wheelchair, caregiver) is currently used
    - What has changed to now require use of a power mobility device
    - Ability to stand up from a seated position without assistance
    - Description of the home setting and the ability to perform activities of daily living in the home
  - Physical examination that is relevant to mobility needs
    - Weight and height
    - Cardiopulmonary examination
    - Musculoskeletal examination
      - Arm and leg strength and range of motion
    - Neurological examination
      - Gait
      - Balance and coordination

The evaluation should be tailored to the individual beneficiary's conditions. The history should paint a picture of the beneficiary's functional abilities and limitations on a typical day. It should contain as much objective data as possible. The physical examination should be focused on the body systems that are responsible for the beneficiary's ambulatory difficulty or impact on the beneficiary's ambulatory ability.

- Most recent Physical Therapy mobility assessment if available
- If recent discharge from SNF/IPR, include therapy notes
- Vendor assessment and itemized codes if applicable

I. POWER WHEELCHAIR (new or replacement)

A. Mobility Assistive Device (MAE) is reasonable and necessary for patients who have a personal mobility deficit sufficient to impair their performance of Mobility-Related Activities of Daily Living (MRADL) such as toileting, feeding, dressing, grooming, and bathing in customary areas in the home and coverage is

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considered when the following has been applied:

1. The patient has a mobility limitation that significantly impairs his/her ability to participate in one or more MRADLs in the home. A mobility limitation is one that:
   - Prevents the patient from accomplishing the MRADLs entirely, or,
   - Places the patient at reasonably determined heightened risk of morbidity or mortality secondary to the attempts to participate in MRADLs, or,
   - Prevents the patient from completing the MRADLs within a reasonable time frame.

B. These other limitations can be ameliorated or compensated sufficiently such that the additional provision of MAE will be reasonably expected to significantly improve the patient's ability to perform or obtain assistance to participate in MRADLs in the home.
   1. A caregiver**, for example a family member, may be compensatory, if consistently available in the patient's home and willing and able to safely operate and transfer the patient to and from the wheelchair and to transport the patient using the wheelchair. The caregiver's need to use a wheelchair to assist the patient in the MRADLs is to be considered in this determination.
   2. The amelioration or compensation requires the patient's compliance with treatment, for example medications or therapy, substantive non-compliance, whether willing or involuntary. This can be justification for denial of wheelchair coverage if it results in the patient continuing to have a significant limitation. It may be determined that partial compliance results in adequate amelioration or compensation for the appropriate use of MAE.

C. The patient or caregiver demonstrates the capability and the willingness to consistently operate the MAE safely.
   1. Safety considerations include personal risk to the patient as well as risk to others. The determination of safety may need to occur several times during the process as the consideration focuses on a specific device.
   2. A history of unsafe behavior in other venues may be considered.

D. If a manual wheelchair or POV does not meet the mobility needs of the patient, and all of the following features provided by a power wheelchair are needed to allow the patient to participate in one or more MRADLs,
   1. The pertinent features of a power wheelchair compared to a POV are typically controlled by a joystick or alternative input device, lower seat height for slide transfers, and the ability to accommodate a variety of seating needs.
   2. The type of wheelchair and options provided should be appropriate for the degree of the patient's functional impairments.
   3. The patient's home should provide adequate access, maneuvering space and surfaces for the operation of a power wheelchair.
   4. Assess the patient's ability to safely use a power wheelchair.
   5. The patient has had a face-to-face evaluation by the prescribing physician within the past 45 days which assesses his/her mobility status, and the need for the power wheelchair.

E. Due to the complexity of determining whether a power wheelchair or power scooter is the best device for a patient, any requests for either of these devices must be submitted by a physiatrist who has examined the patient and done a thorough evaluation.

**Note: If the patient is unable to use a power wheelchair, and if there is a caregiver who is available, willing, and able to provide assistance, a manual wheelchair is appropriate. A caregiver's inability to operate a manual wheelchair can be considered in covering a power wheelchair so that the caregiver can assist the patient.

Home Assessment:

Coverage for the use of an electric wheelchair is determined solely for the needs within the home.
An on-site evaluation of the member's home is necessary to verify that the member can adequately maneuver the device that is provided considering the physical layout, doorway width, doorway thresholds, and surfaces. There must be a written report of this evaluation available upon request.

Associated Special Parts:

The options/accessories are necessary for the patient to perform one or more of the following activities:

1) Function in the home.
2) Perform instrumental activities of daily living.

An option/accessory that is beneficial primarily in allowing the patient to perform leisure or recreational activities is non-covered.

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Anti-rollback device (E0974)	• The patient propels himself/herself and needs the device because of ramps.
Arm of Chair	• Adjustable arm height option (E0973, K0017, K0018, K0020) is covered if the patient requires an arm height that is different than that available using nonadjustable arms and the patient spends at least 2 hours per day in the wheelchair. • An arm trough (E2209) is covered if patient has quadriplegia, hemiplegia, or uncontrolled arm movements.
Fully reclining back (E1226) Has one or more:	• Quadriplegia • Fixed hip angle • Trunk or lower extremity casts/braces that require the reclining back feature for positioning • Excess extensor tone of the trunk muscles and/or • The need to rest in a recumbent position two or more times during the day and transfer between wheelchair and bed is very difficult
Elevating Leg Rests (E0990, K0046, K0047, K0053, K0195)	• The patient has a musculoskeletal condition or the presence of a cast or brace which prevents 90-degree flexion at the knee or • The patient has significant edema of the lower extremities that requires having an elevated leg rest or • The patient meets criteria for and has a reclining back on the wheelchair
Mechanically linked leg elevation feature (E1009) Power leg elevation feature (E1010)	• Meet criteria for elevating leg rest • And is receiving a **covered** power seating system
Hook-on headrest extension	• Has weak neck muscles and needs headrest for support OR • Meets criteria for and has reclining back on wheelchair
Non-standard seat frame (E2201-E2204, E2340-E2343)	• A nonstandard seat width and/or depth is covered only if the patient's dimensions justify the need.
Electronic Interface (E2351)	• An electronic interface to allow a speech generating device to be operated by the power wheelchair control interface is covered if the patient has a **covered** speech generating device.
Swingaway, retractable, or removable hardware (E1028)	• Needed to move the component out of the way so the patient can perform a slide transfer AND • The sole reason is not to allow the patient to move close to desks or other surfaces
Tilt-in-space seat Power tilt seating system (E1002) Power reclining seat system (E1003-E1005) Power tilt and reclining seat system (E1006-E1008)	• Has documented weak upper extremity strength or a disease that will lead to weak upper extremities. AND • Is at risk for skin break down because of inability to reposition body in chair to relieve pressure areas.
Power Assist Device (E0986)	A push-rim activated power assist device for a manual wheelchair(E0986) may be considered medically necessary when the criteria for a wheelchair (noted above) are met and **ALL of the following** criteria are met: • The patient has been self-propelling in a manual wheelchair for at least one year but no longer has sufficient upper extremity function to self-propel a manual wheelchair in the home to perform MRADLs. **AND** • The patient has had a specialty evaluation performed by a physiatrist who has specific training and experience in rehabilitation wheelchair evaluations **AND** • The wheelchair is provided by a supplier that specializes in wheelchairs with a specialist who has direct, in-person involvement in the wheelchair selection for the patient **AND** • The evaluation documents the need for the device to perform mobility related activities *in the patient's home* *Note: In some circumstances, a group 2 power wheelchair would meet mobility needs.

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The following are not covered because they are not primarily medical in nature	• Power seat elevation feature (E2300) • Power standing feature (E2301) • Attendant control (E2331) • Electrical connection devices (E2310 or E2311) with the sole function of connection for a power seat elevation or power stand feature. • Electrical interface used to control lights or other electrical devices
E1399, K0108	• Any part that is requested using either of these miscellaneous codes is subject to review for medical necessity.
The following wheelchair options are not covered:	• "Ability to balance on two wheels" feature for a PWC • Any wheelchair, option, or accessory that is primarily for the purpose of allowing the individual to perform leisure or recreational activities • Articulating (telescoping) elevating leg rests: considered for patients with long legs • Back support systems: Back support systems have a plastic frame which is padded and covered with cloth or other material; they are designed to be attached to a wheelchair base, but do not completely replace the wheelchair back. These back-support systems are considered convenience items, because they are not generally necessary to provide trunk support in members in wheelchairs. An adequate seating system would allow the member to function appropriately in the wheelchair. • Battery charger: A battery charger for a power wheelchair is included in the allowance for a power wheelchair base. A dual mode battery charger for a power wheelchair is considered a convenience item and is not covered. • Canopies • Clothing guards to protect clothing from dirt, mud, or water thrown up by the wheels (similar to mud flaps for cars) • Commode seat, wheelchair (HCPCS code E0968) • Crutch or cane holder: May need to help safely transfer • Electronic balance feature for a PWC • Flat-free inserts (zero pressure tubes): Flat free inserts have a removable ring of firm material that is placed inside of a pneumatic tire. Flat free inserts are intended to allow the wheelchair to continue to move if the pneumatic tire is punctured. • Home modifications: Modifications to the structure of the home to accommodate wheelchairs are not considered treatment of disease and are not covered. Examples of home modifications and installations that are not covered include wheelchair ramps, wheelchair accessible showers, elevators, and lowered bath or kitchen counters and sinks. • Identification devices (such as labels, license plates, name plates) • Lighting systems • Powered seat elevator attachments for electric, powered, or motorized wheelchairs (HCPCS code E2300) • Power or manual standing options or standing wheelchairs (HCPCS code E2301, E2230) • Powered wheelchair seat cushions (HCPCS code E2610) • Remote operation feature for a PWC • Rental or purchase of more than one mobility assistive device at a time • Seat elevator wheelchairs (HCPCS code K0830, K0831) • Shock absorbers • Speed conversion kits • Stair-climbing wheelchairs, computerized or gyroscopic mobility systems (e.g., INDEPENDENCE™ IBOT™ Mobility System, Independence Technology, LLC, Warren, NJ) (K0011) • Transport chairs or rollabout chairs (HCPCS code E1031, E1037, E1038, E1039) • Warning devices, such as horns and backup signals • Wheelchair accessory, tray & half-lap tray (HCPCS code E0950)

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	• Wheelchair lifts (e.g., Wheel-O-Vator, trunk loader) -- devices to assist in lifting wheelchair up stairways, into car trunks, or in vans (see CPB 0459 - Seat Lifts and Patient Lifts) • Wheelchair rack for automobile (auto carrier) -- car attachment to carry wheelchair • Wheelchair tie downs (transit options) • Miscellaneous items needed to adapt to the outside environment for convenience, work, leisure or recreational activities including, but not limited to: - accessory holder: flag, cup, speech generating device - auto carriers - baskets, backpacks, bags, seat pouches used to transport personal belongings - firearm/weapon holder/support - gloves - lifts for car trunk, stairways, seat lifts and individual lifts - lowered seat elevator attachments for powered or motorized wheelchairs - ramps - snow tires for wheelchairs - support or mounting frames for cellular phone & tablets

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

In 2000, almost 1.7 million people in the United States used wheelchairs due to a disability. Of these, 1.5 million people used a manual wheelchair (Kaye et al., 2000). Manual wheelchairs require extensive use of individuals' upper limbs for mobility, transfer and other daily functional activities. This repetitive weight-bearing use of the arms and shoulders may cause upper-extremity problems, and reports of shoulder pain are common. In a recent survey of individuals with thoracic spinal cord injuries, 40% of respondents reported current shoulder pain associated with wheelchair use (Alm et al. 2008).

One way to address shoulder pain in manual wheelchair users is with stretching and strengthening exercises. Several small trials have tested specific exercise programs and found statistically significant reduction in shoulder pain (Nawoczenski et al., 2006; Curtis et al., 1999).

Another option, for individuals who want to continue using manual wheelchairs, is to reduce the force put on the upper extremities by modifying the wheelchair. One modification is the addition of battery-powered wheels that can be fitted to standard manual wheelchairs. These wheels add a motorized boost, or "torque multiplier" allowing the user to go further with the same amount of force. A disadvantage of the battery-powered wheels is that the currently available products are heavy. For example, the Alber E-Motion weighs 53 pounds, excluding the wheelchair (Frankmobility.com). Newer, lighter products are being developed. The Quickie Xtend power assist product weighs 38 pounds (Quickie-wheelchairs.com). Another potential disadvantage of power-assisted wheels is that the batteries need to be recharged, sometimes frequently, which can be disruptive to daily activities.

A different modification to the manual wheelchair is to use the 2-gear wheelchair drive produced by MagicWheels, Inc. (Seattle, WA). The wheelchair drive adapts to most standard wheelchairs and does not include batteries or motors. By sliding a switch, the user can change from a conventional 1:1 gear ratio to a 2:1 ratio. The added weight is lighter than the battery-powered assist products. Depending on options, the additional weight per pair of wheels varies from 8.2-10.5 pounds. The gear shifting is designed to reduce upper body stress and assist the user to navigate ramps, hills and uneven terrain. Newer models include an automatic hill holding feature preventing the wheelchair from sliding backwards between pulls while going uphill, and a downhill assisted braking feature. MagicWheels was founded in 1996 by several partners. The University of Washington, where initial product development research took place, owns stock in MagicWheels as part of a patent licensing agreement.

Evidence and Source Documents

Wheelchair, 2-Gear (aka MAGICWHEELS® 2-Gear Wheelchair Drive)

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Medical Technology Assessment Committee (MTAC)

Wheelchair, 2-Gear (aka MAGICWHEELS® 2-Gear Wheelchair Drive)

BACKGROUND

In 2000, almost 1.7 million people in the United States used wheelchairs due to a disability. Of these, 1.5 million people used a manual wheelchair (Kaye et al., 2000). Manual wheelchairs require extensive use of individuals' upper limbs for mobility, transfer and other daily functional activities. This repetitive weight-bearing use of the arms and shoulders may cause upper-extremity problems, and reports of shoulder pain are common. In a recent survey of individuals with thoracic spinal cord injuries, 40% of respondents reported current shoulder pain associated with wheelchair use (Alm et al. 2008). One way to address shoulder pain in manual wheelchair users is with stretching and strengthening exercises. Several small trials have tested specific exercise programs and found statistically significant reduction in shoulder pain (Nawoczenski et al., 2006; Curtis et al., 1999). Another option, for individuals who want to continue using manual wheelchairs, is to reduce the force put on the upper extremities by modifying the wheelchair. One modification is the addition of battery powered wheels that can be fitted to standard manual wheelchairs. These wheels add a motorized boost, or "torque multiplier" allowing the user to go further with the same amount of force. A disadvantage of the battery-powered wheels is that the currently available products are heavy. For example, the Alber E-Motion weighs 53 pounds, excluding the wheelchair (Frankmobility.com). Newer, lighter products are being developed. The Quickie Xtend power assist product weighs 38 pounds (Quickie-wheelchairs.com). Another potential disadvantage of power-assisted wheels is that the batteries need to be recharged, sometimes frequently, which can be disruptive to daily activities. A different modification to the manual wheelchair is to use the 2-gear wheelchair drive produced by MagicWheels, Inc. (Seattle, WA). The wheelchair drive adapts to most standard wheelchairs and does not include batteries or motors. By sliding a switch, the user can change from a conventional 1:1 gear ratio to a 2:1 ratio. The added weight is lighter than the battery-powered assist products. Depending on options, the additional weight per pair of wheels varies from 8.2-10.5 pounds. The gear shifting is designed to reduce upper body stress and assist the user to navigate ramps, hills and uneven terrain. Newer models include an automatic hill holding feature preventing the wheelchair from sliding backwards between pulls while going uphill, and a downhill assisted braking feature. MagicWheels was founded in 1996 by several partners. The University of Washington, where initial product development research took place, owns stock in MagicWheels as part of a patent licensing agreement. The following information was used in the development of this document and is provided as background only. It is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations. Mechanical wheelchairs and wheelchair components are Class 1 devices according to the FDA. Class 1 devices are subject to general controls such as product listing and labeling requirements but are exempt from the pre-market approval process including safety and effectiveness evaluation.

12/01/2008: MTAC REVIEW

Wheelchair, 2-Gear (aka MAGICWHEELS® 2-Gear Wheelchair Drive)

Evidence Conclusion: There is insufficient evidence to draw conclusions about the impact of the MagicWheels 2-gear wheelchair on functional ability and shoulder and arm pain. There was only one published empirical study on the MagicWheels wheelchair product. The study (Finley et al., 2007) was a small interrupted time series. 17 individuals started the study, and 12 completed the 5-month intervention phase. The study found improvement in shoulder pain, but not overall functional ability, or performance on an incline test when patients used MagicWheels. Shoulder pain decreased when MagicWheels was introduced and increased again after a return to standard wheels. Findings are subject to bias such as the Hawthorne effect (see evidence table for study details).
Articles: The PubMed search yielded 8 articles. Seven of these were on different related clinical topics, with the words "magic" and "wheels" included in the abstract or other part of the citation. No additional articles were identified via the "related articles" function in PubMed. There was only one published empirical article on the MagicWheels wheelchair, and this study was critically appraised: Finley MA, Rodgers MM. Effect of 2-speed geared manual wheelchair propulsion on shoulder pain and function. Arch Phys Med Rehabil 2007; 88: 1622-1627. See Evidence Table.

The use of 2-gear wheelchairs does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPC	Description

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Codes	
Manual Wheelchairs	
K0001	Standard wheelchair
K0002	Standard hemi (low seat) wheelchair
K0003	Lightweight wheelchair
K0004	High strength, lightweight wheelchair
K0005	Ultralightweight wheelchair
K0006	Heavy-duty wheelchair
K0007	Extra heavy-duty wheelchair
K0008	Custom manual wheelchair/base
K0009	Other manual wheelchair/base
E1050	Fully-reclining wheelchair, fixed full-length arms, swing-away detachable elevating legrests
E1060	Fully-reclining wheelchair, detachable arms, desk or full-length, swing-away detachable elevating legrests
E1070	Fully-reclining wheelchair, detachable arms (desk or full-length) swing-away detachable footrest
E1083	Hemi-wheelchair, fixed full-length arms, swing-away detachable elevating legrest
E1084	Hemi-wheelchair, detachable arms desk or full-length arms, swing-away detachable elevating legrests
E1085	Hemi-wheelchair, fixed full-length arms, swing-away detachable footrests
E1086	Hemi-wheelchair, detachable arms, desk or full-length, swing-away detachable footrests
E1087	High strength lightweight wheelchair, fixed full-length arms, swing-away detachable elevating legrests
E1088	High strength lightweight wheelchair, fixed full-length arms, swing-away detachable elevating legrests
E1089	High-strength lightweight wheelchair, fixed-length arms, swing-away detachable footrest
E1090	High-strength lightweight wheelchair, detachable arms, desk or full-length, swing-away detachable footrests
E1092	Wide heavy-duty wheelchair, detachable arms (desk or full-length), swing-away detachable elevating legrests
E1093	Wide heavy-duty wheelchair, detachable arms, desk or full-length arms, swing-away detachable footrests
E1100	Semi-reclining wheelchair, fixed full-length arms, swing-away detachable elevating legrests
E1110	Semi-reclining wheelchair, detachable arms (desk or full-length) elevating legrest
E1130	Standard wheelchair, fixed full-length arms, fixed or swing-away detachable footrests
E1140	Wheelchair, detachable arms, desk or full-length, swing-away detachable footrests
E1150	Wheelchair, detachable arms, desk or full-length swing-away detachable elevating legrests
E1160	Wheelchair, fixed full-length arms, swing-away detachable elevating legrests
E1161	Manual adult size wheelchair, includes tilt in space
E1170	Amputee wheelchair, fixed full-length arms, swing-away detachable elevating legrests
E1171	Amputee wheelchair, fixed full-length arms, without footrests or legrest
E1172	Amputee wheelchair, detachable arms (desk or full-length) without footrests or legrest
E1180	Amputee wheelchair, detachable arms (desk or full-length) swing-away detachable footrests
E1190	Amputee wheelchair, detachable arms (desk or full-length) swing-away detachable elevating legrests
E1195	Heavy-duty wheelchair, fixed full-length arms, swing-away detachable elevating legrests
E1200	Amputee wheelchair, fixed full-length arms, swing-away detachable footrest
E1220	Wheelchair; specially sized or constructed, (indicate brand name, model number, if any) and justification
E1221	Wheelchair with fixed arm, footrests
E1222	Wheelchair with fixed arm, elevating legrests
E1223	Wheelchair with detachable arms, footrests
E1224	Wheelchair with detachable arms, elevating legrests
E1229	Wheelchair, pediatric size, not otherwise specified
E1231	Wheelchair, pediatric size, tilt-in-space, rigid, adjustable, with seating system
E1232	Wheelchair, pediatric size, tilt-in-space, folding, adjustable, with seating system
E1233	Wheelchair, pediatric size, tilt-in-space, rigid, adjustable, without seating system
E1234	Wheelchair, pediatric size, tilt-in-space, folding, adjustable, without seating system

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E1235	Wheelchair, pediatric size, rigid, adjustable, with seating system
E1236	Wheelchair, pediatric size, folding, adjustable, with seating system
E1237	Wheelchair, pediatric size, rigid, adjustable, without seating system
E1238	Wheelchair, pediatric size, folding, adjustable, without seating system
E1240	Lightweight wheelchair, detachable arms, (desk or full-length) swing-away detachable, elevating legrest
E1250	Lightweight wheelchair, fixed full-length arms, swing-away detachable footrest
E1260	Lightweight wheelchair, detachable arms (desk or full-length) swing-away detachable footrest
E1270	Lightweight wheelchair, fixed full-length arms, swing-away detachable elevating legrests
E1280	Heavy-duty wheelchair, detachable arms (desk or full-length) elevating legrests
E1285	Heavy-duty wheelchair, fixed full-length arms, swing-away detachable footrest
E1290	Heavy-duty wheelchair, detachable arms (desk or full-length) swing-away detachable footrest
E1295	Heavy-duty wheelchair, fixed full-length arms, elevating legrest
Power Wheelchairs	
E1239	Power wheelchair, pediatric size, not otherwise specified
K0010	Standard-weight frame motorized/power wheelchair
K0011	Standard-weight frame motorized/power wheelchair with programmable control parameters for speed adjustment, tremor dampening, acceleration control and braking
K0012	Lightweight portable motorized/power wheelchair
K0813	Power wheelchair, group 1 standard, portable, sling/solid seat and back, patient weight capacity up to and including 300 pounds
K0814	Power wheelchair, group 1 standard, portable, captain's chair, patient weight capacity up to and including 300 pounds
K0815	Power wheelchair, group 1 standard, sling/solid seat and back, patient weight capacity up to and including 300 pounds
K0816	Power wheelchair, group 1 standard, captain's chair, patient weight capacity up to and including 300 pounds
K0820	Power wheelchair, group 2 standard, portable, sling/solid seat/back, patient weight capacity up to and including 300 pounds
K0821	Power wheelchair, group 2 standard, portable, captain's chair, patient weight capacity up to and including 300 pounds
K0822	Power wheelchair, group 2 standard, sling/solid seat/back, patient weight capacity up to and including 300 pounds
K0823	Power wheelchair, group 2 standard, captain's chair, patient weight capacity up to and including 300 pounds
K0824	Power wheelchair, group 2 heavy-duty, sling/solid seat/back, patient weight capacity 301 to 450 pounds
K0825	Power wheelchair, group 2 heavy-duty, captain's chair, patient weight capacity 301 to 450 pounds
K0826	Power wheelchair, group 2 very heavy-duty, sling/solid seat/back, patient weight capacity 451 to 600 pounds
K0827	Power wheelchair, group 2 very heavy-duty, captain's chair, patient weight capacity 451 to 600 pounds
K0828	Power wheelchair, group 2 extra heavy-duty, sling/solid seat/back, patient weight capacity 601 pounds or more
K0829	Power wheelchair, group 2 extra heavy-duty, captain's chair, patient weight 601 pounds or more
K0830	Power wheelchair, group 2 standard, seat elevator, sling/solid seat/back, patient weight capacity up to and including 300 pounds
K0831	Power wheelchair, group 2 standard, seat elevator, captain's chair, patient weight capacity up to and including 300 pound
K0835	Power wheelchair, group 2 standard, single power option, sling/solid seat/back, patient weight capacity up to and including 300 pounds
K0836	Power wheelchair, group 2 standard, single power option, captain's chair, patient weight capacity up to and including 300 pounds
K0837	Power wheelchair, group 2 heavy-duty, single power option, sling/solid seat/back, patient weight capacity 301 to 450 pounds
K0838	Power wheelchair, group 2 heavy-duty, single power option, captain's chair, patient weight capacity 301 to 450 pounds
K0839	Power wheelchair, group 2 very heavy-duty, single power option sling/solid seat/back, patient

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	weight capacity 451 to 600 pounds
K0840	Power wheelchair, group 2 extra heavy-duty, single power option, sling/solid seat/back, patient weight capacity 601 pounds or more
K0841	Power wheelchair, group 2 standard, multiple power option, sling/solid seat/back, patient weight capacity up to and including 300 pounds
K0842	Power wheelchair, group 2 standard, multiple power option, captain's chair, patient weight capacity up to and including 300 pounds
K0843	Power wheelchair, group 2 heavy-duty, multiple power option, sling/solid seat/back, patient weight capacity 301 to 450 pounds
K0848	Power wheelchair, group 3 standard, sling/solid seat/back, patient weight capacity up to and including 300 pounds
K0849	Power wheelchair, group 3 standard, captain's chair, patient weight capacity up to and including 300 pounds
K0850	Power wheelchair, group 3 heavy-duty, sling/solid seat/back, patient weight capacity 301 to 450 pounds
K0851	Power wheelchair, group 3 heavy-duty, captain's chair, patient weight capacity 301 to 450 pounds
K0852	Power wheelchair, group 3 very heavy-duty, sling/solid seat/back, patient weight capacity 451 to 600 pounds
K0853	Power wheelchair, group 3 very heavy-duty, captain's chair, patient weight capacity 451 to 600 pounds
K0854	Power wheelchair, group 3 extra heavy-duty, sling/solid seat/back, patient weight capacity 601 pounds or more
K0855	Power wheelchair, group 3 extra heavy-duty, captain's chair, patient weight capacity 601 pounds or more
K0856	Power wheelchair, group 3 standard, single power option, sling/solid seat/back, patient weight capacity up to and including 300 pounds
K0857	Power wheelchair, group 3 standard, single power option, captain's chair, patient weight capacity up to and including 300 pounds
K0858	Power wheelchair, group 3 heavy-duty, single power option, sling/solid seat/back, patient weight 301 to 450 pounds
K0859	Power wheelchair, group 3 heavy-duty, single power option, captain's chair, patient weight capacity 301 to 450 pounds
K0860	Power wheelchair, group 3 very heavy-duty, single power option, sling/solid seat/back, patient weight capacity 451 to 600 pounds
K0861	Power wheelchair, group 3 standard, multiple power option, sling/solid seat/back, patient weight capacity up to and including 300 pounds
K0862	Power wheelchair, group 3 heavy-duty, multiple power option, sling/solid seat/back, patient weight capacity 301 to 450 pounds
K0863	Power wheelchair, group 3 very heavy-duty, multiple power option, sling/solid seat/back, patient weight capacity 451 to 600 pounds
K0864	Power wheelchair, group 3 extra heavy-duty, multiple power option, sling/solid seat/back, patient weight capacity 601 pounds or more
K0868	Power wheelchair, group 4 standard, sling/solid seat/back, patient weight capacity up to and including 300 pounds
K0869	Power wheelchair, group 4 standard, captain's chair, patient weight capacity up to and including 300 pounds
K0870	Power wheelchair, group 4 heavy-duty, sling/solid seat/back, patient weight capacity 301 to 450 pounds
K0871	Power wheelchair, group 4 very heavy-duty, sling/solid seat/back, patient weight capacity 451 to 600 pounds
K0877	Power wheelchair, group 4 standard, single power option, sling/solid seat/back, patient weight capacity up to and including 300 pounds
K0878	Power wheelchair, group 4 standard, single power option, captain's chair, patient weight capacity up to and including 300 pounds
K0879	Power wheelchair, group 4 heavy-duty, single power option, sling/solid seat/back, patient weight capacity 301 to 450 pounds
K0880	Power wheelchair, group 4 very heavy-duty, single power option, sling/solid seat/back, patient weight 451 to 600 pounds

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K0884	Power wheelchair, group 4 standard, multiple power option, sling/solid seat/back, patient weight capacity up to and including 300 pounds
K0885	Power wheelchair, group 4 standard, multiple power option, captain's chair, patient weight capacity up to and including 300 pounds
K0886	Power wheelchair, group 4 heavy-duty, multiple power option, sling/solid seat/back, patient weight capacity 301 to 450 pounds
K0890	Power wheelchair, group 5 pediatric, single power option, sling/solid seat/back, patient weight capacity up to and including 125 pounds
K0891	Power wheelchair, group 5 pediatric, multiple power option, sling/solid seat/back, patient weight capacity up to and including 125 pounds
K0898	Power wheelchair, not otherwise classified
K0899	Power mobility device, not coded by DME PDAC or does not meet criteria
Power Scooters	
E1230	Power operated vehicle (three- or four-wheel nonhighway), specify brand name and model number
K0800	Power operated vehicle, group 1 standard, patient weight capacity up to and including 300 pounds
K0801	Power operated vehicle, group 1 heavy-duty, patient weight capacity 301 to 450 pounds
K0802	Power operated vehicle, group 1 very heavy-duty, patient weight capacity 451 to 600 pounds
K0806	Power operated vehicle, group 2 standard, patient weight capacity up to and including 300 pounds
K0807	Power operated vehicle, group 2 heavy-duty, patient weight capacity 301 to 450 pounds
K0808	Power operated vehicle, group 2 very heavy-duty, patient weight capacity 451 to 600 pounds
K0812	Power operated vehicle, not otherwise classified
Associated Parts and Supplies	
E0950	Wheelchair accessory, tray, each
E0951	Heel loop/holder, any type, with or without ankle strap, each
E0952	Toe loop/holder, any type, each
E0955	Wheelchair accessory, headrest, cushioned, any type, including fixed mounting hardware, each
E0956	Wheelchair accessory, lateral trunk or hip support, any type, including fixed mounting hardware, each
E0957	Wheelchair accessory, medial thigh support, any type, including fixed mounting hardware, each
E0958	Manual wheelchair accessory, one-arm drive attachment, each
E0959	Manual wheelchair accessory, adapter for amputee, each
E0960	Wheelchair accessory, shoulder harness/straps or chest strap, including any type mounting hardware
E0961	Manual wheelchair accessory, wheel lock brake extension (handle), each
E0967	Manual wheelchair accessory, hand rim with projections, any type, replacement only, each
E0968	Commode seat, wheelchair
E0969	Narrowing device, wheelchair
E0970	No. 2 footplates, except for elevating legrest
E0971	Manual wheelchair accessory, antitipping device, each
E0973	Wheelchair accessory, adjustable height, detachable armrest, complete assembly, each
E0974	Manual wheelchair accessory, antirollback device, each
E0978	Wheelchair accessory, positioning belt/safety belt/pelvic strap, each
E0980	Safety vest, wheelchair
E0981	Wheelchair accessory, seat upholstery, replacement only, each
E0982	Wheelchair accessory, back upholstery, replacement only, each
E0983	Manual wheelchair accessory, power add-on to convert manual wheelchair to motorized wheelchair, joystick control
E0984	Manual wheelchair accessory, power add-on to convert manual wheelchair to motorized wheelchair, tiller control
E0985	Wheelchair accessory, seat lift mechanism
E0986	Manual wheelchair accessory, push-rim activated power assist system
E0988	Manual wheelchair accessory, lever-activated, wheel drive, pair
E0990	Wheelchair accessory, elevating legrest, complete assembly, each
E0992	Manual wheelchair accessory, solid seat insert
E0994	Armrest, each
E0995	Wheelchair accessory, calf rest/pad, replacement only, each
E1002	Wheelchair accessory, power seating system, tilt only

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E1003	Wheelchair accessory, power seating system, recline only, without shear reduction
E1004	Wheelchair accessory, power seating system, recline only, with mechanical shear reduction
E1005	Wheelchair accessory, power seating system, recline only, with power shear reduction
E1006	Wheelchair accessory, power seating system, combination tilt and recline, without shear reduction
E1007	Wheelchair accessory, power seating system, combination tilt and recline, with mechanical shear reduction
E1008	Wheelchair accessory, power seating system, combination tilt and recline, with power shear reduction
E1009	Wheelchair accessory, addition to power seating system, mechanically linked leg elevation system, including pushrod and legrest, each
E1010	Wheelchair accessory, addition to power seating system, power leg elevation system, including legrest, pair
E1011	
E1012	Wheelchair accessory, addition to power seating system, center mount power elevating leg rest/platform, complete system, any type, each
E1014	Reclining back, addition to pediatric size wheelchair
E1015	Shock absorber for manual wheelchair, each
E1016	Shock absorber for power wheelchair, each
E1017	Heavy-duty shock absorber for heavy-duty or extra heavy-duty manual wheelchair, each
E1018	Heavy-duty shock absorber for heavy-duty or extra heavy-duty power wheelchair, each
E1020	Residual limb support system for wheelchair, any type
E1028	Wheelchair accessory, manual swingaway, retractable or removable mounting hardware for joystick, other control interface or positioning accessory
E1225	Wheelchair accessory, manual semi-reclining back, (recline greater than 15 degrees, but less than 80 degrees), each
E1226	Wheelchair accessory, manual fully reclining back, (recline greater than 80 degrees), each
E1227	Special height arms for wheelchair
E1228	Special back height for wheelchair
E1296	Special wheelchair seat height from floor
E1297	Special wheelchair seat depth, by upholstery
E1298	Special wheelchair seat depth and/or width, by construction
E1399	Durable medical equipment, miscellaneous
E2201	Manual wheelchair accessory, nonstandard seat frame, width greater than or equal to 20 in and less than 24 in
E2202	Manual wheelchair accessory, nonstandard seat frame width, 24-27 in
E2203	Manual wheelchair accessory, nonstandard seat frame depth, 20 to less than 22 in
E2204	Manual wheelchair accessory, nonstandard seat frame depth, 22 to 25 in
E2205	Manual wheelchair accessory, handrim without projections (includes ergonomic or contoured), any type, replacement only, each
E2206	Manual wheelchair accessory, wheel lock assembly, complete, replacement only, each
E2207	Wheelchair accessory, crutch and cane holder, each
E2208	Wheelchair accessory, cylinder tank carrier, each
E2209	Accessory, arm trough, with or without hand support, each
E2210	Wheelchair accessory, bearings, any type, replacement only, each
E2211	Manual wheelchair accessory, pneumatic propulsion tire, any size, each
E2212	Manual wheelchair accessory, tube for pneumatic propulsion tire, any size, each
E2213	Manual wheelchair accessory, insert for pneumatic propulsion tire (removable), any type, any size, each
E2214	Manual wheelchair accessory, pneumatic caster tire, any size, each
E2215	Manual wheelchair accessory, tube for pneumatic caster tire, any size, each
E2216	Manual wheelchair accessory, foam filled propulsion tire, any size, each
E2217	Manual wheelchair accessory, foam filled caster tire, any size, each
E2218	Manual wheelchair accessory, foam propulsion tire, any size, each
E2219	Manual wheelchair accessory, foam caster tire, any size, each
E2220	Manual wheelchair accessory, solid (rubber/plastic) propulsion tire, any size, replacement only, each
E2221	Manual wheelchair accessory, solid (rubber/plastic) caster tire (removable), any size, replacement only, each

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E2222	Manual wheelchair accessory, solid (rubber/plastic) caster tire with integrated wheel, any size, replacement only, each
E2224	Manual wheelchair accessory, propulsion wheel excludes tire, any size, replacement only, each
E2225	Manual wheelchair accessory, caster wheel excludes tire, any size, replacement only, each
E2226	Manual wheelchair accessory, caster fork, any size, replacement only, each
E2227	Manual wheelchair accessory, gear reduction drive wheel, each
E2228	Manual wheelchair accessory, wheel braking system and lock, complete, each
E2230	Manual wheelchair accessory, manual standing system
E2231	Manual wheelchair accessory, solid seat support base (replaces sling seat), includes any type mounting hardware
E2300	Wheelchair accessory, power seat elevation system, any type
E2301	Wheelchair accessory, power standing system, any type
E2310	Power wheelchair accessory, electronic connection between wheelchair controller and one power seating system motor, including all related electronics, indicator feature, mechanical function selection switch, and fixed mounting hardware
E2311	Power wheelchair accessory, electronic connection between wheelchair controller and 2 or more power seating system motors, including all related electronics, indicator feature, mechanical function selection switch, and fixed mounting hardware
E2331	Power wheelchair accessory, attendant control, proportional, including all related electronics and fixed mounting hardware
E2340	Power wheelchair accessory, nonstandard seat frame width, 20-23 in
E2341	Power wheelchair accessory, nonstandard seat frame width, 24-27 in
E2342	Power wheelchair accessory, nonstandard seat frame depth, 20 or 21 in
E2343	Power wheelchair accessory, nonstandard seat frame depth, 22-25 in
E2351	Power wheelchair accessory, electronic interface to operate speech generating device using power wheelchair control interface
E2398	Wheelchair accessory, dynamic positioning hardware for back
E2601	General use wheelchair seat cushion, width less than 22 inches, any depth
E2602	General use wheelchair seat cushion, width 22 inches or greater, any depth
E2603	Skin protection wheelchair seat cushion, width less than 22 inches, any depth
E2604	Skin protection wheelchair seat cushion, width 22 inches or greater, any depth
E2605	Positioning wheelchair seat cushion, width less than 22 inches, any depth
E2606	Positioning wheelchair seat cushion, width 22 inches or greater, any depth
E2607	Skin protection and positioning wheelchair seat cushion, width less than 22 inches, any depth
E2608	Skin protection and positioning wheelchair seat cushion, width 22 inches or greater, any depth
K0013	Custom motorized/power wheelchair base
K0014	Other motorized/power wheelchair base
K0015	Detachable, nonadjustable height armrest, each
K0017	Detachable, adjustable height armrest, base, replacement only, each
K0018	Detachable, adjustable height armrest, upper portion, replacement only, each
K0019	Arm pad, replacement only, each
K0020	Fixed, adjustable height armrest, pair
K0037	High mount flip-up footrest, each
K0038	Leg strap, each
K0039	Leg strap, H style, each
K0040	Adjustable angle footplate, each
K0041	Large size footplate, each
K0042	Standard size footplate, replacement only, each
K0043	Footrest, lower extension tube, replacement only, each
K0044	Footrest, upper hanger bracket, replacement only, each

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K0045	Footrest, complete assembly, replacement only, each
K0046	Elevating legrest, lower extension tube, replacement only, each
K0047	Elevating legrest, upper hanger bracket, replacement only, each
K0050	Ratchet assembly, replacement only
K0051	Cam release assembly, footrest or legrest, replacement only, each
K0052	Swingaway, detachable footrests, replacement only, each
K0053	Elevating footrests, articulating (telescoping), each
K0056	Seat height less than 17 in or equal to or greater than 21 in for a high-strength, lightweight, or ultralightweight wheelchair
K0065	Spoke protectors, each
K0069	Rear wheel assembly, complete, with solid tire, spokes or molded, replacement only, each
K0070	Rear wheel assembly, complete, with pneumatic tire, spokes or molded, replacement only, each
K0071	Front caster assembly, complete, with pneumatic tire, replacement only, each
K0072	Front caster assembly, complete, with semipneumatic tire, replacement only, each
K0073	Caster pin lock, each
K0077	Front caster assembly, complete, with solid tire, replacement only, each
K0098	Drive belt for power wheelchair, replacement only
K0105	IV hanger, each
K0108	Wheelchair component or accessory, not otherwise specified
K0195	Elevating legrests, pair (for use with capped rental wheelchair base)

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed	Date Last Revised
03/1985	08/03/2010[MDCRPC], 06/07/2011[MDCRPC], 04/03/2012[MDCRPC], 02/05/2013[MDCRPC], 10/07/2014[MPC], 08/04/2015[MPC], 06/07/2016[MPC], 04/04/2017[MPC], 02/06/2018[MPC], 01/08/2019[MPC], 01/07/2020[MPC], 01/05/2021[MPC], 01/04/2022[MPC], 01/10/2023[MPC], 02/13/204[MPC]	12/21/2023

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
05/19/2015	The background statement was edited to state that WCs are for use in the home
08/04/2015	Manual Wheelchair: Added grade levels for severe dependent edema and removed “poor endurance” language
07/02/2016	Added addendum to exclusion list
08/01/2017	MPC approved to adopt indication for any requests for power wheelchair or power scooter must be submitted by a physiatrist who has examined the patient and done a thorough evaluation.
05/01/2018	MPC approved criteria for Power Assist Device
08/27/2019	Clarified qualifications of provider consulting for power assist device.
12/03/2019	MPC approved to adopt criteria for Specialized Wheelchairs: lightweight, ultra-lightweight and high-strength lightweight wheelchairs
05/05/2020	MPC approved to adopt updates to the power wheelchair supporting documentation requirements; clarifying language added for ultra-lightweight wheelchair and power assist device
06/23/2020	Added HCPC code E2398

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06/10/2021	Added statement “This should most commonly be a physiatrist.” to criteria #3 related to evaluation for ultra-light wheelchairs.
09/29/2021	Moved criteria for manual lightweight, high-strength lightweight and ultra-lightweight wheelchairs into the MCG KP-0354 Manual Wheelchair criteria.
5/26/2023	Updated Medicare coverage guidance by adding National Coverage Analysis (NCA) – Decision Memo regarding seat elevation systems.
10/25/2023	Added Medicare Coverage guidance NCD 280.16 Seat Elevation Equipment (power Operated) on Power Wheelchairs
12/09/2023	MPC approved make an exception to CMS payment methodology for knee scooters.
12/21/2023	Added NCD INDEPENDENCE iBOT 4000 Mobility System (280.15)

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Clinical Review Criteria
Whole Body Computed Tomography Scan

A separate criteria document exists for the following services:

- Low-dose whole body CT for Multiple Myeloma use the PET Scan Criteria
- Low-dose CT for Lung Cancer Screening use the Low-Dose CT Cancer Screening Criteria

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Computed Tomography (220.1).
Local Coverage Determinations (LCD)	None
Local Coverage Article	None

For Non-Medicare Members

Service	Criteria
Whole Body Computed Tomography Scan	There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.

If requesting this service, please send the following documentation to support medical necessity:

- Last 3 months of clinical notes from requesting provider &/or consulting specialist.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Computed tomography (CT) is a diagnostic procedure that uses x-rays to obtain cross-sectional images of the body. The images are based on the absorption of x-rays by different body tissues. Many CT systems allow imaging of multiple slices simultaneously so larger volumes of anatomy can be imaged in less time. Whole-body screening is a non-tailored, non-specific CT scan. It has recently been promoted as a general screening test to healthy individuals who have no symptoms or suspicion of disease. The purpose of screening is to prevent or delay, by means of early detection, the development of advanced disease and its adverse side effects. (From Kaiser Technology Assessment material.)

Currently some medical imaging facilities are promoting a new use of computed tomography (CT), also called computerized axial tomography (CAT) scanning. This use is referred to as whole-body CT scanning or whole-body CT

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screening, and it is marketed as a preventive or proactive health care measure to healthy individuals who have no symptoms or suspicion of disease. **At this time the FDA knows of no data demonstrating that whole-body CT screening is effective in detecting any particular disease early enough for the disease to be managed, treated, or cured and advantageously spare a person at least some of the detriment associated with serious illness or premature death.** Any such presumed benefit of whole-body CT screening is currently uncertain, and such benefit may not be great enough to offset the potential harms such screening could cause. (From the FDA consumer Web site.)

Medical Technology Assessment Committee (MTAC)

Whole Body Computed Tomography

07/14/2004: MTAC REVIEW

Evidence Conclusion: (Kaiser conclusions) No studies have been published that evaluate the efficacy of whole body CT screening of asymptomatic individuals.

Articles: (From Kaiser materials) Medline was searched through January 2004 with the search terms “whole body computed tomography” and “disease screening” - with variations. Screening of articles: (From Kaiser materials) No published studies were identified. Additional references: INTC Agenda packet, April 19, 2004. Included materials from Kaiser, Southern California and Hayes, Inc.

The use of whole body computed tomography scanning in the general screening of healthy individuals does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Applicable Codes

Medicare - Considered Medically Necessary when criteria in the applicable policy statements listed above are met
Non-Medicare - Considered Not Medically Necessary

HCPC Codes	Description
S8092	Electron beam computed tomography (also known as ultrafast CT, cine CT)

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
07/14/2004	12/07/2010[MDCRPC], 10/04/2011[MDCRPC], 08/07/2012[MDCRPC], 06/04/2013[MDCRPC], 04/04/2014[MPC], 02/03/2015[MPC], 12/01/2015[MPC], 10/04/2016[MPC], 08/01/2017[MPC], 07/10/2018[MPC], 07/09/2019[MPC], 07/07/2020[MPC], 07/06/2021[MPC], 07/05/2022[MPC], 07/11/2023[MPC]	07/29/2004

[MPC] Medical Policy Committee

Revision History	Description

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Clinical Review Criteria
Wound Care Treatments

- Electrical Stimulation and Electromagnetic Therapy
- Low Frequency, Noncontact, Nonthermal Ultrasound Wound Therapy
- Maggot Debridement Therapy (MDT)
- Noncontact Normothermic Wound Therapy
- OASIS Wound Dressing
- Tissue Engineered Skin Substitutes

A Separate Criteria Document Exists for the Following:
Negative Pressure Wound Therapy Pumps (NPWT)
Platelet Rich Plasma

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	Medicare Manual, Chapter 1, Part 4, Section 270
National Coverage Determinations (NCD)	• Electrical Stimulation (ES) and Electromagnetic Therapy for the Treatment of Wounds (270.1) • Non-Contact Normothermic Wound Therapy (NNWT) (270.2)* **This service is not covered per Medicare criteria* • Treatment of Decubitus Ulcers (270.4) • Porcine Skin and Gradient Pressure Dressings (270.5) • Infrared Therapy Devices (270.6)* **This service is not covered per Medicare criteria*
Local Coverage Determinations (LCD)	• Wound and Ulcer Care (L38904) • Surgical Dressings (L33831)
Local Coverage Article	• Billing and Coding: Wound and Ulcer Care (A58567) • Surgical Dressings – (A54563) • Billing and Coding: Wound Care and Debridement - Provided by a Therapist, Physician, NPP, or as Incident-to Services (A53046) • Use of Amniotic Membrane Derived Skin Substitutes (A56156) **RETIRED**
Kaiser Permanente Medical Policy – Skin Substitutes	Due to the absence of an NCD or LCD, Kaiser Permanente has chosen to use their own Clinical Review Criteria for Skin Substitutes for medical necessity determinations when these products are used in the outpatient hospital or office setting. Refer to the Non-Medicare Skin Substitutes criteria below.

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MLN Matters Article	January 2020 Update of the Ambulatory Surgical Center (ASC) Payment System **Section 4: Skin Substitutes (pp. 5-8)** ▪ **In the Ambulatory Surgery Care Setting** - Medicare considers skin substitutes for wound care to be dressings applied in the Ambulatory Surgery Center (ASC). These are not separately billable and do not need to go for Medical Review. ▪ **In the outpatient hospital or clinic setting** - Medicare considers skin substitutes billable. Refer to the Non-Medicare Skin Substitutes criteria below for medical necessity determinations.

For Non-Medicare Members

Treatment	Criteria Used
Noncontact Normothermic Wound Therapy • Warm-Up Wound Therapy	MCG* A-0351 This service is not medically necessary per MCG* For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access. **If requesting this service, please send the following documentation to support medical necessity:** • Last 6 months of clinical notes from requesting provider &/or specialist
Electrical Stimulation and Electromagnetic Therapy	MCG* A-0242 This service is not medically necessary per MCG* For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access. **If requesting this service, please send the following documentation to support medical necessity:** • Last 6 months of clinical notes from requesting provider &/or specialist
Low Frequency, Noncontact, Non-Thermal Ultrasound Wound Therapy	There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.
Maggot Debridement Therapy (MDT)	No medical necessity review required for this service.

Skin Substitutes
Tissue-engineered skin substitute may be indicated for **ONE or more of the following**: 1. Diabetic foot ulcers, as indicated by **ALL of the following**: ▪ Treated foot has adequate blood supply as evidenced by either the presence of a palpable pedal pulse or an ankle-brachial index (ABI) of ≥ 0.70) ▪ Receiving conventional wound care and optimal glycemic management to continue during treatment ▪ Diabetes mellitus (type 1 or type 2) ▪ Other causes of neuropathy may be approved on a case by case bases by a medical director ▪ Full-thickness foot ulcer with location on plantar, medial, or lateral area, and no exposure of tendon, muscle, capsule, or bone (Full thickness ulcer extends thru dermis and epidermal layers. Subcutaneous fat may be visible, but bone, tendon or muscle are not exposed.) ▪ No allergy to bovine products ▪ No response to four weeks of consistent conventional therapy, including **ALL of the following**: o No weight-bearing (off loading, so there is no pressure on the wound) o Optimal glycemic management o Dressing that promote moist wound healing

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Skin Substitutes

- Serial debridement as clinically indicated
- No wound infection defined as less than or equal to 3+ growth on semi-quantitative wound culture
- No slough or eschar in the wound bed

Only the following products are approved for treatment of diabetic ulcers
Biological skin substitutes: Use Integra/Musculoskeletal Transplant Foundation (MTF)
Synthetic skin substitutes: Use Integra/Smith & Nephew

Integra Biological products: AmnioExcell amniotic allograph, AmnioMatrix amniotic allograft, AmnioExcell plus placental allograph
MTF Biological products: AlloPatch Pliable Allograft Dermal Matrix, AmnioBand Membrane Allograft Placental Matrix, AmnioBand Particulate Allograft Placental Matrix, AmnioBand Viable Allograft Placental Matrix
Smith and Nephew Synthetic products: Oasis Ultra tri-layer Matrix, Oasis Wound Matrix Fenestrated
Integra Synthetic products: Integra Wound Matrix, PriMatrix, PriMatrix Fenestrated, PriMatrix Meshed, PriMatrix Ag, Integra Meshed Dermal Regeneration, Integra Meshed Bilayer Wound Matrix

2. Venous insufficiency ulcers, as indicated by **ALL of the following**:
   - Treated foot has adequate blood supply as evidenced by either the presence of a palpable pedal pulse or an ankle-brachial index (ABI) of ≥ 0.70)
   - Receiving concurrent conventional wound care for a minimum of four weeks, to include compression of extremity (e.g. compression stocking, ace bandage, lymphedema pump – if meets criteria) Receiving concurrent optimal glycemic management, if patient is also diabetic
   - Full-thickness ulcer due to venous insufficiency
   - No allergy to bovine products, porcine and/or ovine products
   - No response to conventional therapy, including ALL of the following:
     - Dressing that promote moist wound healing
     - Serial debridement as clinically indicated
   - No wound infection defined as less than or equal to 3+ growth on semi-quantitative wound culture
   - Compression
   - No slough or eschar in the wound bed

Only the following products are approved for treatment of venous insufficiency ulcers
Biological skin substitutes: Use Integra/Musculoskeletal Transplant Foundation (MTF)
Synthetic skin substitutes: Use Integra/Smith & Nephew

Integra Biological products: AmnioExcell amniotic allograph, AmnioMatrix amniotic allograft, AmnioExcell plus placental allograph
MTF Biological products: AlloPatch Pliable Allograft Dermal Matrix, AmnioBand Membrane Allograft Placental Matrix, AmnioBand Particulate Allograft Placental Matrix, AmnioBand Viable Allograft Placental Matrix
Smith and Nephew Synthetic products: Oasis Ultra tri-layer Matrix, Oasis Wound Matrix Fenestrated
Integra Synthetic products: Integra Wound Matrix, PriMatrix, PriMatrix Fenestrated, PriMatrix Meshed, PriMatrix Ag, Integra Meshed Dermal Regeneration, Integra Meshed Bilayer Wound Matrix

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The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Chronic wounds, wounds with long healing time, and wounds with frequent recurrence are a major health problem. They are a problem for the patient who suffers from them, the clinician who treats them, and the health care system that is overburdened by their cost. It is estimated that chronic wounds affect approximately 2% of the American

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population at an estimated cost of US $20 billion per year. Many factors can impede wound healing, including chronic disease, venous insufficiency, arterial insufficiency, neuropathy, nutritional deficiencies and local features such as pressure, edema, and infection (Fonder, 2008, Rizzi 2010).

No single regimen is universally accepted as the best modality for treating chronic wounds. They are managed through conventional wound care procedures performed by primary care providers, community nurses, pharmacists, and others. In the early 2000s, the concept of wound bed preparation has been proposed as a means of providing a structured and systemic approach to the management of chronic wounds. It is believed to accelerate endogenous healing and/or facilitate the effectiveness of other therapeutic measures. Wound bed preparation involves ongoing wound debridement, management of exudates, and resolution of bacterial imbalance (Schulz 2003, Ramundo 2008).

Wound debridement is defined as the removal of devitalized or contaminated tissue as well as foreign material from the wound bed until healthy tissue is exposed. Efficient debridement reduces the necrotic burden, achieves healthy granulation tissue, and reduces wound contamination and tissue destruction. This can be performed by different enzymatic, autolytic, sharp/surgical, biological, and mechanical techniques. Each has its own advantages and limitations, and the methods that are most efficient at removal of debris, may at the same time be the most detrimental to fragile new growth (Schulz 2003, Beitz, 2005, Ramundo 2008).

Tissue-engineered skin substitutes (i.e., human skin equivalents [HSE]), also referred to as artificial skin, are bioengineered skin products and may be either acellular or cellular. Acellular (i.e., cadaveric human dermis with cellular material removed) products contain a matrix or scaffold composed of materials such as collagen, hyaluronic acid, and fibronectin. The construction of the matrix allows easy access by host cells during the healing process. Cellular products contain living cells such as fibroblasts and keratinocytes within a matrix. The cells contained within a matrix may be allogeneic (i.e., obtained from another individual) or autologous (i.e., obtained from the same individual). Some products are derived from other species (e.g., bovine, porcine) and are referred to as a xenograft. Skin substitutes are generally comprised of epidermal cells, dermal cells or may be composites (i.e., a combination of dermal and epidermal). The substitutes can be used as either temporary or permanent wound coverings. Grafting techniques utilized to apply skin substitutes include autografting (i.e., tissue transplanted from one part of the body to another), allografting (i.e., transplant from one individual to another of the same species), and xenografting (i.e., a graft from one species to another unlike species). Skin substitutes have been proposed for the treatment of multiple conditions including breast reconstruction and chronic wounds nonresponsive to standard therapy.

During breast reconstruction, acellular dermal skin substitutes (i.e., AlloDerm, AlloMax) are primarily used in the setting of tissue expander and breast implant reconstruction. Patients should be in overall good health and have no underlying condition that would restrict blood flow or interfere with the normal healing process (e.g., uncontrolled diabetes, hypertension, previous surgery). These matrixes may be indicated when there is insufficient tissue expander or implant coverage by the pectoralis major muscle and additional coverage is required, as may be the case in a very thin patient; if there is viable but compromised or thin post-mastectomy skin flaps that are at risk of dehiscence or necrosis; or if there is a need to re-establish the inframammary fold and lateral mammary fold landmarks. When used in appropriate candidates, these skin substitutes are proposed to improve control over placement of the inframammary fold and final breast contour, enhance use of available mastectomy skin, reduce the number of expander fills necessary, reduce time to complete expansion and eventual implant exchange, potential improved management of a threatened implant, reduce the need for explanation and the potential for reduction in the incidence of capsular contracture. However, there are ongoing concerns regarding the increased risk of seroma and infection, a higher risk of an implant having to be removed, and tissue flap death.

Evidence and Source Documents

Bilaminate Skin Substitutes
Electrical Stimulation and Electromagnetic Therapy
Low Frequency, Noncontact, Nonthermal Ultrasound Wound Therapy Maggot
Debridement Therapy (MDT)
Medihoney Dressing for Wound Management OASIS
Wound Dressing
Warm-Up Wound Therapy

Medical Technology Assessment Committee

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Bilaminate Skin Substitutes

BACKGROUND

Venous ulcers are a chronic recurring condition associated with long-standing venous hypertension of the lower extremities. They occur in approximately 1-3 patients per thousand in the general population with the incidence rising to 20 per thousand in individuals over 80 years old. The chronicity of care required to treat this condition involves significant time and resources and often treatment is unsuccessful in producing complete venous ulcer healing. Typical treatments include frequent dressing changes, compression bandages, antibiotic and antiseptic use, and mechanical debridement. One proposed treatment of chronic venous ulcers involves covering the ulcer with a natural bilayer skin substitute that is hypothesized to protect the wound and promote healing.

08/11/1999: MTAC REVIEW

Bilaminate Skin Substitutes

Evidence Conclusion: The best, published article reporting original data on the effect of using Apligraf on non-healing venous ulcers is a randomized controlled trial of 309 patients recruited from 5 wound treatment centers. The results of this randomized controlled trial indicate that venous ulcers resolve more quickly when treated with compression and human skin equivalent than when treated with compression alone. The results also suggest that patients treated with compression/human skin equivalent are more likely to have complete healing of a venous ulcer than those who are treated only with compression. The bias introduced by the failure to perform an intention-to-treat analysis could explain some of the differences between treatment groups. The results cannot be generalized to patients with conditions that are associated with poor wound healing or to patients with large venous ulcers. Additionally, the probability of ulcer recurrence after 12 months for patients treated with compression/human skin equivalent relative to that of patients treated only with compression remains unknown. This study has not defined the risk of clinically relevant immunologic rejection of human skin equivalent for patients with venous ulcers.

Articles: Falanga, V et al, *Arch. Dermatol*. 1998;134:292-300 See Evidence Table.

The use of Apligraf human skin equivalent for the treatment of non-healing venous ulcers has been approved by the FDA and therefore meets GHC criteria 1. There is sufficient scientific evidence that Apligraf is medically effective and therefore *Kaiser Permanente Medical Technology Assessment Criteria*.

Electrical Stimulation and Electromagnetic Therapy

BACKGROUND

Chronic wounds have been traditionally known as wounds that take prolonged time to heal, do not heal completely, or recur frequently. There is no agreed upon definition for chronic wounds; Lazarus et al (1994) defined them as wounds of at least 8 weeks in duration that have failed to proceed through an orderly and timely process that produces anatomic and functional integrity. Troxler et al (2006) defined them as wounds that fail to heal with ‘standard therapy’ in an orderly and timely manner. More recently Fonder and colleagues (2008) defined chronic skin wounds as break in the skin of long duration (>6 weeks), or frequent recurrence. Generally, the process of normal healing takes few days to 2 weeks and involves three phases that may overlap in time: 1. inflammatory phase, 2. proliferative phase, and 3. remodeling phase. If any of these phases is compromised, healing will be delayed. Chronic wounds are predominantly due to chronic venous insufficiency, atherosclerosis, pressure sores, or peripheral neuropathy. Chronic ulceration can affect any anatomic region of the body, but the majority is seen in the lower limbs. Pressure sores also known as pressure ulcers are the most common of all chronic wounds, and venous ulcers account for the majority of leg ulcers (70-85%). Diabetic foot ulcers and ischemic ulcers contribute to a significant proportion of the rest (Eaglestein 1997, Simon 2004, Jones 2007, Fonder 2008). Management of chronic wounds has challenged health care providers for generations, and various strategies have been used to accelerate the healing process. Standard care includes debridement of necrotic or infected tissue, maintenance of a moist wound environment, control of infection, wound dressing, nutritional support, and treatment of concurrent conditions that may delay healing. Adjuncts to wound care include several established or emerging therapies. These include compression therapy, pressure relieving beds or cushions, hyperbaric oxygen therapy, topical negative pressure devices, growth factors, skin substitutes, and topical or systemic medications. Selection of therapy is based on the individual patient’s clinical condition, and type and cause of wound. A whole range of other adjunctive treatment modalities, such as laser, ultrasound, and electricity have also been applied to chronic wounds (Cullum 2000, de Araujo 2003, Fonder 2008). Electrical stimulation (ES) or electrotherapy for wound healing is defined as the application of electrical current from electrodes placed directly within a wound or on skin in a close proximity to it. ES has been a topic for research for decades and is often used by physical therapists to promote healing. There are four basic treatment regimens for ES therapy: low intensity direct current (LIDC), high voltage pulsed current (HVPC), alternating current (AC), and transcutaneous

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electrical nerve stimulation (TENS). Electromagnetic therapy is a related therapy but is distinct from other forms of electrotherapy in that it uses an electromagnet to generate the electric current. It has a field effect not a direct effect or a form of irradiation. It covers a wide range of wavelengths including radio-waves and X-rays. Short wave diathermy (SWD) is a non-ionizing radiation present in the radio-waves portion of the electromagnetic spectrum. The frequency of the short- wavelength radio-waves ranges from 10 to 100 MHz. The radiofrequency wave band of 27.12 MHz is used for therapeutic effect in continuous SWD. Electromagnetic therapy can also be delivered in short bursts of energies called Pulsed Short-Wave Diathermy or PSWD (gardener 1999, Ojingwa 2002, Stiller 1992, Olyaee 2006, Callaghan 2008). In vitro and animal studies have showed that electrical stimulation can increase the DNA and collagen synthesis, direct epithelial, fibroblast, and endothelial cell migration into wound sites, inhibit growth of some wound pathogens, and increase tensile strength of wound scar (Bassett 1974, Gordon 2007). Several devices have been used off-label to deliver ES or electromagnetic therapy to cutaneous wounds. The FDA approved electric stimulators as Class III devices for deep brain and bone stimulation and cleared them as class II devices for muscle stimulation. Electromagnetic devices were also FDA cleared for the treatment of selected medical conditions including relief of pain, muscle contracture, joint contractures, and others. None of the ES or electromagnetic devices has been cleared by the FDA, to date, for the treatment of wounds. The objective of this review is to determine whether electric stimulation and /or electromagnetic therapies are effective adjunctive treatments for chronic skin wounds. The technology has not been previously reviewed by MTAC for this indication.

04/09/2008: MTAC REVIEW

Electrical Stimulation and Electromagnetic Therapy

Evidence Conclusion: There is limited evidence on the effect of electric stimulation (ES) or electromagnetic (EM) therapy on the healing of chronic wounds. The body of evidence on ES therapy mainly consists of small randomized and nonrandomized controlled trials that used the therapy off-label to treat chronic wounds, as well as a meta-analysis that pooled the results of 15 randomized and nonrandomized studies. The literature on EM therapy was more limited. There were very few small trials that also used the therapy off- label. Due to this limited number of studies, the authors of the Cochrane reviews were unable pool the results in a meta-analysis. Although a number of the published RCTs were randomized, controlled, blinded, and had clinical outcomes, all had their limitations: they were too small, with short follow-up durations, and with no standardized dose, frequency, or duration for the electric stimulation (ES) or electromagnetic (EM) therapy. Moreover, several studies used the change in ulcer size rather than incidence of /or time to complete healing as their outcome. No adjustments were made for potential confounding factors, and analyses were not based on intention to treat. The results of these trials suggest that electrotherapy might be associated with improved healing, but the evidence is insufficient to draw any conclusions on the benefits of therapy on complete healing or health outcomes. Gardener and colleagues' (1999) pooled the results of nine small RCTs to quantify the effect of ES on chronic wound healing.
They showed a healing rate of 22% per week among patients treated with ES therapy compared to 9% healing rate per week among the controls. There were several differences among the studies included in the patients' characteristics, types of wounds, and devices used to deliver the ES therapy, as well as dose, frequency and duration of therapy. The two Cochrane reviews on EM therapy (Ravaghi 2006, and Manesh 2006) on venous leg ulcers, and pressure ulcers respectively, could not pool the results due to the limited number of included trials. In conclusion, there is insufficient evidence to determine whether the use of ES or EM therapy as adjunctive treatments would lead to healing of chronic wounds or improve the patients' health outcomes.
Articles: The literature search revealed over 90 articles. Several were reviews or non-related to the current report. There was a meta-analysis of randomized and non-randomized controlled studies on ES therapy for chronic wounds, and two small RCTs that were not included in the meta-analysis. There were also two Cochrane reviews on electromagnetic therapy for treating pressure ulcers and venous leg ulcers. The reviews however did not pool the results in meta-analyses due to the limited number of studies. A review by TEC of Blue Cross Blue Shield on electric stimulation and electromagnetic therapy for chronic skin ulcers (2005), and an ECRI report (1996) on electrical stimulation for the treatment of chronic wounds were also identified by the search. The meta-analysis and the two more recent RCTs on ES, as well as the two Cochrane reviews on electromagnetic therapy were critically appraised.
Gardener SE, Frantz R, Schmidt FL. Effect of electrical stimulation on chronic wound healing: a meta-analysis. Wound Rep Reg 1999; 7:495-503. See Evidence Table. Ravaghi H, Flemming K, Cullum NA, et al. Electromagnetic therapy for treating venous leg ulcers. (Review). Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No.:CD002933. DOI:10.1002/14651858. CD002933.pub3. See Evidence Table. Manesh O, Flemming K, Cullum NA, et al. Electromagnetic therapy for treating pressure ulcers. (Review). Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No.:CD002930. DOI:10.1002/14651858. CD002930.pub3. See Evidence Table. Peters EJ, Lavery LA, Armstrong DG, et al. Electrical stimulation as an adjunct to heal diabetic foot ulcers: a randomized clinical trial. Arch Phys Med Rehabil. 2001;82:721-725, See Evidence Table. Houghton PE, Kinacaid CB, Lovell M, et al. Effect of electrical stimulation on chronic leg ulcer size and appearance. Phys Ther 2003;83:17-28 See Evidence Table.

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The use of Electrical stimulation and electromagnetic therapy in the treatment of chronic skin wounds does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Low Frequency, Noncontact, Nonthermal Ultrasound Wound Therapy

BACKGROUND

Chronic wounds, wounds with long healing time, and wounds with frequent recurrence are a major health problem. They are a problem for the patient who suffers from them, the clinician who treats them, and the health care system that is overburdened by their cost. It is estimated that chronic wounds affect approximately 2% of the American population at an estimated cost of US $20 billion per year. Many factors can impede wound healing, including chronic disease, venous insufficiency, arterial insufficiency, neuropathy, nutritional deficiencies and local features such as pressure, edema, and infection (Fonder, 2008, Rizzi 2010). No single regimen is universally accepted as the best modality for treating chronic wounds. They are managed through conventional wound care procedures performed by primary care providers, community nurses, pharmacists, and others. In the early 2000s, the concept of wound bed preparation has been proposed as a means of providing a structured and systemic approach to the management of chronic wounds. It is believed to accelerate endogenous healing and/or facilitate the effectiveness of other therapeutic measures. Wound bed preparation involves ongoing wound debridement, management of exudates, and resolution of bacterial imbalance (Schulz 2003, Ramundo 2008). Wound debridement is defined as the removal of devitalized or contaminated tissue as well as foreign material from the wound bed until healthy tissue is exposed. Efficient debridement reduces the necrotic burden, achieves healthy granulation tissue, and reduces wound contamination and tissue destruction. This can be performed by different enzymatic, autolytic, sharp/surgical, biological, and mechanical techniques. Each has its own advantages and limitations, and the methods that are most efficient at removal of debris, may at the same time be the most detrimental to fragile new growth (Schulz 2003, Beitz, 2005, Ramundo 2008). Noncontact, low frequency ultrasound therapy was recently introduced as a modality for promoting wound healing through wound cleansing and maintenance debridement. The therapy is thought to produce a number of biophysical effects that are associated with wound healing. These include increased protein and collagen synthesis, angiogenesis, production of growth hormone by macrophages, endothelial production of nitric oxide synthesis; and leukocyte adhesion. One of the main mechanisms of action for ultrasound therapy, as shown by in vitro studies, is achieved through the process of cavitation. This involves the production and vibration of micron-sized bubbles within the coupling medium and fluids in the tissues. As the bubbles collect and condense, they are compressed before moving to the next area. This movement and compression can potentially cause changes in the cellular activities of the tissues subjected to the ultrasound. Acoustic streaming is another mechanism by which ultrasound generates biologic activity producing a unidirectional movement of fluid along and around cell membranes. A more recent hypothesis known as the frequency resonance theory uses the above concepts at the protein and genetic level and result in a broad range of cellular effects that promote healing. Ultrasound energy is also believed to have a direct bactericidal action caused by the cavitation effects produced by the ultrasound waves (Ennis 2005 Ramundo 2008). The sound waves generated by the therapeutic ultrasound devices have lower frequencies than those generated by diagnostic devices (25-40 kHz vs. 200,000-400,000 kHz respectively). Ultrasound MIST therapy devices use saline to couple the ultrasound energy to tissue within the wound bed. This is accomplished by the noncontact non-thermal application of a fine oxygenated fluid (sterile saline) stream spray to the wound bed through which the ultrasound energy is transmitted from the applicator tip to the wound tissue. This noncontact ultrasound is believed to provide cellular stimulation, increase blood flow, and reduce bioburden with much less pain or thermal effect than other direct contact devices. It is usually applied three times a week for a duration dependent on the wound dimensions. The therapy should be performed in a closed environment area to avoid spread of microbes, and the clinician delivering the therapy should wear protective gear (Ramundo 2008, FDA webpage). Ultrasound MIST therapy (Celleration, Inc, Eden Prairie, MN), was cleared by the FDA in 2004 to promote healing of wounds through wound cleansing and maintenance debridement by the removal of yellow slough, fibrin, tissue exudates and bacteria. Its use is contraindicated for malignant wounds, radiation wounds, for tissue previously treated with radiation, and for patients with bleeding disorders, or thrombophlebitis.

02/01/2010: MTAC REVIEW

Low Frequency, Noncontact, Nonthermal Ultrasound Wound Therapy

Evidence Conclusion: The literature search revealed two published RCTs on the low frequency noncontact ultrasound therapy for the treatment of wounds. The two trials were funded by the manufacturer. In one trial, Ennis and colleagues, 2005, compared the ultrasound therapy to a sham device for the treatment of patients with diabetic foot ulcers. Patients in the two treatment groups also received wound conventional therapy. The trial was randomized and controlled and had clinically important outcome. However, it had several methodological flaws which limit generalization of its results. The study had a very low completion rate (41%) due to dropouts or violations of the protocol, and the ulcers in the sham treatment group were significantly lager in size and with a

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longer duration than those in the investigational group, which are potential sources of bias and confounding. The results show significant difference in the wound closure favoring the ultrasound therapy group when the analysis included only those who completed the trials, but no significant differences were observed when the analysis was based on intention to treat. Kavros and colleagues, 2007, compared the effects of the ultrasound therapy plus standard wound care to standard wound care alone in 70 patients with non-healing ischemic lower-extremity wounds. The trial was also randomized and controlled, but was not blinded, and the outcomes were mainly based on measurements which are subject to potential error, and observational bias. Moreover, the authors did not discuss if there were any dropouts, rate of compliance, or adverse events associated with the intervention. Overall, the results of the trial show that patients managed with MIST therapy in addition to standard treatment, achieved a significantly higher >50% wound closure rate in 12 weeks than those managed with standard therapy alone. A secondary analysis of the trial showed that patients with critical limb ischemia with baseline TcPO2 <20 with dependency were significantly less likely to achieve >50% healing by week 12, using standard treatment with or without MIST therapy. In conclusion, the published literature does not provide sufficient evidence to determine that non-thermal, noncontact, low frequency ultrasound therapy “Mist therapy “is safe to use, or that it has similar or better outcomes than those achieved by other debridement methods or standard wound care management procedures.

Articles: The literature search yielded two RCTs, on the low frequency ultrasound therapy using the MIST therapy system for the treatment of chronic wounds, one non-randomized retrospective comparative study and prospective case series. The two RCTs were critically appraised. Ennis WJ, Formann P, Mozen N, et al. Ultrasound therapy for recalcitrant diabetic foot ulcers: Results of a randomized, double-blind, controlled, multicenter study. Ostomy Wound Management.2005;51:24-39. See Evidence Table. Kavros SJ, Miller JL, Hanna SW. Treatment of ischemic wounds with noncontact, low-frequency ultrasound The Mayo Clinic experience, 2004-2006. Adv skin Wound Care 2007; 20:221-226. See EvidenceTable.

The use of Low frequency, noncontact, nonthermal ultrasound therapy for the treatment of wounds does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Maggot Debridement Therapy (MDT)

BACKGROUND

Chronic wounds, wounds with long healing time or frequent recurrence, are major health care and quality of life burdens. Approximately 1-2% of individuals in the United States are likely to be affected by leg ulceration at some time in their life. Many factors can impede wound healing, including chronic disease, vascular insufficiency, nutritional deficiencies and local features such as infection, pressure and edema (Fonder et al., 2008). Preparation of the wound bed is an important component of optimal healing. Proper preparation includes debridement of nonviable tissue, management of inflammation and infection, and establishment of proper moisture balance. Wound debridement serves several purposes. It removes necrotic tissue which can present physical barriers to healing, decreases the potential for infection, enhances the ability to assess wound depth, and helps to remove bacteria that may prevent healing (Beitz, 2005). Debridement methods include hydrogels, enzymatic agents, dextranomer polysaccharide beads or paste, adhesive zinc oxide tape, and sharp debridement. A systematic review of studies on different debridement methods concluded that there was insufficient evidence to recommend one method of debridement over another (Bradley et al., 1999). Maggot debridement therapy (MDT) is another method for wound debridement. Maggot or larval therapy has been used in some form for centuries, including treating battle wounds in Napoleon’s army in the 1550s. Dr. William Baer, often called the founder of modern maggot therapy, observed the effects of maggots on the wounds of soldiers during World War I and he later refined the technique to use sterile maggots under controlled conditions. MDT increased in popularity after WWI and, by the 1930s, was widely used in the U.S. and Europe. Its use decreased after the advent of antibiotics in the 1940s. As of the late 1990s there has been resurgence in interest due to antibiotic resistance, particularly methicillin-resistant Staphylococcus aureus (MRSA) and the lack of other reliably effective methods (Gupta, 2008). Modern MDT involves the use of specially bred larvae, most commonly of the green-bottle fly Lucilia sericata species. Larvae 1-2 mm long larvae hatch from eggs in 12-24 hours and, when they feed on necrotic tissue in the moist environment of wounds, they mature in 4-5 days, at which time they measure about 10mm. Larvae need to be sterile to prevent contamination and should be used within 8 hours of hatching or stored in refrigerator at 8-10o C to slow their metabolism. They require an optimal body temperature, moist environment and adequate oxygen supply. The general procedure is to introduce larvae to the wound at a density of 5-8 per cm2 and cover with a containment dressing that allows oxygen to pass through. Dressings are generally changed once a day to avoid build-up of secretions, and the larvae are changed every 2-3 days. Wounds commonly require 2-6 treatment cycles for complete debridement (Gupta et al., 2008; Chan et al., 2007; FDA materials). The exact mechanisms by which maggots debride wounds are not fully understood. It is generally believed that there is a combination of: 1) Mechanical action: probing from the maggots’ pair of mandibles/hooks may facilitate debridement; 2) Enzymatic action: Three proteolytic enzymes have been identified in maggot

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excretions/secretions (ES) that can degrade extracellular matrix components, including laminin and fibronectin. The ES also have antibacterial substances which appear to have an inhibitory effect on Gram-positive and Gram-negative bacteria including MRSA. Maggots may also secrete cytokines which aid in wound healing; 3) Digestion: Maggots appear to ingest bacteria and kill them in their alimentary tract (Chan et al., 2007). There are no reports that MDT is associated with major adverse effects or complications. Minor discomfort has been reported, and excessive pressure on the wound may kill some of the maggots, resulting in uneven healing. There is also the issue of social acceptance of larval therapy, the widely-cited "yuck" factor, for patients and providers. In 2004, FDA cleared Medical Maggots (Monarch Labs, Irvine, CA) for commercial production as a Class II medical device. The approved indication is debridement of non-healing necrotic skin and soft tissue wounds.

04/06/2009: MTAC REVIEW
Maggot Debridement Therapy (MDT)
Evidence Conclusion: There is fair evidence from one RCT that wound debridement is significantly faster with maggot debridement therapy than hydrogel, but that there is no significant difference in time to complete wound healing (Dumville et al., 2009). In the RCT, median time to healing was 236 days in the larvae therapy groups and 245 in the hydrogel group. Time to debridement was 14 days in the group receiving loose larvae, 28 days in the bagged larvae group and 72 days in the hydrogel group. The efficacy of maggot therapy for debridement is supported by the results of a retrospective cohort study, and several case series. The RCT found significantly higher reports of ulcer-related pain in the larvae therapy groups in the 24 hours before removal of the first treatment compared to hydrogel and did not report on pain during subsequent treatments. There is insufficient evidence on the efficacy of maggot therapy for MRSA eradication compared to standard wound care approaches. The number of MRSA-positive wounds in the RCT was too small to draw conclusions about eradication.
Articles: The search yielded two RCTs, one of which had a sample size of 12 patients and was excluded from further review. There was also one non-randomized comparative study and several case series. The larger RCT, cohort study and the three largest case series (n>50) were critically appraised. Citations are as follows: Dumville JC, Worthy G, Bland JM et al. Larval therapy for leg ulcers (VenUS II): randomized controlled trial. BMJ 2009; 338; online first. See Evidence Table. Sherman RA. Maggot versus conservative debridement therapy for the treatment of pressure ulcers. Wound Rep Reg 2002; 10: 208-214. See Evidence Table. Steenvoorde P, Jacob CE, Van Doorn L, Oskam J. Maggot debridement therapy of infected ulcers: patient and wound factors influencing outcome- a study on 101 patients with 117 wounds. Ann R Coll Surg Engl 2007; 89: 596-602. See Evidence Table. Wolff H, Hansson C. Larval therapy- an effective method of ulcer debridement. Clin Exper Dermatol 2003; 134-137. See Evidence Table. Courtenay M, Church JCT, Ryan TJ. Larva therapy in wound management. J Royal Soc Med 2000; 93: 72-73. See Evidence Table.

The use of maggot debridement therapy for the treatment of chronic and infected wounds does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Medihoney Dressing for Wound Management
BACKGROUND
Honey has been used in wound care for thousands of years. The ancient Egyptians, Greeks, Romans, Chinese, and other early cultures used it as a remedy for wounds either alone or in combination with other ingredients. Its healing benefits were passed from generation to generation, and honey is still traditionally used in many parts of the world. Recently there has been a resurgent interest by the medical profession in using topical honey for wound treatment, mainly due to the increasing number of bacterial strains developing resistance to antibiotics. It is only in the last few decades that researchers started to investigate honey's mechanism of action in wound healing (Molan 2008, Lay-flurrie 2008). Honey is a viscous supersaturated sugar solution derived from nectar gathered and modified by the honeybee. It contains approximately 30% glucose, 40% fructose, 5% sucrose, 20% water and many other substances as amino acids, vitamins, minerals, and enzymes. In-vitro and animal studies indicate that honey has several therapeutic potentials. Its high osmolarity due to the sugar content causes bacterial cell wall shrinkage and inhibition of growth. Many bacteria grow and multiply in a neutral pH environment (6.5-7.0) and cannot thrive in the acidic pH of honey which ranges from 3.2 to 4.2. Researchers have reported that it in addition to its antibacterial properties, honey enhances tissue growth by drawing fluid from the underlying circulation providing both a moist environment and topical nutrition to the tissues. They also found that honey leads to cytokine release, promote autolytic debridement, deodorize malodorous wounds, and stimulates anti-inflammatory activity that reduces pain, edema, and exudate, and minimizes scarring (Molan 1999, Sato 2000, White 2005, Bell 2007). There are many different types of honey but the Manuka honey, a monofloral honey derived from the leptospermum tree species known as tea trees in Australia and New Zealand, has received particular interest for wound healing. Some researchers claim that it has a broad-spectrum antibacterial activity and is exceptionally effective for several bacterial species that commonly infect surgical wounds as Staphylococcus aureus and

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Pseudomonas aeruginosa (Lusby 2002, Visavadia 2008). Therapeutic honey is typically raw and does not undergo heat treatment like culinary honey. It is sterilized by gamma irradiation which destroys any bacterial spores while retaining its biologic activities. Honey dressings are available in various commercial preparations such as honey gel ointment, honey-impregnated tulle dressings, honey impregnated calcium alginate dressings, and honey-based sheet hydrogel dressings (Molan 1999, Lusby 2002 Visavadia 2008, Eddy 2008, Lay-flurrie 2008). Derma Sciences Medihoney Dressing with Active Manuka Honey received FDA approval for providing a moist environment conducive to wound healing. These are tulle dressings comprised of 95% Active Manuka Honey and 5% calcium alginate, and are offered in several sizes including 0.5, 1, and 1.5 ounces. According to the FDA, Medihoney dressings are indicated for the management of light to moderately exuding wounds as: diabetic foot ulcers, venous or arterial leg ulcers, partial or full thickness pressure ulcers/sores, first and second partial thickness burns, and traumatic and surgical wounds. Honey dressings should be avoided in patients with a known history of allergy to either honey or bee venom. It was also reported (Lay-flurrie 2008) that patients with diabetes should have their blood sugar monitored as they may be at higher risk of hyperglycemia due to the sugar content of honey.

12/01/2008: MTAC REVIEW
Medihoney Dressing for Wound Management
Evidence Conclusion: To date, there are no published high-quality studies to support the use honey in wound dressings. Jull and colleagues performed a systematic review (Cochrane review) of 19 randomized and quasi-randomized trials to determine the efficacy of honey on the healing of acute and chronic wounds. The meta-analysis had generally valid methodology. However, its strength is only as good as the trials it includes, and the majority was of low methodological quality. Moreover, 11 of the 19 studies were conducted by one and the same author in a single center. There was significant clinical and statistical heterogeneity between the studies which did not enable pooling of the results in the meta-analysis. Overall, the results of subgroup meta-analyses only showed a significant benefit of honey dressings (2 trials, n=992) in reducing time to complete healing of mild to moderate partial thickness burns vs. conventional dressings. The Jull et al's RCT, 2008 compared the effect of Manuka honey dressings to usual care for the treatment of venous ulcers. It was randomized, controlled and multicenter, and analysis was based on intention to treat. However, the trial was open-label, and a range of dressings were used in the control group, which are potential sources of bias. Its results showed no statistically significant differences between the honey dressing and the usual care in rate or time to complete healing. On the other hand, honey dressings were associated with significantly higher rates of overall adverse events, ulcer pain (NNH=7), and ulcer deterioration (NNH=10). Gethin and colleagues' trial compared Manuka honey to hydrogel dressings used for the treatment of venous ulcers. The trial was unblinded, small, and did not recruit the predetermined number of patients required to provide sufficient statistical power. The results of the trial showed no statistically significant differences between the Manuka honey and hydrogel therapy in desloughing the wound (percent of wound area covered by slough), or rate of slough removal in venous ulcers at 4 weeks. There was however, a higher rate of ulcer healing in the Manuka honey group (44%) vs. the hydrogel group (33%) with a risk ratio of 1.38, and NNT =9 in 12 weeks. The authors did not discuss how they defined wound healing. Conclusion: There is insufficient good quality evidence to determine whether the use of Medihoney dressings would improve the rate of healing in acute wounds as burns and traumatic wounds. There is insufficient evidence to determine whether the use of Medihoney improves the rate of healing in chronic wounds including venous ulcers, arterial ulcers, diabetic ulcers, and pressure ulcers.
Articles: The search revealed over 120 articles on the use of honey for wound care. The number of published articles dropped to just over 20 articles when the search was limited to Manuka or Medihoney. Many were review articles or opinion pieces on the benefits of honey in wound management. There was a Cochrane review on honey as a topical treatment of wounds, and a number of RCTs on the use of honey in the treatment of acute wounds due to burns. The majority of the latter trials were conducted in one center, and by one and the same author. The literature on the use of honey for chronic ulcers was limited. There were three RCTs on honey dressings for venous ulcers, two of which were conducted by the same investigators (Gethin and colleagues 2008) among the same group of patients but reported different outcomes. No randomized controlled trials on the use of honey in diabetic foot ulcers, ischemic, or pressure ulcers were identified. There were only very small non-randomized trials, case series and case reports. The Cochrane review and the three trials on the use of honey for venous ulcers were critically appraised: Jull AB, Rodgers A, Walker N. Honey as a topical treatment for wounds Cochrane Database of Systematic Reviews 2008, Isssue4. Art No.: CD005083.DOI10.1002/14651858.CD005083pub2: 16:1085-1100. See Evidence Table. Jull A, Walker N, Parag V, et al. Randomized clinical trial of honey- impregnated dressings for venous leg ulcers. Br J Surg 2008; 85:175-182 See Evidence Table. Gethin G, Cowman S. Manuka honey vs. hydrogel –a prospective, open label, multicenter, randomized controlled trial to compare desloughing efficacy and healing outcomes in venous ulcers. J Clin Nurs 2008; August 23 See Evidence Table. Gethin G, Cowman S. Bacteriological changes in sloughing venous leg ulcers treated with Manuka honey or hydrogel: an RCT. J wound

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Care 2008;17:241-247 See Evidence Table.

The use of Medihoney dressing in the treatment of wound management does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

OASIS Wound Dressing

BACKGROUND

OASIS® Wound Matrix (Cook Biotech, Inc.) is a biosynthetic skin substitute that is derived from porcine small intestine submucosa. This material is approximately 0.15 mm thick and consists primarily of a collagen-based extracellular matrix. However, unlike other purified collagen wound care products, biologically important components of the extracellular matrix such as glycosaminoglycans, proteoglycans, fibronectin, basic fibroblast growth factor, and transformind growth factor β are retained in the small intestine submucosa (Barber 2008, Chern 2009, Limová 2010). OASIS® Wound Matrix has a shelf life of 24 months and is FDA approved for use in patients with various partial- and full-thickness wounds such trauma wounds, ulcers, tunneled/undetermined wounds, draining wounds, and surgical wounds. It is not approved for use in patients with third-degree burn or with known allergies to porcine materials. According to the manufacturer's Web site, side-effects of OASIS Wound Matrix include: infection, chronic inflammation, allergic reaction, excessive redness, pain, swelling, and blistering. Additionally, the initial application of the wound dressing may be associated with transient, mild, localized inflammation (Cook Biotech, Inc 2011).

10/11/2000: MTAC REVIEW

OASIS Wound Dressing

Evidence Conclusion: Given the fact that there are no peer-reviewed articles on this topic, there is insufficient (no) evidence to determine the efficacy of this type of the Oasis Cook® wound care dressing.

Articles: Articles were selected based on study type. There were no peer-reviewed articles, so no articles were reviewed. Informational materials on the company's Web site (www.cookgroup.com) were reviewed, but no evidence tables were created.

The use of OASIS Wound Dressing in the treatment of non-healing partial thickness dermal wound does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

06/20/2011: MTAC REVIEW

OASIS Wound Dressing

Evidence Conclusion: *OASIS® versus usual care* - The first RCT included 50 subjects and compared the efficacy and tolerability of OASIS® Wound Matrix versus petrolatum-impregnated gauze in patients with difficult to heal mixed arterial/venous or venous leg ulcers. Results from this study suggest that patients treated with OASIS® have faster healing times, were more likely to experience complete wound closure, and required fewer dressing changes compared to usual care. Additionally, after 8 weeks patients treated with OASIS® had significantly more granulation tissue compared to usual care. No adverse events were observed in either treatment group. Results from this study should be interpreted with caution as it had several methodological limitations (Romanelli 2010). *OASIS® versus Hyaloskin®* - The second RCT included 54 subjects and compared the effectiveness of OASIS® Wound Matrix versus Hyaloskin® for the treatment of mixed arterial/venous leg ulcers. Results from this study suggest that patients treated with OASIS® Wound Matrix were more likely to experience wound closure compared to patients treated with Hyaloskin®. Additionally, patients treated with OASIS® Wound Matrix reported greater comfort, less pain, and required fewer dressing changes. No adverse events were observed in either treatment group. Results from this study should be interpreted with caution as it had several methodological limitations (Romanelli 2007). *OASIS® plus compression therapy versus compression therapy alone* - The third RCT included 120 subjects and compared the effectiveness of OASIS® Wound Matrix plus compression versus compression therapy alone for the treatment of chronic leg ulcers. The primary outcome was complete wound closure. Results from this study suggest that subjects who received OASIS® Wound Matrix plus compression therapy were significantly more likely to experience complete wound closure compared to standard care plus compression therapy. There was no significant difference in adverse events between the two groups. The most frequently occurring complications were allergic reaction or intolerance to secondary dressing and wound infection. Results from this study should be interpreted with caution as it had several methodological limitations (Mostow 2005). *Conclusion:* Evidence from three RCTs suggest that OASIS® Wound Matrix may be a safe and effective treatment for leg ulcers; however, results from these studies should be interpreted with caution as all of the trials had methodological limitations. For example, two of the trials were funded by the manufacturers of OASIS® Wound Matrix. Only one study performed an intent-to-treat analysis and assessed power and none of the studies provided confidence intervals.

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Articles: The literature search revealed several RCTs that evaluated the safety and efficacy of OASIS® Wound Matrix for the treatment of various partial- and full-thickness wounds. Three recent RCTs were selected for review. Two of these studies were performed by the same investigator. Another trial was excluded because it did not have sufficient power (Niezgoda 2005). The following studies were critically appraised:
Romanelli M, Dini V, and Bertone M. Randomized comparison of OASIS® Wound Matrix versus moist wound dressing in the treatment of difficult-to-heal wounds of mixed arterial/venous etiology. *Adv Skin Wound Care 2010;* 23:34-38. See Evidence Table. Romanelli M, Dini V, Bertone M, et al. OASIS® Wound Matrix versus Hyaloskin® in the treatment of difficult-to-heal wounds of mixed arterial/venous aetiology. *Int Wound J 2007;* 4:3-7. See Evidence Table. Mostow EN, Hataway D, Dalsing M, et al. Effectiveness of an extracellular matrix graft (OASIS® Wound Matrix) in the treatment of chronic leg ulcers. *J Vasc Surg 2005;* 41:837-843. See Evidence Table.

The use of OASIS Wound Dressing in the treatment of non-healing partial thickness dermal wound does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Warm-Up Wound Therapy

BACKGROUND
Noncontact normothermic wound therapy (The Warm-up therapy system) is used for the treatment of partial- and full-thickness wounds such as pressure ulcers, venous ulcers, diabetic ulcers, surgical wounds, and arterial wounds. Noncontact normothermic wound therapy is intended to speed the healing of wounds and venous ulcers by warming the wound and thereby increasing blood flow and allowing sufficient moisture in the wound to help cells grow and divide. The Warm-up therapy system consists of the following components: a noncontact wound cover, a temperature control unit with an AC adapter and a warming card. The non-contact wound cover is placed over the wound; the cover is raised so it does not touch the wound. It is designed to maintain warmth and humidity and to absorb exudate. There is space to insert the warming card into the wound cover. The temperature control unit, which is portable, controls the temperature of the warming card. The manufacturer recommends three warming sessions per day, heating the wound to 38°C (Augustine Medical Web site). Anodyne Therapy is another treatment for increasing the rate of wound healing; it is also used to treat patients with peripheral neuropathy. Treatment consists of monochromatic near-infrared photo energy (MIRE). The recommended course of treatment is 12 sessions of MIRE. For patients with peripheral neuropathy, the intention is to increase local circulation and restore sensation. MIRE has been shown to increase nitric oxide (NO) in the blood and plasma of normal adults (Horwitz, 1999). An elevation in NO may be beneficial for wound healing and increased circulation.

10/08/2003: MTAC REVIEW
Warm-Up Wound Therapy
Evidence Conclusion: *Noncontact Normothermic Therapy (Warm-up wound therapy)* - Combining the evidence from the current and previous MTAC reviews, four randomized controlled trials comparing Warm-up wound therapy to standard care were critically appraised (McCulloch and Kloth in the current review, Warwick and Price from the 2002 review). All of the studies were subject to selection bias due to the limited sample sizes (the treatment groups are likely to be dissimilar on characteristics that may affect outcome). The Price study had the strongest methodology and did not find a statistically significant difference in healing rates in an intention to treat analysis; the study may have been underpowered. The other three RCTs found statistically significant improvement in healing according to one or more outcome variables, but were subject to biases including improper randomization, lack of intention to treat analysis, potential data manipulation and funding by the manufacturer.
Articles: *Noncontact Normothermic Therapy* - The search yielded 8 articles. There were four new RCTs, sample sizes were n=16, n=20, n=36 and n=40. The two RCTs with the larger sample sizes were critically appraised: McCulloch J, Knight A. Noncontact normothermic wound therapy and offloading in the treatment of neuropathic foot ulcers in patients with diabetes. *Ostomy/Wound Management* 2002; 48: 38-44. See Evidence Table. Kloth LC, Berman JE, Nett M et al. A randomized controlled clinical trial to evaluate the effects of noncontact normothermic wound therapy on chronic full-thickness pressure ulcers. *Adv SkinWound Care* 2002; 15: 270-276. See Evidence Table.

The use of Warm-up Wound Therapy in the treatment of partial and full-thickness wounds does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

04/10/2002: MTAC REVIEW
Warm-Up Wound Therapy
Evidence Conclusion: Two relatively small RCTs evaluating the efficacy of noncontact normothermic wound therapy (Warm-up® Therapy System) for accelerating the healing rate of pressure ulcers were reviewed. The

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Price study, which had the stronger methodology, found no significant differences in healing rates in an intention to treat analysis. Patients receiving Warm-up wound therapy took an average of 5 fewer days for their wound to be reduced to 25% of original size. This difference was not have been statistically significant, but the study may have been under-powered. Whitney found a statistically significant improvement in the linear rate of healing using Warm-up wound therapy. However, the Whitney study had substantial threats to validity (e.g. no power analysis, substantial dropout; no intention to treat analysis). The absolute difference in healing was 0.008 cm/day. The clinical significance of this difference in healing rates needs to be considered. The two RCTs reviewed had pressure ulcers as the outcome; no conclusions can be drawn about the effectiveness of this treatment for other types of wounds.

Articles: The search yielded 6 articles on this treatment, all of which were empirical and had small sample sizes (most had sample sizes of 20 or less). There were three RCTs with clinical outcomes. One had n=13 and was not reviewed. The other two RCTs (n=40 and n=58) were critically appraised: Whitney JD, Salvadalena G, Higa L, Mich M. Treatment of pressure ulcers with noncontact normothermic wound therapy: healing and warming effects. J WOCN 2001; 28:244-52. See Evidence Table. Price P, Bale S, Crook H, Harding KGH. The effect of a radiant heat dressing on pressure ulcers. J Wound Care 2000; 9:201-205. See Evidence Table.

The use of Warm-up Wound Therapy in the treatment of partial and full-thickness wounds does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Applicable Codes

Skin Substitutes - Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPC Codes	Description
Q4102	Oasis wound matrix, per sq. cm
Q4104	Integra bilayer matrix wound dressing (BMWD), per sq. cm
Q4105	Integra dermal regeneration template (DRT) or Integra Omnigraft dermal regeneration matrix, per sq. cm
Q4108	Integra matrix, per sq. cm
Q4110	PriMatrix, per sq. cm
Q4124	OASIS ultra tri-layer wound matrix, per sq. cm
Q4128	FlexHD, AllopatchHD, or Matrix HD, per sq. cm
Q4137	AmnioExcel, AmnioExcel Plus or BioDExcel, per sq. cm
Q4139	AmnioMatrix or BioDMatrix, injectable, 1 cc
Q4151	AmnioBand or Guardian, per sq. cm
Q4168	AmnioBand, 1 mg
A2011	Supra sdrm, per square centimeter
A2012	Suprathel, per square centimeter
A2013	Innovamatrix fs, per square centimeter
A4100	Skin substitute, fda cleared as a device, not otherwise specified
Q4224	Human health factor 10 amniotic patch (hhf10-p), per square centimeter
Q4225	Amniobind, per square centimeter
Q4256	Mlg-complete, per square centimeter
Q4257	Relese, per square centimeter
Q4258	Enverse, per square centimeter

Skin Substitutes - Considered not medically necessary:
**There are many products available - this list is not all-inclusive.*

HCPC Codes	Description
A2014	Omeza Collagen Matrix, per 100 mg
A2015	Phoenix Wound Matrix, per sq cm
A2016	PermeaDerm B, per sq cm
A2017	PermeaDerm Glove, each
A2018	PermeaDerm C, per sq cm
A2019	Kerecis Omega3 MariGen Shield, per sq cm

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A2020	AC5 Advanced Wound System (AC5)
A2021	NeoMatriX, per sq cm
C9358	Dermal substitute, native, nondenatured collagen, fetal bovine origin (SurgiMend Collagen Matrix), per 0.5 sq. cm
C9360	Dermal substitute, native, nondenatured collagen, neonatal bovine origin (SurgiMend Collagen Matrix), per 0.5 sq. cm
C9361	Collagen matrix nerve wrap (NeuroMend Collagen Nerve Wrap), per 0.5 cm length
C9363	Skin substitute (Integra Meshed Bilayer Wound Matrix), per sq. cm
C9364	Porcine implant, Permacol, per sq. cm
Q4100	Skin substitute, not otherwise specified
Q4101	Apligraf, per sq. cm
Q4103	Oasis burn matrix, per sq. cm
Q4106	Dermagraft, per sq. cm
Q4107	GRAFTJACKET, per sq. cm
Q4111	GammaGraft, per sq. cm
Q4112	Cymetra, injectable, 1 cc
Q4113	GRAFTJACKET XPRESS, injectable, 1 cc
Q4114	Integra flowable wound matrix, injectable, 1 cc
Q4115	AlloSkin, per sq. cm
Q4116	AlloDerm, per sq. cm
Q4117	HYALOMATRIX, per sq. cm
Q4118	MatriStem micromatrix, 1 mg
Q4121	TheraSkin, per sq. cm
Q4122	DermACELL, DermACELL AWM or DermACELL AWM Porous, per sq. cm
Q4123	AlloSkin RT, per sq. cm
Q4125	ArthroFlex, per sq. cm
Q4126	MemoDerm, DermaSpan, TranZgraft or IntéguPly, per sq. cm
Q4127	Talymed, per sq. cm
Q4130	Strattice TM, per sq. cm
Q4132	Grafix Core and GrafixPL Core, per sq. cm
Q4133	Grafix PRIME, GrafixPL PRIME, Stravix and StravixPL, per sq. cm
Q4134	HMatrix, per sq. cm
Q4135	Mediskin, per sq. cm
Q4136	E-Z Derm, per sq. cm
Q4138	BioDFence DryFlex, per sq. cm
Q4140	BioDFence, per sq. cm
Q4141	AlloSkin AC, per sq. cm
Q4142	XCM biologic tissue matrix, per sq. cm
Q4143	Repriza, per sq. cm
Q4145	EpiFix, injectable, 1 mg
Q4146	Tensix, per sq. cm
Q4147	Architect, Architect PX, or Architect FX, extracellular matrix, per sq. cm
Q4148	Neox Cord 1K, Neox Cord RT, or Clarix Cord 1K, per sq. cm
Q4149	Excellagen, 0.1 cc
Q4150	AlloWrap DS or dry, per sq. cm
Q4152	DermaPure, per sq. cm
Q4153	Dermavest and Plurivest, per sq. cm
Q4154	Biovance, per sq. cm
Q4155	Neox Flo or Clarix Flo 1 mg
Q4156	Neox 100 or Clarix 100, per sq. cm
Q4157	Revitalon, per sq. cm
Q4158	Kerecis Omega3, per sq. cm
Q4159	Affinity, per sq. cm
Q4160	Nushield, per sq. cm
Q4161	bio-ConneKt wound matrix, per sq. cm
Q4162	WoundEx Flow, BioSkin Flow, 0.5 cc
Q4163	WoundEx, BioSkin, per sq. cm

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Q4164	Helicoll, per sq. cm
Q4165	Keramatrix or Kerasorb, per sq. cm
Q4166	Cytal, per sq. cm
Q4167	Truskin, per sq. cm
Q4169	Artacent wound, per sq. cm
Q4170	Cygnus, per sq. cm
Q4171	Interfyl, 1 mg
Q4173	PalinGen or PalinGen XPlus, per sq. cm
Q4174	PalinGen or ProMatrX, 0.36 mg per 0.25 cc
Q4175	Miroderm, per sq. cm
Q4176	NeoPatch, per sq. cm
Q4177	FlowerAmnioFlo, 0.1 cc
Q4178	FlowerAmnioPatch, per sq. cm
Q4179	FlowerDerm, per sq. cm
Q4180	Revita, per sq. cm
Q4181	Amnio Wound, per sq. cm
Q4182	Transcyte, per sq. cm
Q4183	Surgigraft, per sq cm
Q4184	Cellesta, per sq cm
Q4185	Cellesta Flowable Amnion (25 mg per cc); per 0.5 cc
Q4186	Epifix, per sq. cm
Q4187	Epicord, per sq cm
Q4188	AmnioArmor, per sq cm
Q4189	Artacent AC, 1 mg
Q4190	Artacent AC, per sq cm
Q4191	Restorigin, per sq cm
Q4192	Restorigin, 1 cc
Q4193	Coll-e-Derm, per sq cm
Q4194	Novachor, per sq cm
Q4195	PuraPly, per sq cm
Q4196	PuraPly AM, per sq cm
Q4197	PuraPly XT, per sq cm
Q4198	Genesis Amniotic Membrane, per sq cm
Q4200	SkinTE, per sq cm
Q4201	Matrion, per sq cm
Q4202	Keroxx (2.5g/cc), 1cc
Q4203	Derma-Gide, per sq cm
Q4204	XWRAP, per sq cm
Q4205	Membrane Graft or Membrane Wrap, per sq cm
Q4206	Fluid Flow or Fluid GF, 1 cc
Q4208	Novafix, per sq cm
Q4209	SurGraft, per sq cm
Q4210	Axolotl Graft or Axolotl DualGraft, per sq cm
Q4211	Amnion Bio or AxoBioMembrane, per sq cm
Q4212	AlloGen, per cc
Q4213	Ascent, 0.5 mg
Q4214	Cellesta Cord, per sq cm
Q4215	Axolotl Ambient or Axolotl Cryo, 0.1 mg

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Q4216	Artacent Cord, per sq cm
Q4217	WoundFix, BioWound, WoundFix Plus, BioWound Plus, WoundFix Xplus or BioWound Xplus, per sq cm
Q4218	SurgiCORD, per sq cm
Q4219	SurgiGRAFT-DUAL, per sq cm
Q4220	BellaCell HD or Surederm, per sq cm
Q4221	Amnio Wrap2, per sq cm
Q4222	ProgenaMatrix, per sq cm
Q4226	MyOwn Skin, includes harvesting and preparation procedures, per sq cm
Q4227	AmnioCoreTM, per sq cm
Q4229	Cogenex Amniotic Membrane, per sq cm
Q4230	Cogenex Flowable Amnion, per 0.5 cc
Q4231	Corplex P, per cc
Q4232	Corplex, per sq cm
Q4233	SurFactor or NuDyn, per 0.5 cc
Q4234	XCellerate, per sq cm
Q4235	AMNIOREPAIR or AltiPly, per sq cm
Q4237	Cryo-Cord, per sq cm
Q4238	Derm-Maxx, per sq cm
Q4239	Amnio-Maxx or Amnio-Maxx Lite, per sq cm
Q4240	CoreCyte, for topical use only, per 0.5 cc
Q4241	PolyCyte, for topical use only, per 0.5 cc
Q4242	AmnioCyte Plus, per 0.5 cc
Q4244	Procenta, per 200 mg
Q4245	AmnioText, per cc
Q4246	CoreText or ProText, per cc
Q4247	Amniotext patch, per sq cm
Q4248	Dermacyte Amniotic Membrane Allograft, per sq cm
Q4249	AMNIPLY, for topical use only, per sq cm
Q4250	AmnioAmp-MP, per sq cm
Q4251	Vim, per sq cm
Q4252	Vendaje, per sq cm
Q4253	Zenith Amniotic Membrane, per sq cm
Q4254	Novafix DL, per sq cm
Q4255	REGUaRD, for topical use only, per sq cm
Q4259	Celera Dual Layer or Celera Dual Membrane, per sq cm
Q4260	Signature APatch, per sq cm
Q4261	TAG, per sq cm
Q4262	Dual Layer Impax Membrane, per sq cm
Q4263	SurGraft TL, per sq cm
Q4264	Cocoon Membrane, per sq cm
Q4265	NeoStim TL, per sq cm
Q4266	NeoStim Membrane, per sq cm
Q4267	NeoStim DL, per sq cm

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Q4268	SurGraft FT, per sq cm
Q4269	SurGraft XT, per sq cm
Q4270	Complete SL, per sq cm
Q4271	Complete FT, per sq cm
A2001	InnovaMatrix AC, per sq cm
A2002	Mirragen Advanced Wound Matrix, per sq cm
A2003	bio-ConneKt Wound Matrix, per sq cm
A2004	XCelliStem, per sq cm
A2005	Microlyte Matrix, per sq cm
A2006	NovoSorb SynPath dermal matrix, per sq cm
A2007	Restrata, per sq cm
A2008	TheraGenesis, per sq cm
A2009	Symphony, per sq cm
A2010	Apis, per sq cm
Q4199	Cygnus matrix, per sq cm
Q4272	Esano a, per square centimeter
Q4273	Esano aaa, per square centimeter
Q4274	Esano ac, per square centimeter
Q4275	Esano aca, per square centimeter
Q4276	Orion, per square centimeter
Q4277	Woundplus membrane or e-graft, per square centimeter
Q4278	Epieffect, per square centimeter
Q4280	Xcell amnio matrix, per square centimeter
Q4281	Barrera sl or barrera dl, per square centimeter
Q4282	Cygnus dual, per square centimeter
Q4283	Biovance tri-layer or biovance 3l, per square centimeter
Q4284	Dermabind sl, per square centimeter

Normothermic Wound Therapy – Considered not medically necessary:

HCPC Codes	Description
A6000	Noncontact wound-warming wound cover for use with the noncontact wound-warming device and warming card
E0231	Noncontact wound-warming device (temperature control unit, AC adapter and power cord) for use with warming card and wound cover
E0232	Warming card for use with the noncontact wound-warming device and noncontact wound-warming wound cover

Low Frequency, Noncontact, Non-Thermal Ultrasound Wound Therapy -
Medicare - Considered Medically Necessary when criteria in the applicable policy statements listed above are met
Non-Medicare – Considered not medically necessary

CPT Codes	Description
97610	Low frequency, non-contact, non-thermal ultrasound, including topical application(s), when performed, wound assessment, and instruction(s) for ongoing care, per day

Electrical Stimulation and Electromagnetic Therapy – Considered not medically necessary:

HCPC	Description

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Codes	
E0761	Nonthermal pulsed high frequency radiowaves, high peak power electromagnetic energy treatment device
E0769	Electrical stimulation or electromagnetic wound treatment device, not otherwise classified
G0281	Electrical stimulation, (unattended), to one or more areas, for chronic Stage III and Stage IV pressure ulcers, arterial ulcers, diabetic ulcers, and venous stasis ulcers not demonstrating measurable signs of healing after 30 days of conventional care, as part of a therapy plan of care
G0282	Electrical stimulation, (unattended), to one or more areas, for wound care other than described in G0281
G0295	Electromagnetic therapy, to one or more areas, for wound care other than described in G0329 or for other uses
G0329	Electromagnetic therapy, to one or more areas for chronic Stage III and Stage IV pressure ulcers, arterial ulcers, diabetic ulcers and venous stasis ulcers not demonstrating measurable signs of healing after 30 days of conventional care as part of a therapy plan of care

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

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Date Created	Date Reviewed	Date Last Revised
11/25/2002	03/02/2010P[MDCRPC], 01/04/2011P[MDCRPC] ,11/01/2011P[MDCRPC], 09/04/2012[MDCRPC], 07/02/2013P[MDCRPC], 05/06/2014P[MPC], 12/02/2014P[MPC], 10/06/2015[MPC], 08/02/2016[MPC], 06/06/2017[MPC], 04/03/2018[MPC], 04/02/2019[MPC], 04/07/2020[MPC], 04/06/2021[MPC], 04/05/2022[MPC], 04/04/2023[MPC], 02/13/2024[MPC]	11/22/2023

[MPC] Medical Policy Committee

Revision History	Description
07/29/2015	Added Medicare language for skin substitutes
10/06/2015	Added new products to indications and non-coverage
08/02/2016	Added new products to the exclusion/non-coverage list
05/02/2017	MPC approved to utilize KP criteria for Skin-Engineered substitutes for Medicare members
01/23/2018	Added the 2018 new HCPC codes Q4176-82
09/27/2018	Added C9360, C9361, C9363, C9364
09/30/2019	Revised skin substitute criteria to meet state mandate requirements
11/05/2019	MPC approved to adopt the revisions to skin substitutes criteria, effective 04/01/2020: specifically updating the list of approved products for diabetic ulcers and venous insufficiency ulcers as directed by the Kaiser Permanente National Surgical Core Group (SCG) and the National Product Council (NPC) as listed in the criteria above
04/07/2020	Added the LCA for Amniotic Derived Skin Substitutes and updated the link to the MLN Matters article on ASC payment for skin substitutes
04/28/2020	Added code Q4195
04/05/2021	Added codes to the “Skin Substitutes - Considered not medically necessary” section
04/06/2021	Removed platelet rich plasma codes as there is a separate criteria page for that service.
04/05/2022	Updated applicable codes. Added LCD/LCA for Wound and Ulcer Care
10/26/2022	Updated applicable codes, including new codes released 01/01/22 and 04/01/22.
03/03/2023	Updated applicable new codes released 10/01/2022 to the “Skin Substitutes- considered not medically necessary” section including HCPC codes A2014, A2015, A2016, A2017, A2018.
03/06/2023	Updated applicable new codes released 07/01/2022 to the “Skin Substitutes- considered not medically necessary” section including HCPC codes Q4259, Q4260, Q4261.
04/18/2023	Updated Medicare Billing and Coding article link A58567 and A53046
11/22/2023	Updated new HCPC codes for Non-Covered Skin Substitutes, effective 7/1/2023.

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Revision History	Description
1/22/2024	Updated Medicare Hyperlinks

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KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Spinal Decompression Device

- Coflex
- Vertiflex Superion

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Percutaneous Image-Guided Lumbar Decompression for Lumbar Spinal Stenosis (150.13)
Local Coverage Determinations (LCD)	None
Local Coverage Article (LCA)	None

For Non-Medicare Members

Kaiser Permanente has elected to use the MCG* Spinal Distraction Devices (A-0494) for medical necessity determinations. This service is not covered per MCG guidelines. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.

MCG*are proprietary and cannot be published and/or distributed. However, on an individual member basis, Kaiser Permanente can share a copy of the specific criteria document used to make a utilization management decision. If one of your patients is being reviewed using these criteria, you may request a copy of the criteria by calling the Kaiser Permanente Clinical Review staff at 1-800-289-1363 or access the MCG Guideline Index using the link provided above.

If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist (orthopedic surgeon, orthopedics, chiro, physiatrist, neurosurgeon)
- Most recent back/spine imaging

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Lumbar spinal stenosis refers to the narrowing of the spinal canal resulting in compression of the spinal cord. The decrease in size of the spinal canal is believed to be due to a combination of degenerative processes including bulging of the intervertebral disc, hypertrophy of the ligamentum flavum, facet joint hypertrophy with bone spurring and spondylolisthesis. Symptoms include pain and numbness in the lower back, legs and buttocks after lumbar extension and walking. Symptoms are generally relieved by flexion of the lower back or sitting. Spinal stenosis is the most prevalent diagnosis for spinal surgery; it affects approximately 0.5% of Americans older than 50 (Batt & Carlson, 2006; CTAF technology assessment).

Functional loss associated with lumbar spinal stenosis is typically slow and thus an initial course of non-surgical

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therapy is recommended. Conservative management is particularly indicated for patients with mild to moderate symptoms. Initial recommended therapies are activity modification (e.g. avoiding aggravating activities) and use of oral medications such as NSAIDS and salicylates. Other medications that have been found to be helpful for some patients are oral corticosteroids, tricyclic antidepressants and salmon calcitonin. Epidural steroid injections are another commonly used another conservative treatment. These can reduce the radicular pain associated with acute exacerbations of neurogenic claudication (leg or buttock pain). In addition to the various types of pain relief or pain reduction discussed above, physical therapy can be helpful, especially flexion-based exercises. Surgical treatment, specifically decompression surgery, may be appropriate for selected patients. Patients whose function is limited (e.g. limitations in walking and activities of daily living) are potential surgical candidates. Intractable pain, especially neurogenic claudication, not responding to non-surgical therapies, is another reason for considering surgery. Laminectomy is considered the “gold standard” for decompression in patients with lumbar spinal stenosis (Yuan et al., 2005).

The X-Stop Interspinous Process Decompression System (St. Francis Medical Technologies, Alameda, CA) is proposed as a minimally invasive alternative to surgical treatment of lumbar spinal stenosis in patients with a moderate level of symptoms. Patients with severe symptoms are not eligible to receive this device and may be candidates for laminectomy. X-Stop consists of an oval titanium implant that fits between the adjacent spinous processes at the level of spinal stenosis and a wing assembly that prevents the implant from moving from side-to-side. The spinal processes are thin projections from back of spinal bones to which muscles and ligaments are attached. X-Stop is designed to remain permanently in place without attaching to the bones and ligaments in the back. The device is intended to slightly flex the affected area and to prevent extension to avoid nerve root impingement (manufacturers’ materials; FDA materials; CTAF technology assessment).

The device is usually implanted under local anesthesia with fluoroscopy guidance. The procedure involves making a 4-5 cm midline incision over the spinous processes of the affected levels. An attempt is made to keep the supraspinous and interspinous ligaments intact. The implant size is determined (it is available in 5 sizes) and an appropriately sized implant is inserted. After fastening the wing assembly, the incision is closed (manufacturers’ materials; FDA materials; CTAF technology assessment).

X-Stop was approved by the FDA in November 2005. As specified in the FDA premarket application (PMA) approval letter, X-Stop:

- Is indicated for patients age 50 and older with neurogenic intermittent claudication secondary to a confirmed diagnosis of lumbar spinal stenosis;
- Is indicated for patients with moderately impaired physical function who experience relief in flexion from leg, buttock and/or groin pain, with or without back pain, and have undergone at least 6 months of non-operative treatment;
- May be implanted at 1 or 2 lumbar levels in patients for whom surgery is indicated (no more than 2 levels).
- Is not currently indicated for patients with mildly impaired physical function.

As part of the approval agreement, the manufacturer agreed to conduct a study on the long-term safety and effectiveness of X-Stop.

Prior to FDA approval, the FDA’s Orthopedic and Rehabilitation Devices Advisory Panel recommended disapproval in August, 2004. A majority of committee members felt that the pivotal clinical trial (discussed below in evidence summary) had substantial threats to validity. After the panel decision, the company submitted additional data to the FDA and defended their study methodology including the use of a relatively new self-report instrument as the primary outcome.

Medical Technology Assessment Committee (MTAC)

X-stop Interspinous Process Decompression System

02/05/2007: MTAC REVIEW

Evidence Conclusion: There is one published RCT that evaluated the safety and effectiveness of the X-Stop system. This was the pivotal clinical trial presented to the FDA. The investigators, who included the device inventors, reported that patients who received the X-Stop had significantly better clinical outcomes than patients receiving non-operative treatment. The study had numerous threats to validity including a lack of blinding, use of subjective outcomes, an inappropriate comparison group and possibly inadequate randomization, and thus provides insufficient evidence for concluding that X-Stop is safe and effective. In addition, there is no comparative pain or functional outcome data beyond two years.

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Articles: The safety and efficacy of the X-Stop system compared to standard treatment for patients with the FDA approved indication for device use. The ideal study would be a randomized, double-blind controlled trial comparing the X-Stop system to the best-accepted alternative treatment or a sham intervention.

The search yielded one unblinded RCT that compared X-Stop with conservative management. There were no double-blind trials or trials comparing X-Stop to a sham intervention. Five publications were identified based on the single RCT. The two articles that reported primary clinical outcomes were critically appraised. Zucherman et al. (2004) reported 1 year outcomes and Zucherman et al., 2005 reported 2 year outcomes. Other publications using RCT data include a case series analysis on a sub-set of treated patients (Kondrashov 2006), another sub-analysis on patients with lumbar degenerative spondylolisthesis (Anderson et al., 2006) and an in-depth look at the quality of life outcomes that were reported in the main outcome papers (Hsu et al., 2006). The secondary publications from the RCT and small case series identified in the search were not reviewed. *The articles that were critically appraised (in a single evidence table) were:* Zucherman JF et al. A prospective randomized multi-center study for the treatment of lumbar spinal stenosis with the X-Stop interspinous implant: 1-year results. Eur Spine J 2004; 12:22-31. Zucherman JF et al. A multicenter, prospective, randomized trial evaluating the X-Stop interspinous process decompression system for the treatment of neurogenic intermittent claudication: 2-year follow-up results. Spine 2005; 30: 1351-1358. See Evidence Table.

The use of X-stop Interspinous Process Decompression System in the treatment of lumbar spinal stenosis does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

Applicable Codes

Considered Not Medically Necessary

CPT® or HCPC Codes	Description
C1821	Interspinous process distraction device (implantable)
22867	Insertion of interlaminar/interspinous process stabilization/distraction device, without fusion, including image guidance when performed, with open decompression, lumbar; single level
22868	Insertion of interlaminar/interspinous process stabilization/distraction device, without fusion, including image guidance when performed, with open decompression, lumbar; second level (List separately in addition to code for primary procedure)
22869	Insertion of interlaminar/interspinous process stabilization/distraction device, without open decompression or fusion, including image guidance when performed, lumbar; single level
22870	Insertion of interlaminar/interspinous process stabilization/distraction device, without open decompression or fusion, including image guidance when performed, lumbar; second level (List separately in addition to code for primary procedure)

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

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Date Created	Date Reviewed	Date Last Revised
03/21/2007	02/05/2007, 05/21/2007 MDCRPC, 04/29/2008 MDCRPC, 02/9/2009 MDCRPC, 12/18/2009 MDCRPC, 09/07/2010 MDCRPC, 07/05/2011 MDCRPC, 05/01/2012 MDCRPC, 03/05/2013 MDCRPC, 01/07/2014 MPC, 11/04/2014 MPC, 09/01/2015 MPC, 07/05/2016 MPC, 05/02/2017 MPC, 03/06/2018 MPC, 02/05/2019 MPC, 02/04/2020 MPC, 02/02/2021 MPC, 02/07/2023 MPC	02/02/2021

MDCRPC Medical Director Clinical Review and Policy Committee
MPC Medical Policy Committee

Revision History	Description
04/12/2019	Added Coflex to Medicare Covered Criteria

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02/02/2021	Added Vertiflex Superion product to criteria; removed products that are no longer in the market (DIAM, Wallis, X-Stop) from criteria. Added NCD (150.13) Percutaneous image-guided lumbar decompression for lumbar spinal stenosis for Medicare Members.

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