Health Technology Assessment Program

Selected Technologies 2019

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STATE OF WASHINGTON
HEALTH CARE AUTHORITY
626 8th Avenue, SE • P.O. Box 45502 • Olympia, Washington 98504-5502

April 1, 2019

To whom it may concern:

SUBJECT: 2019 Health Technology Assessment Topic Selection

As the Director of the Health Care Authority, I select technologies for review by the program in consultation with other agencies and the Health Technology Clinical Committee (HTCC) (70.14 RCW). Technologies are selected when there are concerns about safety, efficacy or value (cost-effectiveness), when state expenditures are or could be high, and when there is adequate evidence to conduct a review. Technologies are selected for re-review when new evidence is available that could change a previous determination.

For the current selection cycle, I reviewed the proposed topics and the comments received from interested individuals and groups who responded in the first comment period (March 13-27, 2019). Based on this review I have selected the following technologies for review:

	Technology	Primary criteria ranking		
		Safety	Efficacy	Cost
1	**Cell-free DNA (cfDNA)**	**Med**	**Med**	**High**
	Policy context/reason for selection: Cell-free DNA testing is used for prenatal screening of chromosome abnormalities. There is uncertainty about the appropriateness of cell-free DNA testing for some populations including those at low-risk for concerning findings.			
2	**Stem cell therapy for musculoskeletal pain**	**High**	**High**	**High**
	Policy context/reason for selection: Stem cell therapy for joint pain is an outpatient procedure that begins with collection of stem cells from a patient (autologous) or from another person (allog eneic). The cells may be cultured or concentrated and then injected into the affected area. The topic is proposed based on concerns related to the safety, efficacy and value for stem cell injections for musculoskeletal pain.			

	Technology	Primary criteria ranking		
		Safety	Efficacy	Cost
3	**Tinnitus: non-pharmaceutical treatments**	**Med**	**High**	**High**
	Policy context/reason for selection: Tinnitus is the perception of noise or ringing in the ears. There are a variety of potential non-drug treatments for the condition, but the long and short-term effectiveness of these treatments is not certain. Treatments to be considered include tinnitus retraining therapy (TRT), tinnitus feedback therapy (TFT), and other combinations of noise-masking and cognitive therapy. This topic is proposed based on high levels of concern related to efficacy and cost.			
4	**Whole exome sequencing (WES)**	**High**	**Med**	**Med**
	Policy context/reason for selection: Whole exome sequencing (WES) is a laboratory test designed to identify and analyze the sequence of genes in a person's DNA (deoxyribonucleic acid). WES is often considered when the clinical presentation of patient, usually when very young, is suspected to be caused by or associated with a genetic difference or abnormality. The topic is proposed based on concerns related to the safety, efficacy and value of the test.			

Additionally, I have selected *Femoroacetabular impingement syndrome (FAI)* and *Vagus nerve stumulation (VNS) for epilepsy and depression* for re-review based on the newly available published evidence.

At this time *Stereotactic Radiation Therapy and Stereotactic Body Radiation Therapy (SRS/SBRT)* are not selected for re-review. The HTA program monitors the literature on this topic with detailed literature searches including a recently concluded search (December 2018). Based on these searches and consideration by the participating agencies and the HTCC new evidence is not likely to change the previous determination.

Upon publication of the selected list of technologies, a 30-day comment period will begin whereby any interested person or group may provide information relevant to review of these topics. HTA will begin work to review these technologies following this comment period.

Should you have any questions or concerns, please contact Josh Morse, HTA Program Director, by telephone at 360-725-0839 or via email at josh.morse@hca.wa.gov.

Sincerely,

[redacted]

Susan E. Birch MBA, BSN, RN
Director

cc: Josh Morse, HTA Program Director, CQCT, HCA

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Washington State Health Care Authority

Technologies selected

		Safety	Efficacy	Cost
1	**Cell-free DNA (cfDNA)**	**Med**	**Med**	**High**
	Policy context/reason for selection: Cell-free DNA testing is used for prenatal screening of chromosome abnormalities. There is uncertainty about the appropriateness of cell-free DNA testing for some populations including those at low-risk for concerning findings.			
2	**Stem cell therapy for musculoskeletal pain**	**High**	**High**	**High**
	Policy context/reason for selection: Stem cell therapy for joint pain is an outpatient procedure that begins with collection of stem cells from a patient (autologous) or from another person (allogeneic). The cells may be cultured or concentrated and then then injected into the affected area. The topic is proposed based on concerns related to the safety, efficacy and value for stem cell injections for musculoskeletal pain.			
3	**Tinnitus: non-pharmaceutical treatments**	**Med**	**High**	**High**
	Policy context/reason for selection: Tinnitus is the perception of noise or ringing in the ears. There are a variety of potential non-drug treatments for the condition, but the long and short-term effectiveness of these treatments is not certain. Treatments to be considered include tinnitus retraining therapy (TRT), tinnitus feedback therapy (TFT), and other combinations of noise-masking and cognitive therapy. This topic is proposed based on high levels of concern related to efficacy and cost.			
4	**Whole exome sequencing (WES)**	**High**	**Med**	**Med**
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Technologies considered, not proposed

	Technology
1	Dorsal root ganglion stimulation
2	Non-invasive testing: fibrosis for patients
3	Balloon tubuloplasty for eustachian tube dysfunction
4	Percutaneous heart pump

Technologies considered for re-review:

Technologies are considered for re-review at least every eighteen months based on availability of new evidence that may change the decision. *(Detailed criteria are included below*). All technologies with determinations beyond 18 months since the final determination previously reviewed by the Health Technology Clinical Committee (HTCC) are listed below, along with information on whether they have been selected for re-review.

	Technology	Originally reviewed	Recommended for re-review
1	**Femoroacetabular impingement syndrome (FAI)**	**September 2011**	**Yes**
	New evidence supports re-review at this time.		
2	**Screening and monitoring tests for osteopenia and osteoporosis**	**November 2014**	**No**
	New information does not support re-review at this time.		
3	**Spinal cord stimulators**	**October 2009**	**No**
	Literature search conducted in 2018 (attached). New information does not support re-review at this time.		
4	**Stereotactic radiation surgery and stereotactic body radiation therapy (SBRT)**	**March 2013**	**No**
	Literature search conducted in 2018 (attached). New information does not support re-review at this time.		
5	**Testosterone testing**	**May 2015**	**No**
	New information does not support re-review at this time.		
6	**Vagus nerve stimulation (VNS) for epilepsy and depression**	**August 2009**	**Yes**
	New evidence and indications for new populations support re-review at this time.		

The HTA program has not received or identified new evidence to support review of the following for at least 18 months.

HTA decisions	Originally reviewed	Latest review/ scan
Applied behavioral analysis (ABA) therapy for autism	2011	June 2011
Appropriate breast imaging	2015	March 2015
Arthroscopic knee surgery	2008	August 2008
Artificial discs - cervical (re-review)	2008	January 2017
Artificial discs - lumbar (re-review)	2008	January 2017
Autologous blood or platelet-rich plasma injections	2016	July 2016
Bariatric surgery and pediatric bariatric surgery <18 (re-review)	2007	May 2015
Bariatric surgery and pediatric bariatric surgery 18-21 (re-review)	2007	May 2015
Bone growth stimulators	2009	August 2009
Breast magnetic resonance imaging (MRI)	2010	October 2010
Bronchial thermoplasty	2016	May 2016
Calcium scoring	2010	May 2010
Cardiac nuclear imaging	2013	September 2013
Cardiac stents (re-review)	2009	March 2016
Carotid artery stenting	2013	March 2016
Catheter ablation for supraventricular tachyarrhythmia	2013	May 2013
Cervical fusion – degenerative disc disease	2013	March 2013
Cochlear implants	2013	May 2013
Computed tomographic angiography (CTA)	2009	November 2008
Extracorporeal membrane oxygenation (ECMO)	2016	March 2016
Electrical neural stimulations (ENS)	2009	October 2009
Extracorporeal shock wave therapy (ESWT)	2017	March 2017
Fecal microbiota transplantation (FMT)	2017	November 2016
Functional neuroimaging for primary degenerative dementia and mild cognitive impairment	2015	January 2015
Hip Resurfacing (re-review)	2014	November 2013
Hyaluronic Acid/viscosupplementation (re-review)	2010	November 2013
Hyperbaric oxygen therapy (HBO2)	2013	March 2013
Imaging for rhinosinusitis	2015	May 2015
Intensity modulated radiation therapy (IMRT)	2012	September 2012
Knee joint replacement or knee arthroplasty – unicompartmental/ computer navigated	2010	September 2012

HTA decisions	Originally reviewed	Latest review/ scan
Lumbar fusion – degenerative disc disease (re-review) (originally Discography)	2007	November 2015
Microprocessor-controlled lower limb prosthetics - knee	2012	November 2011
Negative pressure wound therapy (NPWT)	2017	November 2016
Non-pharmacologic treatments for treatment resistant depression	2014	March 2014
Pharmacogenomic testing for selected conditions (mental health and substance abuse)	2017	January 2017
Robotic assisted surgery	2012	May 2012
Routine ultrasound for pregnancy	2010	October 2012
Sleep apnea diagnosis and treatment in adults	2012	March 2012
Spinal injections (re-review)	2011	March 2016
Tympanostomy tubes in children	2016	November 2015

March 27th, 2019

VIA Electronic Mail to: shtap@hca.wa.gov

Washington State Health Care Authority
HTA Comments
Cherry Street Plaza
626 8th Avenue SE
Olympia, WA 98501

RE: Prospective HTA Technology Topics: Cell-free DNA (cfDNA)

To Whom It May Concern,

On behalf of Roche Diagnostics Corporation, I am pleased to submit comments regarding the above-captioned Prospective HTA technology topic, Cell-free DNA (cfDNA).

We respectfully request the Washington State Health Care Authority expand coverage of noninvasive prenatal testing (NIPT) to include average risk women on Medicaid based on the evidence outlined below.

Advancements in genetic testing enable physicians to have more informed conversations with patients considering prenatal care, planning and management. As is recommended by leading professional societies, it is critical that all patients, regardless of risk, be educated and informed about the availability of proven tests, including screening for Down (trisomy 21), Edwards (trisomy 18) and Patau (trisomy13) syndromes.[9] The current WA Medicaid NIPT coverage restriction of high risk impedes access to this standard of care screening.

Expanded NIPT coverage of average risk pregnancies is warranted based upon outcomes published from the Non-Invasive Examination of Trisomy (NEXT) randomized controlled clinical trial. In this study by Norton et al (2015),[1] a head-to-head comparison of Harmony NIPT to first-trimester combined screening (FTS) in the general pregnancy population was performed. In this cohort of 15,841 patients, it included 76% of patients under the age of 35 (n=11,994) with a mean gestational age at testing of 12.5 weeks. Overall, NIPT was found to be superior to standard trisomy 21 screening with Harmony detecting all 38 of 38 cases of trisomy 21 and FTS detecting 30 of the 38 cases. In addition, Harmony had a significantly lower false positive rate of 0.06% (9 of 15,803) as compared to the FTS false positive rate of 5.4% (854 of 15,803). As a result, the Harmony NIPT test had a significantly higher PPV rate over that of first-trimester combined screening.

Diagnostic Accuracy
Supporting studies further demonstrate high levels of sensitivity and specificity using cfDNA screening which correlates to very low rates of false positive and false negative results. Nicolaides[2] for example, considered trisomy risk scores for 95.1% (1,949 of 2,049) of evaluable cases including all 8 with trisomy 21 and 2 of the 3 with trisomy 18. The trisomy risk score was 99% in the 8 cases of trisomy 21, and 2 of trisomy 18 and <1% in 99.9% (1,937 of 1,939) of euploid cases. Noninvasive prenatal testing using chromosome-selective sequencing in a routinely screened population identified trisomies 21 and 18 with a false-positive rate of 0.1%.

In another study for the general screening population, Fairbrother et al (2013)[3] published results from an observational study of pregnant women who underwent prenatal screening for fetal trisomy from July 30, 2012 to December 1, 2012. The cohort included 289 women with mean age of 32.3 years (range: 17.8-42.0) who were screened at 13.0 gestational age weeks (range: 10.1-20.7). NIPT results were provided for 98.6% of patients. With NIPT, all patients had a risk less than 1:10,000 for trisomy 21, 18, or 13. With first trimester screening, 4.5% of patients had screening results indicating an increased risk for trisomy 21. One patient who had an elevated trisomy 21 risk with first trimester screening elected to have an amniocentesis, which revealed a euploid fetus. Researchers concluded that NIPT has the potential to be a highly effective screening method as a standard test for risk assessment of fetal trisomies 21, 18, and 13 in the general pregnant population.

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Cost Effective
Studies assessing the cost effectiveness of NIPT have demonstrated first-line testing to be cost-equivalent or cost-saving.[4-8] A study by Fairbrother et al (2016)[4] directly compared costs derived from combined screening with NIPT using a representative general pregnancy population from the United States. Researchers modeled a 70% screening uptake for both combined screening and NIPT testing, resulting in an evaluable population of 2,800,000 pregnant women. Use of NIPT as a first line screening test identified 15% more trisomy cases, but reduced invasive procedure by 88% and reduced iatrogenic normal fetal loss by 94%. Researchers found NIPT first-line testing to be cost-equivalent at $655, or cost-saving at $453 (2014, $USD).

NIPT Access for All Pregnant Women
Based on the body of evidence, the American College of Obstetricians & Gynecologists and the Society for Maternal Fetal Medicine amended their position statement in May 2016 to now recommend cfDNA be offered as a screening option and all women, regardless of age, should be offered screening for aneuploidy.[9] In July 2016, the American College of Medical Genetics and Genomics (ACMG) also revised its Position Statement, supporting NIPT across the maternal age spectrum. As reported by Gregg et al,[10] ACMG recommends informing all pregnant women that NIPT is the most sensitive screening option for traditionally screened aneuploidies (i.e., Patau, Edwards, and Down syndromes). ACMG notes the high PPV associated with NIPT provides benefits to patients by enabling them to more easily weigh the advantages and disadvantages of follow-up diagnostic testing. Additional benefits of NIPT include earlier implementation (e.g. beginning at week 10) with no gap across the gestational age spectrum, unlike conventional screening methods.

In conclusion, we request HCA expand coverage of NIPT to provide all pregnant women on Medicaid with this highly accurate and cost effective screening technology based on the robust evidence available, ACOG and ACMG recommendations and standard clinical practice. If you have any questions about these comments, please contact me at 317-363-7435 or via electronic mail to alan@roche.com.

Sincerely,

Alan T. Wright, MD, MPH
Chief Medical Officer
Roche Diagnostics Corporation
9115 Hague Road
Indianapolis, Indiana

References

1. Norton ME, Jacobsson B, Swamy GK, Laurent LC, Ranzini AC, Brar H, Tomlinson MW, Pereira L, Spitz JL, Hollemon D, Cuckle H, Musci TJ, Wapner RJ. Cell-free DNA analysis for noninvasive examination of trisomy. N Engl J Med. 2015 Apr 23;372(17):1589-97.

2. Nicolaides KH, Syngelaki A, Ashoor G, Birdir C, Touzet G. Noninvasive prenatal testing for fetal trisomies in a routinely screened first-trimester population. Am J Obstet Gynecol. 2012 Nov;207(5):374.e1-6.

3. Fairbrother G, Johnson S, Musci TJ, Song K. Clinical experience of noinvasive prenatal testing with cell-free DNA for fetal trisomies 21, 18, and 13, in a general screening population. Prenat Diagn. 2013 Jun;33(6):580-3.

4. Fairbrother G, Burigo J, Sharon T, Song K. Prenatal screening for fetal aneuploidies with cell-free DNA in the general pregnancy population: a cost-effectiveness analysis. The Journal of Maternal-Fetal & Neonatal Medicine. 2016;29(7):1160-1164.

5. Walker BS, Nelson RE, Jackson BR, Grenache DG, Ashwood ER, Schmidt RL. A Cost-Effectiveness Analysis of First Trimester Non-Invasive Prenatal Screening for Fetal Trisomies in the United States. PLoS One. 2015 Jul 2;10(7):e0131402.

6. Benn P, Curnow KJ, Chapman S, Michalopoulos SN, Hornberger J, Rabinowitz M (2015) An Economic Analysis of Cell-Free DNA NonInvasive Prenatal Testing in the US General Pregnancy Population. PLoS ONE 10(7): e0132313.

7. Iwarsson E, Jacobsson B, Dagerhamn J, Davidson T, Bernabé E, Heibert Arnlind M. Analysis of cell-free fetal DNA in maternal blood for detection of trisomy 21, 18 and 13 in a general pregnant population and in a high risk population – a systematic review and meta-analysis. Acta Obstet Gynecol Scand. 2017 Jan;96(1):7-18.

8. Kagan KO, Sroka F, Sonek J, Abele H, Lüthgens K, Schmid M, Wagner P, Brucker S, Wallwiener D, Hoopmann M. Firsttrimester risk assessment based on ultrasound and cell-free DNA vs combined screening: a randomized controlled trial. Ultrasound Obstet Gynecol. 2017 Sep 19.

9. ACOG and SMFM Practice Guideline 163, revised May 2016.

10. Gregg AR, Skotko BG, Benkendorf JL, Monaghan KG, Bajaj K, Best RG, Klugman S, Watson MS. Noninvasive prenatal screening for fetal aneuploidy, 2016 update: a position statement of the American College of Medical Genetics and Genomics. Genet Med. 2016 Oct;18(10):1056-65.

Coalition for Access to Prenatal Screening

Wednesday, March 27, 2019

Judy Zerzan, M.D., Chief Medical Officer
Washington State Health Care Authority
626 8th Avenue SE
Olympia, Washington 98501

Re: The Coalition for Access to Prenatal Screening comment on cell-free DNA non-invasive prenatal screening as a potential technology for assessment

Dear Dr. Zerzan,

The Coalition for Access to Prenatal Screening (CAPS) is pleased to submit this comment letter on proposed health technology selections for the Health Technology Assessment (HTA) to the Washington State Health Care Authority.

Washington's HTA program uses "scientific evidence to determine if health services are safe and effective."[i] Given that the safety and efficacy of cell-free DNA non-invasive prenatal screening (NIPS or NIPT) has been extensively validated and documented in the peer-reviewed literature for the general obstetric population as described below, CAPS requests that the HCA approve coverage of NIPS for high- and average-risk women in Washington State without undergoing the HTA process.

As early as 2013, the Blue Cross Blue Shield Association's Technical Evaluation Center found NIPS eligible for coverage in all pregnant women; in 2018 they reiterated their stance and determined that "the technology results in a meaningful improvement in the net health outcomes". Societal guidelines support NIPS as an option for first-tier screening in the general obstetric population. In addition, as of March 2019, commercial insurers responsible for a majority of privately covered lives in the U.S. provide reimbursement for NIPS regardless of prior risk.

However, if HCA decides to conduct a health technology assessment on NIPS, CAPS requests that the primary criteria ranking for safety, efficacy and cost are updated to reflect the true nature of NIPS.

We are particularly concerned about the HCA's reliance on the Ontario Health Technology Assessment of noninvasive prenatal screening, published on February 19, 2019, for determining the clinical utility and economic impact of NIPS in the general obstetric population. While this assessment is extensive, its review of NIPS literature does not extend beyond September 2017, and it excludes important recent peer-reviewed publications in this area. Critically, the Ontario assessment is based on the core assumption that the only relevant economic comparison is between (1) NIPS as a first-tier option and (2) NIPS as a second-tier option performed after traditional prenatal screening.

This premise is fundamentally flawed: first-tier NIPS is already widely covered by commercial and public payors in the U.S, endorsed or accepted by all professional societies in the U.S, and consistently documented in many peer-reviewed studies as the screening method with fewer false positives and false negatives. In comparison, second-tier NIPS has not been endorsed by any professional society or adopted by any major health care system in the U.S., and is not specifically covered by any commercial or public payor in the U.S.

After a woman receives a positive aneuploidy screen (either NIPS or standard screening), the standard of care for a physician is to recommend an invasive diagnostic test if the woman chooses. Proposing to use NIPS as a second screen before diagnostic testing would impose unacceptable delays for women seeking diagnostic information to make decisions about their pregnancies. Therefore, we find the Ontario assessment inappropriate as a guide for the costs or uses of NIPS.

We believe that any evaluation that has real world implications should start with real world assumptions and use the extensive practical experience accumulated to date with NIPS in the general obstetric population.

Blue Cross Blue Shield Association Technology Assessment

The Blue Cross Blue Shield Association Technology Evaluation Center (TEC) examines new technologies and provides consultation "to member Blue Cross and Blue Shield plans to assist them in determining the eligibility for coverage of new and emerging technologies."[ii]

The TEC takes the following into account when recommending coverage:

- Final approval from the appropriate government regulatory agency.
- Scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.
- The technology must improve the net health outcome.
- The technology must be as beneficial as any established alternative.
- The improvement must be attainable outside the investigational settings.

TEC conducted two assessments of NIPS. In its assessment of NIPS for Trisomy 21, TEC stated: "Nucleic acid sequencing-based testing of maternal plasma for trisomy 21 with confirmatory testing of positive results (as is expected to be performed in a real-world clinical setting) in both high-risk women and average-risk women being screened for trisomy 21 meets the TEC criteria."

TEC conducted a separate assessment of NIPS for Trisomies 13 and 18. "Sequencing-based analysis of cell-free fetal DNA obtained from maternal plasma to screen for the presence of

fetal T13 or T18—followed by diagnostic karyotype analysis of screen-positive results—in either high-risk or average-risk pregnant women being screened for fetal autosomal aneuploidies meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria," reads the assessment.

We believe this assessment, in addition to a numerous clinical studies, provides HTA with the scientific evidence it needs to recommend coverage of NIPS for all women. Therefore, we do not support NIPS undergoing the HTA process.

Insurance Coverage of NIPS for All Women

60 major commercial health insurance plans cover NIPS for all women. This includes over 40 Blue Cross Blue Shield plans, Cigna, Anthem, and Wellmark.

- **From Anthem's policy** on NIPS – GENE.00026, Cell-Free Fetal DNA-Based Prenatal Testing:
    - "With regard to women at low-risk for aneuploidy, noninvasive cell-free DNA-based screening for fetal aneuploidy is considered as an acceptable screening option for fetal aneuploidy (trisomy 13, 18 and 21) in average-risk women carrying a single gestation."[iii]
- **From Cigna's policy** on NIPS – Genetic Testing for Reproductive Carrier Screening and Prenatal Diagnosis:
    - "One benefit of [NIPS] screening is the potential decrease in the number of invasive procedures, and therefore, the decrease in the potential for miscarriage as a complication of invasive testing."[iv]
- **From Wellmark's policy** on NIPS – Noninvasive Prenatal Screening for Fetal Aneuploidies Using Cell-Free Fetal DNA in Maternal Plasma:
    - "Current national guidelines have recommended that all pregnant women be offered screening for fetal aneuploidy, referring specifically to T21, T18 and T13 before 20 weeks of gestation, regardless of age."
    - "[S]creening with cell-free fetal DNA will result in fewer missed cases of Down syndrome, fewer invasive procedures, and fewer cases of pregnancy loss following invasive procedures."
    - "[T]he evidence is sufficient to determine this testing results in a meaningful improvement in net health outcomes for both high risk and average risk singleton pregnancies ."[v]

Five state Medicaid programs cover NIPS for all women regardless of risk: Florida, Minnesota, Ohio, Pennsylvania, Virginia. The Virginia Department of Medical Assistance Services reviewed its coverage for noninvasive prenatal screening in 2018 for Medicaid members and instituted no age restrictions in its coverage.[vi] The Pennsylvania Department of Human Services announced it updated its coverage policy to cover all women in a Medical Assistance Bulletin in January 2019.[vii]

Correspondence from Medicaid officials confirming NIPS coverage of all women in their respective states is listed below:

- Statement from Jessica Kenny, Registered Nursing Consultant, Florida Bureau of Medicaid Policy, Agency for Health Care Administration (August 21, 2018)[viii]
    - "Fee-for service Florida Medicaid does not put any restrictions on CPT code 81507 and 81420."
- Statement from Diogo Reis, Minnesota Medicaid (October 1, 2018)[ix]
    - "I am writing in response to your letter to Marie Zimmerman, Minnesota Medicaid Director, regarding coverage of CPT codes 81420 and 81507. Ms. Zimmerman asked me to respond to your question. Minnesota's Medicaid program already covers both codes you inquired about with no requirement related to age. Additionally, neither code has a prior authorization requirement."
- Letter from Ryan Spindler, Ohio Department of Medicaid (October 12, 2018)
    - "There are currently no coverage restrictions for coverage of this NIPS test for the individuals in our fee-for-service (FFS) program."[x]

Primary Criteria Ranking

While CAPS does not believe NIPS should undergo the HTA process, if it is selected, we respectfully request that HCA change the rankings of the primary criteria assigned to NIPS as they are inaccurate.

NIPS received the following rankings from HCA with which we disagree:

- Safety: Medium
- Efficacy: Medium
- Cost: High

Safety: Potential harm from NIPS is low

The HCA expands on the safety criteria as "potential harm/safety concerns" for the patient.[xi] The HCA describes this further as "identifying the potential degree of harm that an individual may experience if the technology is used."

NIPS involves taking a small (10 cc) sample of venous blood (standard phlebotomy) from the mother's arm, identical to the blood draw required for serum screening. This blood draw is part of the current "standard screening" paradigm currently covered by HCA for women under the age of 35.

This type of peripheral blood collection has been widely employed for many decades for most blood-based testing around the world and is generally considered to have an excellent safety profile with very few complications. When comparing safety, NIPS screens with a higher sensitivity and specificity for aneuploidies than standard screening, which is

covered for women under the age of 35 by Washington HCA. The standard screening paradigm, with its far higher number of false positives (10x to 100x compared to NIPS), presents higher safety concerns, given the complications (up to and including pregnancy loss) that accompany invasive diagnostic procedures triggered by false positive screening results.[xii]

We request the change of the safety concerns ranking from "medium" to "low" for NIPS; and suggest the parallel initiation of a de novo HTA safety evaluation for the standard screening method, given the emergence of NIPS as a method that did not exist when standard screening was first adopted.

Efficacy: Concern about NIPS accuracy and appropriateness is low

The HCA describes the efficacy category as "concerns about therapeutic efficacy or diagnostic accuracy and appropriateness of outcomes for patients."

For Trisomy 21, NIPS has higher sensitivity, a lower false positive rate, and higher positive predictive value as compared to standard screening.[xii] Norton et al. examines 15,841 pregnant women who underwent both standard screening and NIPS, of which nearly 12,000 were under the age of 35.

The false positive rate for all patients under standard screening was 5.4%. In comparison, the false positive rate of NIPS for all patients was 0.06%. This false positive rate is nearly 100 times lower than the current standard screening.

NIPS identifies Trisomies 21, 18 or 13 at far superior rates to standard screening in the general population:[xii]

- Trisomy 21
    - NIPS: 80.9%
    - Standard screening: 3.4%
- Trisomy 18
    - NIPS: 90%
    - Standard screening: 14%
- Trisomy 13
    - NIPS: 50%
    - Standard screening: 3.4%

Major professional societies validate the clinical appropriateness of NIPS for all women. The American College of Medical Genetics (ACMG) recommends "[i]nforming all pregnant women that NIPS is the most sensitive screening option for traditionally screened aneuploidies (i.e., Patau, Edwards, and Down syndromes)."[xiii]

A joint statement from the Society for Maternal Fetal Medicine (SMFM) and the American College of Obstetricians and Gynecologists (ACOG) states, "all women should be offered the

option of aneuploidy screening or diagnostic testing for fetal genetic disorders, regardless of maternal age."[xiv]

Numerous studies have found NIPS is clinically effective in low-risk and high-risk women:

- "Noninvasive prenatal testing using chromosome-selective sequencing in a routinely screened population identified trisomies 21 and 18 with a false-positive rate of 0.1%."[xv]
- "Routine screening for trisomies 21, 18 and 13 by cfDNA testing at 10 weeks is feasible and has a lower FPR than does combined testing, but abnormal results require confirmation by CVS."[xvi]
- "Noninvasive prenatal testing allows a more suitable and efficient workflow for our patients' needs, together with invasive procedures allows a higher prenatal detection of chromosomal aneuploidies."[xvii]
- "There was no significant difference in test performance between the 72,382 high-risk and 40,287 low-risk subjects…This technique can provide equally high sensitivity and specificity in screening for trisomy 21 in a low-risk, as compared to high-risk, population."[xviii]

NIPS is proven to be more effective at screening for aneuploidies than standard screening. Studies and professional societies have found it to be clinically appropriate for all women. Furthermore, a review published in NEJM in late 2018 and authored by Diana Bianchi, Director of the National Institute of Child Health and Human Development, found that:

> *In three large-scale studies, the test performance of cfDNA sequencing was compared with that of multiple-marker screening in the general obstetrical population. In all three studies, the false positive rates associated with cfDNA screening were less than one tenth as high as that with multiple-marker screening, and positive predictive values were significantly higher. The clinical significance of the lower false positive rates is that fewer women are made anxious by a falsely abnormal screening test result, and fewer invasive diagnostic procedures that carry a risk of miscarriage, such as amniocentesis and chorionic villus sampling, are needed to determine the fetal karyotype. Some studies have already shown a 40 to 76% reduction in the number of these procedures since 2012.*
>
> *Some guidelines also support cfDNA testing for all women, because it is the most sensitive test for these common autosomal aneuploidies. In fact, the positive predictive values of cfDNA testing among low-risk women are higher than the positive predictive values of multiple-marker screening among high-risk women.*[xix]

This review, which incidentally was not included in the Ontario HTA assessment because of its cutoff date, concluded:

> *Sequencing of cfDNA for detection of the common fetal autosomal aneuploidies is likely to be increasingly adopted by publicly funded programs as a first-tier test for*

both high-risk and low-risk women because of its superior performance in screening for the common aneuploidies.

Therefore, we request the change of the NIPS efficacy concerns ranking from "medium" to "low"; and suggest the parallel initiation of a de novo HTA efficacy evaluation for the standard screening method, given the emergence of NIPS as a method that did not exist when standard screening was first adopted.

Cost: The cost of NIPS as a screen for all women is low or cost neutral

HCA considers the "estimated total direct cost per year (estimated increase/decrease)" when assigning a ranking for cost concerns. Furthermore, the "cost criterion is directed at identifying the potential budget impact (degree of change) technology coverage or non-coverage would have for the participating agencies."

Introduction of NIPS as a first-tier screen in the general pregnancy population has been estimated to be cost neutral at a price of $619–$744 in multiple peer-reviewed modeling studies.[xx,xxi,xxii]

NIPS can identify more aneuploidies, and at the same time reduce unnecessary invasive procedures, and this in turn results in far fewer procedure-related losses of unaffected pregnancies.[xxiii]

Furthermore, as noted previously, the Ontario assessment relies on a flawed core assumption that the only relevant economic comparison is between (1) NIPS as a first-tier option and (2) NIPS as a second-tier option performed after traditional prenatal screening. The second-tier option has not been endorsed or adopted by any society, payor, or major health system in the US. Nevertheless, the Ontario assessment admitted that their assessment included "only one study [that] compared first-tier NIPT with traditional prenatal screening", even though multiple such studies had been available as of their literature review cutoff date. The Ontario assessment referenced a study that included a positive assessment of NIPS:[xxiv]

For the general pregnancy population, NIPT identified 15% more trisomy cases, reduced invasive procedures by 88%, and reduced iatrogenic fetal loss by 94% as compared to FTS [first trimester screening]. The cost per trisomy case identified with FTS was $497 909. At a NIPT unit cost of $453 and below, there were cost savings as compared to FTS.

For these reasons, CAPS respectfully requests the cost concern category for NIPS be changed to "low."

Ontario Health Technology Assessment

CAPS is concerned about the usage of a publication from the Ontario Health Technology Assessment Series entitled, "Noninvasive Prenatal Testing for Trisomies 21, 18, and 13, Sex Chromosome Aneuploidies and Microdeletions" in decisions by the HCA on NIPS.

The Ontario assessment calculated an uptake rate of 68% among average risk pregnant women with a single gestation pregnancy.[xxv] "Assuming that uptake is constant over the next 5 years, we estimated that about 96,602 and 100,653 pregnant people would accept prenatal screening in years 1 and 5, respectively," states the document.

Over five years, the Ontario assessment projected that first-tier NIPS would cost Ontario's health system an additional $35 million when compared to second-tier NIPS. This analysis is inappropriate as the standard of care following a positive screen is to make a diagnosis using existing invasive methods (CVS/amniocentesis), depending on the woman's willingness to undergo such a procedure.

Ontario proposes that women with a positive serum screening undergo second-tier NIPS, which creates additional delays. The delays created by this system could alter the choices available to women and significantly raise the cost of some of their options.

Furthermore, the Ontario assessment does not reflect the population of Washington State. The uptake rate in Ontario will be different than the rate in Washington State. The number of state-financed pregnancies in Washington State is also lower than total yearly pregnancies in Ontario so this comparison should not be used in Washington State's coverage decisions.

This analysis also infers first-tier NIPS involves more diagnostic procedures due to "inconclusive test result[s]," and this translates to higher costs as well. This is problematic for several reasons: NIPS failures occur far less often than standard screening false positives (most labs document NIPS failure rates of 0.1% to 1% whereas standard screening has a well-documented 5% false-positive rate). Also, the next step for any standard screen positive result – as recommended by all existing professional society guidelines – is an invasive confirmatory procedure; whereas a no-result NIPS can often be repeated in several weeks' time with 50% or greater success.

The Ontario assessment states: "Some guidelines acknowledge that NIPT is an effective screening strategy as a second-tier test" but fails to reference any such guidelines. In fact, to the best of our knowledge, no U.S professional society has released practice guidelines on the usage of NIPS as a second-tier strategy. Instead, all US professional societies have released statements that encourage health care providers to either recommend first tier NIPS as the most sensitive screening option available (ACMG Position Statement, July 2016); or to regard first-tier NIPS as an option that should be available to all patients

subject to the clinical judgment of their healthcare providers. ACOG Committee Opinion No. 693 (April 2017) stated:

> *Although some national organizations provide recommendations about offering testing in certain circumstances, the exact type of testing often is not specified (e.g., Practice Bulletin No. 163, Screening for Fetal Aneuploidy, recommends that all women be offered prenatal screening for aneuploidy early in pregnancy but does not specify which test to use).*
>
> *Obstetrician–gynecologists and other health care providers generally have latitude in selecting the test that is most appropriate for their practice setting. For scenarios in which different testing options are acceptable alternatives, obstetrician–gynecologists and other health care providers should determine which tests will be offered as the standard in their practices so that, in accordance with the ethical principle of justice, similar testing strategies are made available to all patients.*

A reimbursement policy that specifically limits access to certain screening methods in effect removes the latitude of healthcare providers to make appropriate decisions for their patients, as lack of coverage effectively dictates the decisions that will be made by providers and patients in most cases. Essentially, the test that will be used will be the test that is reimbursed.

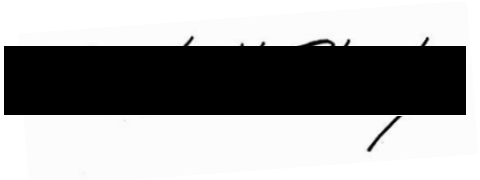
Given all these considerations, the suggestion to use NIPS in a second-tier capacity is a hypothetical alternative and should not color discussions about the Washington HCA's coverage of NIPS for women under the age of 35.

Conclusion: HCA should approve coverage of NIPS for all women in Washington State without undergoing a Health Technology Assessment

CAPS welcome discussions within HCA on the validity of NIPS for all pregnant women. However, we disagree on the notion it needs to undergo a lengthy technology review process when ample evidence supports its use as a safe, effective, and cost-efficient screening method. We urge HCA to recognize that the lack of Medicaid coverage of NIPS for women under the age of 35 creates two standards of care for pregnant women in Washington State. We do not believe that this screen or any screen should be mandated for every pregnant woman in the state. Our goal is to ensure that this highly accurate screen is available to any pregnant woman who wishes to receive it; and that healthcare providers have latitude in prescribing the test that is most appropriate for their practice setting.

Thank you for the opportunity to comment.

Sincerely,



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[i] Health Technology Assessment. (n.d.). Retrieved from https://www.hca.wa.gov/about-hca/health-technology-assessment

[ii] Institute of Medicine (US) Council on Health Care Technology. (1988, January 01). Blue Cross and Blue Shield Association Technology Evaluation and Coverage Program. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK218445/

[iii] Anthem. (2018). *Cell-Free DNA-Based Prenatal Testing*. Retrieved from https://www.anthem.com/medicalpolicies/policies/mp_pw_c150729.htm

[iv] Cigna. (2019). *Genetic testing for Reproductive Carrier Screening and Prenatal Diagnosis.* Retrieved from https://cignaforhcp.cigna.com/public/content/pdf/coveragePolicies/medical/mm_0514_coveragepositioncriteria_genetic_testing_repro_carrier_prenatal.pdf

[v] Wellmark. (2018). Noninvasive Prenatal Screening for Fetal Aneuploidies Using Cell-Free Fetal DNA in Maternal Plasma. Retrieved from https://www.wellmark.com/Provider/MedPoliciesAndAuthorizations/MedicalPolicies/policies/non-invasive_prenatal_test_NPIT.aspx#covered

[vi] Lee, J. S. (n.d.). [Letter written August 17, 2018 to Marily Rhudy].

[vii] Pennsylvania Department of Human Services. (2019). Updates to Laboratory Services on the Medical Assistant Program Fe Schedule; Prior Authorization for Noninvasive Prenatal Screening (NiPS). Retrieved form http://www.dhs.pa.gov/cs/groups/webcontent/documents/bulletin_admin/c_284582.pdf

[viii] Kenny, J. (2018, August 21). Consideration of Reimbursement by Florida Medicaid for Noninvasive Prenatal Screening for All Women [E-mail to H.Baer].

[ix] Reis, D. (2018, October 1). Noninvasive Prenatal Screening [E-mail to H. Baer].

[x] Spindler, R. (2018, October 12). Clarification of Coverage for Noninvasive Prenatal Screening for All Women under CPT Codes 81420 and 81507 [E-mail to M. Rhudy].

[xi] Prioritization Criteria. (n.d.). Retrieved from https://www.hca.wa.gov/assets/program/prioritization_criteria.pdf

[xii] Norton, M. E., Jacobsson, B., Swamy, G. K., Laurent, L. C., Ranzini, A. C., Brar, H., . . . Wapner, R. J. (2015). Cell-free DNA Analysis for Noninvasive Examination of Trisomy. *New England Journal of Medicine,372*(17), 1589-1597. doi:10.1056/nejmoa1407349

[xiii] Gregg, A. R., Skotko, B. G., Benkendorf, J. L., Monaghan, K. G., Bajaj, K., Best, R. G., . . . Watson, M. (2016). Noninvasive prenatal screening for fetal aneuploidy, 2016 update: A position statement of the American College of Medical Genetics and Genomics. *Genetics in Medicine,18*, 1056-1065. doi:10.1038/gim.2016.97

[xiv] Counseling About Genetic Testing and Communication of Genetic Test Results [Editorial]. (2017, April). *American College of Obstetricians and Gynecologists*. Retrieved from https://www.acog.org/Clinical-Guidance-and-Publications/Committee-Opinions/Committee-on-Genetics/Counseling-About-Genetic-Testing-and-Communication-of-Genetic-Test-Results

[xv] Nicolaides, K. H., Syngelaki, A., Ashoor, G., & Birdir, C. (2012). Noninvasive prenatal testing for fetal trisomies in a routinely screened first-trimester population. *American Journal of Obstetrics & Gynecology,207*(5). doi:10.1016/j.ajog.2012.08.033

[xvi]Gil, M. M., Quezada, M. S., Bregant, B., Ferraro, M., & Nicolaides, K. H. (2013). Implementation of maternal blood cell-free DNA testing in early screening for aneuploidies. *Ultrasound in Obstetrics & Gynecology,42*(1), 34-40. doi:10.1002/uog.12504

[xvii] Zhou, Q., Pan, L., Chen, S., Chen, F., Hwang, R., Yang, X., . . . Xu, C. (2014). Clinical application of noninvasive prenatal testing for the detection of trisomies 21, 18, and 13: A hospital experience. *Prenatal Diagnosis,34*(11), 1061-1065. doi:10.1002/pd.4428

[xviii] Zhang, H., Gao, Y., Jiang, F., Fu, M., Yuan, Y., Guo, Y., . . . Wang, W. (2015). Non-invasive prenatal testing for trisomies 21, 18 and 13: Clinical experience from 146 958 pregnancies. *Ultrasound in Obstetrics & Gynecology,45*(5), 530-538. doi:10.1002/uog.14792

[xix] Bianchi DW & Chiu RW. Sequencing of circulating cell-free dna during pregnancy. N Engl J Med 2018;379: 464-473

[xx] Benn P, Curnow KJ, Chapman S, Michalopoulos SN, Hornberger J, Rabinowitz M. An Economic Analysis of Cell-Free DNA Non-Invasive Prenatal Testing in the US General Pregnancy Population. *PLoS One*. 2015;10(7):e0132313.

Walker BS, Nelson RE, Jackson BR, Grenache DG, Ashwood ER, Schmidt RL. A Cost-Effectiveness Analysis of First Trimester Non-Invasive Prenatal Screening for Fetal Trisomies in the United States. *PLoS One*. 2015;10(7):e0131402.

[xxi] Fairbrother G, Burigo J, Sharon T, Song K. Prenatal screening for fetal aneuploidies with cell-free DNA in the general pregnancy population: a cost-effectiveness analysis. *J Matern Fetal Neonatal Med.* 2015:1-5.

[xxii] Walker BS, Nelson RE, Jackson BR, Grenache DG, Ashwood ER, Schmidt RL. A Cost-Effectiveness Analysis of First Trimester Non-Invasive Prenatal Screening for Fetal Trisomies in the United States. *PLoS One*. 2015;10(7):e0131402.

[xxiii] Fairbrother, G., Burigo, J., Sharon, T., & Song, K. (2015, May 25). Prenatal screening for fetal aneuploidies with cell-free DNA in the general pregnancy population: A cost-effectiveness analysis. Retrieved from https://www.tandfonline.com/doi/full/10.3109/14767058.2015.1038703

[xxiv] Fairbrother G, Burigo J, Sharon T, Song K. Prenatal screening for fetal aneuploidies with cell-free DNA in the general pregnancy population: a cost-effectiveness analysis. J Matern Fetal Neonatal Med. 2016;29(7):1160-4.

[xxv] Health Quality Ontario (2019). Noninvasive Prenatal Testing for Trisomies 21, 18, and 13, Sex Chromosome Aneuploidies, and Microdeletions: A Health Technology Assessment. *Ontario health technology assessment series*, *19*(4), 1-166.

Washington State Health Care Authority

Submit competed petition to: shtap@hca.wa.gov; **or**
Atten: Health Technology Assessment
PO Box 42712, Olympia, Washington 98504-2712; **or**
FAX (360) 586-8827

Petition for technology review or re-review

Your name:	American Society for Radiation Therapy Payer Relations Committee
Mailing address:	251 18th Street S, 8th Floor, Arlington VA 22202
E-mail address:	Jessica.adams@astro.org
Telephone number:	703-839-7396

Note: Not all questions will apply to all technologies. For assistance email the HTA program at the address above, or phone (360) 725-5126 (TTY 711).

Technology topic Stereotactic radiation surgery and stereotactic body radiation therapy (SBRT)

If this topic has been reviewed by the health technology assessment program in the past, skip to question 7, below. See technologies HTCC has previously reviewed.

1. Background information

- Does this technology have FDA approval? ☐ Yes ☐ No
- When was this technology approved?
- For what indications has FDA approved this technology?
- Why do you believe this technology merits consideration for assessment?
- Proposed research questions.

Click here to enter text.

2. Potential patient harm(s) or safety concerns

- What is the potential for patient harm, related to use of this technology?
- What are the likelihood and severity of the potential harms or adverse outcomes that may result from recommended use of this technology?
- Are there significant potential harms associated with this technology compared to alternatives?

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3. Therapeutic efficacy, effectiveness or diagnostic accuracy

- What is the potential effectiveness of this technology on the indicated clinical condition? (e.g., prevent/reduce mortality; increase quality of life)
- How are indicated conditions diagnosed? Is there a consensus on diagnosis?
- For diagnostic technologies: Is this technology compared to a "gold standard" technology?

- What is the diagnostic accuracy or utility?
- What published, peer-reviewed literature documents the efficacy of this technology or the science that underlies it? Please enclose publications or bibliography.

Click here to enter text.

4. Estimated total cost per year

- What are the direct health care costs of this technology (annual or lifetime)?
- What is the potential cost-effectiveness of this new technology compared with other alternatives?
- Which private insurers reimburse for use of this technology? Please provide contact information and phone numbers.

Click here to enter text.

5. Secondary considerations

- **Number of persons affected** - What are the numbers of people affected by this technology in the State of Washington?
- **Severity of condition(s)** - What is the severity of the condition treated by this technology? Does it result in premature death; short or long term disability? How would this technology increase the quality of care for the State of Washington?
- **Policy-related urgency -** Is there a particular urgency related to this technology? Is it new and rapidly diffusing? How long has this technology been in use? Is there a standard of care? Is this technology or proposed use(s) controversial?
- **Potential or observed variation** - What is the observed or potential for under, or overuse of this technology? Are there any variations in use or outcomes by region or other characteristics?
- **Special populations and ethical concerns** - Is use limited to small populations; what characteristics are present (e.g., race, ethnicity, religion, rare condition, socioeconomic status) that may impact policy decision?

Click here to enter text.

6. References

- List other organizations that have completed technology assessments on this topic (please provide date of technology assessments and links).
- Cite any Center for Medicare and Medicaid Services (CMS) national coverage decision on this topic and the date issued.
- Provide list of key references used in preparing this petition.

- Have any relevant medical organizations (e.g., American Medical Association) expressed an opinion on this technology? If so, please provide verification documents and contact names, numbers and links.
- Bibliography or reference list of requestor attached: ☐ Yes ☐ No

Click here to enter text.

7. For re-review petitions only

Re-review of a technology requires new evidence that could change a previous decision. What new evidence should be considered? Please provide specific publication information and/ or references.

The American Society for Radiation Oncology (ASTRO) submits their SBRT Model Policy as evidence for consideration. ASTRO model policies were developed as a means to efficiently communicate what ASTRO believes to be correct coverage policies for radiation oncology services. The ASTRO model policies do not serve as clinical guidelines and they are subject to periodic review and revision without notice. The ASTRO model policies may be reproduced and distributed, without modification, for noncommercial purposes.

ASTRO members are medical professionals, who practice at hospitals and cancer treatment centers in the United States and around the globe and make up the radiation therapy treatment teams that are critical in the fight against cancer. These teams often include radiation oncologists, medical physicists, medical dosimetrists, radiation therapists, oncology nurses, nutritionists and social workers, and treat more than one million cancer patients each year. We believe this multi-disciplinary membership makes us uniquely qualified to provide input on the inherently complex issues related to Medicare payment policy and coding for radiation oncology services.

The SBRT Model Policy can be accessed here, and it enclosed:
https://www.astro.org/uploadedFiles/_MAIN_SITE/Daily_Practice/Reimbursement/Model_Policies/Content_Pieces/ASTROSBRTModelPolicy.pdf

ASTRO Model Policies

STEREOTACTIC BODY RADIATION THERAPY (SBRT)

This Model Policy[1] addresses coverage for stereotactic body radiation therapy (SBRT).

Description

SBRT is a radiation treatment modality that couples a high degree of anatomic targeting accuracy and reproducibility with very high doses of extremely precise, externally generated, ionizing radiation. The therapeutic intent of SBRT is to maximize cell-killing effect on the target(s) while minimizing radiation-related injury in adjacent normal tissues. SBRT is used to treat extra-cranial sites as opposed to stereotactic radiosurgery (SRS), which is used to treat intra-cranial. For a discussion of the codes relevant to SRS, refer to ASTRO's SRS Model Policy[11].

The adjective "stereotactic" describes a procedure during which a target lesion is localized relative to a known three-dimensional reference system that allows for a high degree of anatomic accuracy. Examples of devices used in SBRT for stereotactic guidance may include a body frame with external reference markers in which a patient is positioned securely, a system of implanted fiducial markers that can be visualized with low-energy (kV) X-rays and CT imaging-based systems used to confirm the location of a tumor immediately prior to treatment.

Treatment

SBRT Treatment Planning

Treatment planning for SBRT generally follows the same process and procedures as IMRT and three-dimensional conformal therapy plans. As with either treatment planning methods, SBRT planning determines the field size(s), gantry angles and other beam characteristics to achieve the desired radiation dose distribution. SBRT plans are highly customized to the target volume(s) and may be geometrically more accurate than conventionally fractionated external beam treatment plans.

Imaging

Three-dimensional image acquisition of the target region by simulation is an essential prerequisite to SBRT treatment planning. In general, a CT scan of the target region is performed and serves as the baseline image set used for dose calculations and, for selected cases, for coregistration of MR or PET images sets in order to better define the target and surrounding anatomy. If respiratory or other normal organ motion is expected to produce significant movement of the target region during radiation therapy delivery, the radiation oncologist may additionally elect to order multiphasic treatment planning image sets to account for motion when rendering target volumes. Some SBRT treatment systems such as automated robotic delivery may not require multiphasic imaging but is still able to deliver breathing-corrected treatment.

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a. Contouring

Defining the target and avoidance structures is a multi-step process:

i. The radiation oncologist reviews the three-dimensional images and outlines the treatment target on each slice of the image set. The summation of these contours defines the Gross Tumor Volume (GTV). For multiple image sets, the physician may outline separate GTVs on each image set to account for the effect of normal organ motion upon target location and shape. Some patients may not have GTVs if they have had previous treatment with surgery or chemotherapy, in which case treatment planning will be based on CTVs as described below.

ii. The radiation oncologist draws a margin around the GTV to generate a Clinical Target Volume (CTV), which encompasses the areas at risk for microscopic disease (i.e., not visible on imaging studies). Other CTVs may be created based on the estimated volume of residual disease. For multiple image sets, the physician may draw this margin around an aggregate volume containing all image set GTVs to generate an organ-motion CTV, or Internal Target Volume (ITV).

iii. To account for potential daily patient setup variation and/or organ and patient motion, a final margin is then added to create a Planning Target Volume (PTV).

iv. Nearby normal structures that could potentially be harmed by radiation (i.e., "organs at risk" or OARs) are also contoured.

b. Radiation dose prescribing

The radiation oncologist assigns specific dose requirements for the PTV, which typically includes a prescribed dose that must be given to at least 90 to 95 percent of the PTV. Additionally, PTV dose requirements routinely include dose constraints for the OARs (e.g., upper limit of mean dose, maximum allowable point dose and/or a critical volume of the OAR that must not receive a dose above a specified limit). A treatment plan that satisfies these requirements and constraints should maximize the potential for disease control and minimize the risk of radiation injury to normal tissue.

c. Dosimetric planning, calculations and dose verification

The medical physicist or a supervised dosimetrist calculates a multiple static beam and/or modulated arc treatment plan to deliver the prescribed radiation dose to the PTV and simultaneously satisfy the normal tissue dose constraints by delivering significantly lower doses to nearby organs. Dose-volume histograms are prepared for the PTV and OARs. Here, an arc is defined as a discrete complete or partial rotation of the linear accelerator gantry during which there is continuous motion of the multileaf collimator (MLC) to deliver an optimized radiation dose distribution within the patient. The calculated beams or arcs are then delivered either to a phantom or a dosimetry measuring device to confirm that the intended dose distribution for the patient is physically verifiable and that the beams or arcs are technically feasible.

Documentation of all aspects of the treatment planning process is essential.

SBRT Treatment Delivery

Treatment of extra-cranial sites requires accounting for internal organ motion as well as for patient motion. Thus, reliable immobilization or repositioning systems must often be combined with devices capable of decreasing organ motion or accounting for organ motion – e.g., use of respiratory gating or robotic target tracking for target sites in the chest or upper abdomen. Additionally, all SBRT is performed with at least one form of image guidance to confirm proper patient positioning and tumor localization prior to delivery of each fraction. The ASTRO/ACR Practice Guidelines for SBRT outline the responsibilities and training requirements for personnel involved in the administration of SBRT[9].

SBRT may be delivered in one to five sessions (fractions). Each fraction requires an identical degree of precision, localization and image guidance. Since the goal of SBRT is to maximize the potency of the radiation therapy by completing an entire course of treatment within an extremely accelerated time frame, any course of radiation

treatment extending beyond five fractions is not considered SBRT and is not to be billed as such. SBRT is meant to represent a complete course of treatment and not be used as a boost following a conventionally fractionated course of treatment.

SBRT may be used as an alternative to surgery for treating various lesions and may be an effective and safer alternative than conventional radiation therapy for certain presentations of cancers and other non-cancer targets. Direct physician involvement, image guidance and immobilization are integral to stereotactic treatment for these diverse body sites. The medical physicist should perform a second check calculation before initiating the first treatment to ensure the monitor units used to deliver the planned treatment are correct. With a radiation oncologist, the medical physicist should ensure all of the treatment parameters are correct, including image guidance, respiratory motion compensation or any other complex positioning aids that may be employed to accurately treat the patient.

Documentation Requirements

The patient's record must support the medical necessity of treatment. Supporting clinical records should include not only the patient's medical history and physical examination findings but also the patient's current functional status, commonly described by an overall performance status score (e.g., Karnofsky Performance Status or Eastern Cooperative Oncology Group (ECOG) Performance Status score). A radiation oncologist must evaluate the clinical and technical aspects of the treatment and document this evaluation as well as the resulting management decision. Clinical record documentation of the technical aspects of treatment planning and delivery should include details of the prescribed dose to the target and relevant dose-limiting normal structures and the actual dose delivered and dates of treatment delivery. For Medicare claims of SBRT, the HCPCS/CPT® code(s) may be subject to Correct Coding Initiative (CCI) edits. This policy does not take precedence over CCI edits. Please refer to the CCI for correct coding guidelines and specific applicable code combinations prior to billing Medicare.

Indications and Limitations of Coverage and/or Medical Necessity

Indications for Coverage

SBRT is indicated for primary tumors and tumors metastatic to the lung, liver, kidney, adrenal gland or pancreas.

SBRT is also indicated for treatment of pelvic and head and neck tumors that have recurred after primary irradiation when each of the following criteria is met, and each is specifically documented in the medical record.

1. The patient's general medical condition (namely, the performance status) justifies aggressive, curative treatment to a primary, non-metastatic cancer, or
2. Metastatic disease requiring palliation cannot be treated by conventional methods due to proximity of adjacent prior irradiated volumes and other measures are not appropriate or safe for the particular patient, or
3. The patient's general medical condition (namely, the performance status) justifies aggressive local therapy to one or more deposits of metastatic cancer in an effort either to achieve total disease clearance in the setting of oligometastatic disease or to reduce the patient's overall burden of systemic disease for a specifically defined clinical benefit, and
4. The targeted tumor(s) can be completed encompassed with acceptable risk to nearby critical normal structures.

Multiple ICD diagnosis codes fit this description of covered indications and are listed in this coverage policy below.

Other Neoplasms

a. Prostate Cancer

Many clinical studies supporting the efficacy and safety of SBRT in the treatment of localized prostate cancer have been published. At least one study has shown excellent five-year biochemical control rates with very low rates of serious toxicity. Additionally, numerous studies have demonstrated the safety of SBRT for prostate cancer after a follow-up interval long enough (two to three years) to provide an opportunity to observe the incidence of late genitourinary or gastrointestinal toxicity.

While it is necessary to observe patients treated for prostate cancer for extended intervals to gauge the rate of long-term (e.g., beyond 10 years) biochemical control and overall survival, the interim results reported appear at least as good as other forms of radiation therapy administered to patients with equivalent risk levels followed for the same post-treatment duration.

It is ASTRO's opinion that data supporting the use of SBRT for prostate cancer have matured to a point where SBRT should be considered an appropriate alternative for select patients with low- to intermediate-risk disease.

b. Bone Metastases

SBRT has been demonstrated to achieve durable tumor control when treating lesions in vertebral bodies or the paraspinous region, where extra care must be taken to avoid excess irradiation of the spinal cord when tumor-ablative doses are administered. There is an important clinical distinction between the status of patients described above and a patient with widely metastatic disease for whom palliation is the major objective. In one setting, a patient with limited metastatic disease and good performance status is treated with the intention of eradicating all known active disease or greatly reducing the total disease burden in a manner that can extend progression-free survival. For such a patient, SBRT can be a reasonable therapeutic intervention. However, for uncomplicated, previously untreated bone metastases in a patient with widespread progressive disease in the spine or elsewhere and where the prognosis is unfavorable, it is generally appropriate to use a less technically complex form of palliative radiation therapy rather than SBRT.

c. Other Indications for SBRT

For patients with tumors of any type arising in or near previously irradiated regions, SBRT may be appropriate when a high level of precision and accuracy is needed to minimize the risk of injury to surrounding normal tissues. Also, in other cases where a high dose per fraction treatment is indicated SBRT may be appropriate. The medical necessity for SBRT should be documented in the patient's medical record.

ICD-9-CM and ICD-10-CM Codes That May Be Associated with Medical Necessity

Note: Diagnosis codes are based on the current ICD-9-CM codes that are effective at the time of Model Policy publication. Any updates to ICD-9-CM or ICD-10-CM codes will be reviewed by ASTRO, and coverage should not be presumed until the results of such review have been published.

The following ICD diagnosis codes support medical necessity under this Model Policy:

DIAGNOSIS	ICD-9 CODE(S)	ICD-10 CODE(S)
PRIMARY TUMORS		
Lung cancer	162.2 - 162.9	C34.00 – C34.92
Prostate cancer	185	C61
Pancreatic cancer	157.0-157.9	C25.0-C25.9
Renal cancer	189.0, 189.1	C64.1-C65.9
Liver or bile duct cancer	155.0, 155.1, 155.2	C22.0-C22.9
Adrenal gland cancer	194.0, 194.6	C74.00-C74.92 C75.5
METASTATIC TUMORS		
Lung metastasis	197.0	C78.00-C78.02
Liver metastasis	197.7	C78.7
Renal metastasis	198.0	C79.00-C79.02
Adrenal gland metastasis	198.7	C79.70-C79.72
Thoracic lymph nodes metastasis	196.1	C77.1
Bone metastasis	198.5	C79.51, C79 52
RECURRENT TUMORS AFTER PRIOR RT		
Abdominal and pelvic cancer	195.2, 195.3	C76.2, C76 3
Gynecologic cancer	179-184.9	C51.0-C58
Rectal and anal cancer	154.0-154.8	C19-C21.8
Head and neck cancer	140.0-146.8 147.0-149.9 160.0-161.9	C00.0-C10.8 C11.0-C14.8 C30.0-C32.9
Lymph node metastasis	196.0-196.9	C77.0-C77.9
Prior radiotherapy, any site	990*	T66.XXXA*

**ICD-9-CM 990 or ICD-10-CM T66.XXXA (Effects of Radiation, Unspecified) may only be used where prior radiation therapy to the site is the governing factor necessitating SBRT in lieu of other radiation therapy. An ICD diagnosis code for the anatomic diagnosis must also be used.*

Limitations of Coverage

SBRT is not considered medically necessary under any of the following circumstances:

1. Treatment is unlikely to result in clinical cancer control and/or functional improvement.
2. The tumor burden cannot be completely targeted with acceptable risk to nearby critical normal structures.
3. Patients with poor performance status (Karnofsky Performance Status less than 40 or ECOG Status of 3 or worse; see below for further scoring information regarding Karnofsky Performance Status and ECOG Status).

Karnofsky Performance Status Scale[4]

100 Normal; 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.
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 needs.
50 Requires considerable assistance and frequent medical care.
40 Disabled; requires special care and assistance.
30 Severely disabled; hospitalization is indicated although death not imminent.
20 Very sick; hospitalization necessary; active supportive treatment is necessary.
10 Moribund, fatal processes progressing rapidly.
0 Dead.

ECOG Performance Status Scale[8]

Grade 0: Fully active, able to carry on all pre-disease performance without restriction.
Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
Grade 2: Ambulatory and capable of all self-care but unable to carry out and work activities. Up and about more than 50 percent of waking hours.
Grade 3: Capable of only limited self-care, confined to bed or chair more than 50 percent of waking hours.
Grade 4: Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
Grade 5: Dead.

Physicians' Current Procedural Terminology (CPT®)/HCPCS Section

Note: CPT is a trademark of the American Medical Association (AMA).

SBRT Treatment Planning

There are no specific codes for clinical treatment planning and simulation for SBRT. However, because of the complexity of SBRT and the need for three-dimensional conformal or IMRT dosimetric treatment planning, the following codes are usually appropriate for SBRT cases. Use of IMRT planning is based on the delivery system and medical necessity.

CPT® CODE	DESCRIPTION	SBRT-SPECIFIC GUIDELINES
77263	Therapeutic radiology treatment planning; complex	Given the complexity of clinical decision-making for SBRT, a complex clinical treatment planning code is justified.
+77293	Respiratory motion management simulation (List separately in addition to code for primary procedure).	May be reasonable to perform and report once per course of SBRT for cases in which target movement during respiration must be accounted for during treatment planning (e.g., tumors of the thorax and upper abdomen).
77295 OR 77301	3-dimensional radiotherapy plan, including dose-volume histograms Intensity modulated radiotherapy plan, including dose-volume histograms for target and critical structure partial tolerance specifications (Dose plan is optimized using inverse planning technique for modulated beam delivery [eg, binary, dynamic MLC] to create highly conformal dose distribution. Computer plan distribution must be verified for positional accuracy based on dosimetric verification of the intensity map with verification of treatment set-up and interpretation of verification methodology)	Report either treatment planning code only once per course of SBRT.
77470	Special treatment procedure (eg, total body irradiation, hemibody radiation, per oral or endocavitary irradiation) (77470 assumes that the procedure is performed 1 or more times during the course of therapy, in addition to daily or weekly patient management) (For intraoperative radiation treatment delivery and management, see 77424, 77425, 77469)	Given additional time and effort required of SBRT, a special treatment procedure code may be justified with appropriate specific documentation.

Medical Radiation Physics, Dosimetry and Treatment Devices

There are no SBRT specific codes for medical radiation physics, dosimetry, treatment devices and special services. However, the following codes can be used as described below.

CPT® CODE	DESCRIPTION	SBRT-SPECIFIC GUIDELINES
77300	Basic radiation dosimetry calculation, central axis depth dose calculation, TDF, NSD, gap calculation, off axis factor, tissue inhomogeneity factors, calculation of non-ionizing radiation surface and depth dose, as required during course of treatment, only when prescribed by the treating physician	One unit for each arc in linear accelerator system. One unit for each shot in Cobalt-60. Maximum limit of 10 units.
77370	Special medical radiation physics consultation	May be reasonable and necessary if ordered by the radiation oncologist.
77334	Treatment devices, design and construction; complex (irregular blocks, special shields, compensators, wedges, molds or casts)	One unit for each unique combination of beam angle and collimator pattern or each unique arc; certain carrier limitations may apply. One unit for each helmet in Cobalt-60.
77338	Multi-leaf collimator (MLC) device(s) for intensity modulated radiation therapy (IMRT), design and construction, per IMRT plan	If IMRT planning code 77301 is used for coding treatment planning then one CPT 77338 should be used to code for the devices.

SBRT Treatment Delivery

Historically, in the hospital outpatient environment, CMS has utilized G-codes to distinguish between robotic and non-robotic SBRT and SRS. The agency recently reviewed current radiation therapy equipment technology and found that most linac-based treatment platforms incorporate some type of robotic capability. CMS therefore concluded that it is no longer necessary to continue distinguishing robotic and non-robotic linear accelerators.

Beginning January 1, 2014, CPT® code 77373 can be reported in place of HCPCS codes G0251, G0339 and G0340. The chart below provides a crosswalk of CPT and corresponding HCPCS codes:

HCPCS CODE	DESCRIPTOR	CPT® CODE	DESCRIPTOR
G0251	Linear accelerator based stereotactic radiosurgery, delivery including collimator changes and custom plugging, fractionated treatment, all lesions, per session, maximum five sessions per course of treatment	**77373**	SBRT delivery
G0339	Image-guided robotic linear accelerator-based stereotactic radiosurgery, 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		

CPT® CODE	DESCRIPTION	SBRT-SPECIFIC GUIDELINES
77373	Stereotactic body radiation therapy, treatment delivery, per fraction to 1 or more lesions, including image guidance, entire course not to exceed 5 fractions (Do not report 77373 in conjunction with 77385, 77386, 77401, 77402, 77407, 77412) (For single fraction cranial lesion[s], see 77371, 77372)	Technical code for up to but no more than 5 fractions in the freestanding setting. This code includes all image guidance on the days of treatment delivery; therefore, do not report 77373 in conjunction with 77014 on the days of treatment delivery. This code will be paid only once per day of treatment regardless of the number of sessions or lesions. Note that this code should be used in place of 0082T, which has been deleted as of January 1, 2007.

When reporting SBRT delivery, it is not appropriate to bill more than one treatment delivery code on the same date of service, even though stereotactic therapy may be delivered using either conformal or intensity modulated techniques (e.g., SBRT delivered using MLC-modulated beams should be reported using CPT code 77373 only and not using 77373 with 77385 or 77386). Likewise, only one SBRT delivery unit is to be reported even if multiple targets are treated using different setup and field arrangement parameters on the same day.

Radiation Treatment Management

CPT® Category I code 77435 (SBRT treatment management) should be used by the radiation oncologist to report treatment management during SBRT. This code may be reported once per SBRT course.

The physician work for 77435 can be summarized as follows: The radiation oncologist evaluates the patient prior to the procedure. Under the direct supervision of the radiation oncologist, the patient is set up on the treatment table and all the treatment parameters are verified. Image guidance and respiratory correlation, if required, may be achieved through a variety of methods, all of which are supervised, corrected and approved in real-time by the physician. The physician assesses and approves all of the ongoing images used for localization, tumor tracking and any gating application, as well as any complementary single (beam's eye) view localization images for any of the fields or arcs used to deliver a dose. The radiation oncologist remains available throughout SBRT treatment to manage the execution of the treatment and make real-time adjustments in response to patient motion, target movement or equipment issues to ensure accuracy and safety. The physician also evaluates the patient post-procedure. All other work generally associated with CPT code 77427 (Radiation treatment management, five treatments) is included and should not be separately coded.

Much of the radiation oncologist's work in establishing the above treatment parameters is performed in conjunction with the qualified medical physicist, who should be present and participate in delivering SBRT.

CPT® CODE	DESCRIPTION	SBRT-SPECIFIC GUIDELINES
77435	Stereotactic body radiation therapy, treatment management, per treatment course, to one or more lesions, including image guidance, entire course not to exceed 5 fractions (Do not report 77435 in conjunction with other treatment management codes 77427- 77432) (The same physician should not report both stereotactic radiosurgery services (32701, 63620, 63621) and radiation treatment management (77435)	Professional charge for treatment management performed by the radiation oncologist. This code can be reported only once for the entire course of treatment and not per fraction. It will apply to all lesions treated during that entire course of treatment. It should not be reported in conjunction with any other treatment management codes (777472-77432).

REFERENCES

General

1. Benedict SH, Yenice KM, Followill D, et al. Stereotactic body radiation therapy: The report of AAPM Task Group 101. *Med Phys.* 2010; 37(8): 4078-4101.
2. Chang R, Timmerman R. Stereotactic Body Radiation Therapy: A Comprehensive Review. *Am J Clin Oncol.* 2007; 30(6): 637-644.
3. Halperin EC, Perez, CA, Brady LW. *Principles and Practice of Radiation Therapy*, 5th edition. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.
4. Karnofsky DA, Burchenal JH. (1949). "The Clinical Evaluation of Chemotherapeutic Agents in Cancer." In: MacLeod CM (Ed), *Evaluation of Chemotherapeutic Agents*. Columbia Univ Press. Page 196.
5. Kavanagh BD and Timmerman RD (Eds.) *Stereotactic Body Radiation Therapy*, Philadelphia, PA: Lippincott Williams & Wilkins; 2005.
6. Lo S, Fakiris A, Chang E, et al. *Stereotactic body radiation therapy*: a novel treatment modality. Nat Rev *Clin Oncol*. 2010; 7(1): 44-54.
7. Martin A, Gaya A, Stereotactic Body Radiotherapy: A Review. *Clin Oncol* (*R Coll Radiol*). 2010; 22(3): 157-172.
8. Oken MM, Creech RH, Tormey DC, et al. Toxicity And Response Criteria of The Eastern Cooperative Oncology Group. Am J *Clin Oncol*. 1982; 5(6):649-655.
9. Potters L, Kavanagh B, Galvin JM, et al. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) practice guideline for the performance of stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys.* 2010; 76(2): 326-332.
10. Solberg TD, Balter JM, Benedict SH, et al. Quality and safety considerations in stereotactic radiosurgery and stereotactic body radiation therapy: Executive summary. *Pract Radiat Oncol.* 2012; 2(1): 2-9.
11. Stereotactic Radiosurgery (SRS) Model Coverage Policy. American Society for Radiation Oncology Web site. https://www.astro.org/uploadedFiles/Main_Site/Practice_Management/Reimbursement/SRSMPJuly2011.pdf Published July 25, 2011. Accessed April 9, 2014
12. Timmerman RD, Kavanagh BD, Cho LC, et al. Stereotactic Body Radiation Therapy in Multiple Organ Sites. *J Clin Oncol.* 2007; 25(8): 947-952.

Bone Metastasis

13. Chang EL, Shiu AS, Lii MF, et al. Phase I clinical evaluation of near-simultaneous computed tomographic image-guided stereotactic body radiotherapy for spinal metastases. *Int J Radiat Oncol Biol Phys.* 2004; 9(5): 1288-1294.
14. Chang EL, Shiu AS, Mendel E, et al. Phase I/II study of stereotactic body radiotherapy for spinal metastasis and its pattern of failure. *J Neurosurg Spine.* 2007; 7(2): 151-160.
15. Choi CY, Adler JR, Gibbs IC, et al. Stereotactic Radiosurgery for Treatment of Spinal Metastases Recurring in Close Proximity to Previously Irradiated Spinal Cord. *Int J Radiat Oncol Biol Phys.* 2010; 78(2): 499-506.
16. Degen JW, Gagnon GJ, Voyadzis JM, et al. Cyberknife stereotactic radiosurgical treatment of spinal tumors for pain control and quality of life. *J Neurosurg Spine.* 2005; 2(5): 540-549.
17. Gagnon GJ, Nasr NM, Liao JJ, et al. Treatment of spinal tumors using CyberKnife fractionated stereotactic radiosurgery: pain and quality of life assessment after treatment in 200 patients. *Neurosurgery.* 2009; 64(2): 297-306.
18. Gerstzen PC, Ozhasoglu C, Burton SA, et al. CyberKnife frameless stereotactic radiosurgery for spinal lesions: clinical experience in 125 cases. *Neurosurgery.* 2004; 55(1): 89-98.
19. Haley M, Gerszten P. Stereotactic Radiosurgery in the Management of Cancer Pain. *Curr Pain Headache Rep.* 2009; 13(4): 277–281.
20. Janjan N, Lutz S, Bedwinek J, et al. Therapeutic Guidelines for the Treatment of Bone Metastasis: A Report from the American College of Radiology Appropriateness Criteria Expert Panel on Radiation Oncology. *J Palliat Med.* 2009, 12(5): 417-426.
21. Nelson JW, Yoo DS, Sampson JH, et al. Stereotactic body radiotherapy for lesions of the spine and paraspinal regions. *Int J Radiat Oncol Biol Phys.* 2009; 73(5): 1369-1375.
22. Sahgal A, Ames C, Chou D, et al. Stereotactic Body Radiotherapy Is Effective Salvage Therapy for Patients with Prior Radiation of Spinal Metastases. *Int J Radiat Oncol Biol Phys.* 2008; 71: 652-665.

Oligometastatic Disease

23. Corbin KS, Hellman S, Weichselbaum RR. Extracranial oligometastases: a subset of metastases curable with stereotactic radiotherapy. *J Clin Oncol.* 2013; 31(11): 1384-1390.
24. McCammon R, Schefter TE, Gaspar LE, et al. Observation of dose control relationship for lung and liver tumors after stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys.* 2009; 73(1): 112-118.
25. Milano MT, Katz AW, Okunieff P. Patterns of recurrence after curative-intent radiation for oligometastases confined to one organ. *Amer J Clin Oncol.* 2010; 33(2): 157-163.
26. Milano MT, Katz AW, Muhs AG, et al. A prospective pilot study of curative-intent stereotactic radiation therapy in patients with 5 or fewer oligometastatic lesions. *Cancer.* 2008; 112(3): 650-658.
27. Milano MT, Katz AW, Zhang H, et al. Oligometastases treated with stereotactic body radiotherapy: long-term follow-up of a prospective study. *Int J Radiat Oncol Biol Phys.* 2012; 83(3): 878-886.
28. Milano MT, Zhang H, Metcalfe SK, et al. Oligometastatic breast cancer treated with curative-intent stereotactic body radiation therapy. *Breast Cancer Res Treat.* 2009; 115(3): 601-608.

Head and Neck

29. Chen HH, Tsai ST, Wang MS, et al. Experience in fractionated stereotactic body radiation therapy boost for newly diagnosed nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys.* 2006; 66(5): 1408-1414.
30. Hara W, Loo BW, Goffinet DR, et al. Excellent local control with stereotactic radiotherapy boost after external beam radiotherapy in patients with nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys.* 2008; 71(2): 393-400.
31. Kawaguchi K, Sato K, Horie A, et al. Stereotactic radiosurgery may contribute to overall survival for patients with recurrent head and neck carcinoma. *Radiat Oncol.* 2010; 5:51.
32. Kim JH, Kim MS, Yoo SY, et al. Stereotactic body radiotherapy for refractory cervical lymph node recurrence of nonanaplastic thyroid cancer. *Otolayngol Head Neck Surg.* 2010; 142(3): 338-43.
33. Ozigit G, Cengiz M, Yazici G, et al. A retrospective comparison of robotic stereotactic body radiotherapy and three-dimensional conformal radiotherapy for the reirradiation of locally recurrent nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys.* 2011; 81(4):e263-268.
34. Rwiegema J, Heron D, Ferris R, et al. Fractionated stereotactic bod.y radiation therapy in the treatment of previously-irradiated recurrent head and neck carcinoma. Updated report of the University of Pittsburgh experience. *Am J Clin Oncol.* 2010; 33(3): 286-293.
35. Unger KR, Lominska CE, Deeken JF, et al. Fractionated Stereotactic Radiosurgery for Reirradiation of Head-and-Neck Cancer. *Int J Radiat Oncol Biol Phys*. 2010; 77(5): 1411-1419.
36. Vargo JA, Wegner RE, Heron DE, et al. Stereotactic body radiation therapy for locally recurrent, previously irradiated nonsquamous cell cancers of the head and neck. *Head Neck.* 2012; 34(8): 1153-61.
37. Wu SX, Chua DT, Deng ML, et al. Outcome of fractionated stereotactic radiotherapy for 90 patients with locally persistent and recurrent nasopharyngeal carcinoma. *Int J Radiati Oncol Biol Phys.* 2007; 69(3): 761-769.

Kidney and Adrenal Gland – Primary and Metastatic Tumors

38. Casamassima F, Livi L, Masciullo S, et al. Stereotactic radiotherapy for adrenal gland metastases: University of Florence experience. *Int J Radiat Oncol Biol Phys.* 2012; 82(2): 919-923.
39. Chawla S, Chen Y, Katz A, et al. Stereotactic body radiotherapy for treatment of adrenal metastases. *Int J Radiat Oncol Biol Phys.* 2009; 75(1): 71-75.
40. Holy R, Piroth M, Pinkawa M, et al. Stereotactic body radiation therapy (SBRT) for treatment of adrenal gland metastases from non-small cell lung cancer. *Strahlenther Onkol.* 2011; 187(4): 245-251.
41. Siva S, Pham D, Gill S, et al. A systematic review of stereotactic radiotherapy ablation for primary renal cell carcinoma. *BJU Int.* 2012; 110(11 Pt B): E737-743.
42. Svedman C, Karlsson K, Rutkowska E, et al. Stereotactic body radiotherapy of primary and metastatic renal lesions for patients with only one functioning kidney. *Acta Oncol.* 2008; 47(8): 1578-1583.

Liver – Primary and Metastatic Tumors

43. Andolino DL, Johnson CS, Maluccio M, et al. Stereotactic body radiotherapy fopr [rimary helatocellular carcinoma. *Int J Radiat Oncol Biol Phys.* 2011; 81:e447-453.
44. Bujold A, Massey CA, Kim JJ, et al. Sequential phase I and phase II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. *J Clin Oncol.* 2013; 31(13): 1631-1639.
45. Chang DT, Swaminath A, Kozak M, et al. Stereotactic body radiotherapy for colorectal liver metastases: A pooled analysis. *Cancer.* 2011; 117(17): 4060-4069
46. Choi BO, Choi IB, Jang HS, et al. Stereotactic body radiation therapy with or without transarterial chemoembolization for patients with primary hepatocellular carcinoma: preliminary analysis. *BMC Cancer.* 2008; 8: 351.
47. Ibarra RA, Rojas D, Snyder L, et al. Multicenter results of stereotactic body radiotherapy (SBRT) for non-resectable primary liver tumors. *Acta Oncol*. 2012; 51(5): 575-583.
48. Katz AW, Carey-Sampson M, Muhs AG, et al. Hypofractionated stereotactic body radiation therapy (SBRT) for limited hepatic metastases. *Int J Radiat Oncol Biol Phys.* 2007; 67(3): 793-798.
49. Kwon JH, Bae SH, Kim JY, et al. Long-term effect of stereotactic body radiation therapy for primary hepatocellular carcinoma ineligible for local ablation therapy or surgical resection. Stereotactic radiotherapy for liver cancer. *BMC Cancer.* 2010; 10:475.
50. Lee MT, Kim JJ, Dinniwell R, et al. Phase I study of individualized stereotactic body radiotherapy for liver metastases. *J Clin Oncol.* 2009; 27: 1585–1591.
51. McCammon R, Schefter TE, Gaspar LE, et al. Observation of a dose-control relationship for lung and liver tumors after stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys.* 2009; 73(1): 112-118.
52. Méndez Romero A, Wunderink W, Hussain SM, et al. Stereotactic body radiation therapy for primary and metastatic liver tumors: A single institution phase I-II study. *Acta Oncol.* 2006; 45(7): 831-837.
53. Méndez Romero A, Wunderink W, van Os RM, et al. Quality of life after stereotactic body radiation therapy for primary and metastatic liver tumors. *Int J Radiat Oncol Biol Phys.* 2008; 70(5): 1447-1452.
54. Price TR, Perkins SM, Sandrasegaran K, et al. Evaluation of response after stereotactic body radiotherapy for hepatocellular carcinoma. *Cancer.* 2012; 118(12): 3191-3198.
55. Rusthoven KE, Kavanagh BD, Cardenes H, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. *J Clin Oncol.* 2009; 27(10): 1572-1578.
56. Tao C, Yang LX. Improved radiotherapy for primary and secondary liver cancer: Stereotactic body radiation therapy. *Anticancer Research*. 2012; 32(2): 649-655.
57. Tse RV, Hawkins M, Lockwood G, Kim JJ, Cummings B, Knox J, Sherman M, Dawson LA. Phase I study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *J Clin Oncol.* 2008; 26(4):657-664.

Lung – Primary and Metastatic Tumors

58. Andratschke N, Zimmermann F, Boehm E, et al. Stereotactic radiotherapy of histologically proven inoperable stage I non-small cell lung cancer: patterns of failure. *Radiother Oncol.* 2011; 101(2): 245-249.
59. Barriger RB, Forquer JA, Brabham JG, et al. A dose-volume analysis of radiation pneumonitis in non-small cell lung cancer patients treated with stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys.* 2012; 82(1): 457-462.
60. Baumann P, Nyman J, Hoyer M, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. *J Clin Oncol* 2009; 27(20): 3290–3296.
61. Baumann P, Nyman J, Hoyer M, et al. Stereotactic body radiotherapy for medically inoperable patients with stage I non-small cell lung cancer - a first report of toxicity related to COPD/CVD in a non-randomized prospective phase II study. *Radiother Oncol.* 2008; 88(3): 359-367.
62. Bradley JD, El Naqa I, Drzymala RE, et al. Stereotactic body radiation therapy for early-stage non-small cell lung cancer: the pattern of failure is distant. *Int J Radiat Oncol Biol Phys.* 2010; 77(4):1146-1150.
63. Chang JY, Balter PA, Dong L, et al. Stereotactic body radiation therapy in centrally and superiorly located stage I or isolated recurrent non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2008; 72(4): 967–971.
64. Chen Y, Guo W, Lu Y,et al. . Dose-individualized stereotactic body radiotherapy for T1-3N0 non-small cell lung cancer: long-term results and efficacy of adjuvant chemotherapy. *Radiother Oncol.* 2008; 88(3): 351-358.
65. Fakiris, AJ, McGarry RC, Yiannoutsos CT, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study. *Int J Radiat Oncol Biol Phys.* 2009; 75(3): 677–682.
66. Guckenberger M, Wulf J, Mueller G, et al. Response relationship for image-guided stereotactic body radiotherapy of pulmonary tumors: relevance of 4d dose calculation. *Int J Radiat Oncol Biol Phys*. 2009; 73(2): 442-448.
67. Henderson M, McGarry R, Yiannoutsos C, et al. Baseline pulmonary function as a predictor for survival and decline in pulmonary function over time in patients undergoing stereotactic body radiotherapy for the treatment of stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2008; 72(2): 404-409.
68. Joyner M, Salter BJ, Papanikolaou N, et al. Stereotactic body radiation therapy for centrally located lung lesions. *Acta Oncol.* 2006; 45(7): 802-807.
69. Koto M, Takai Y, Ogawa Y, et al. A phase II study on stereotactic body radiotherapy for stage I non-small cell lung cancer. *Radiother Oncol.* 2007; 85(3): 429-434.
70. Matsuo Y, Shibuya K, Nagata Y, et al. Prognostic factors in stereotactic body radiotherapy for non-small cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2011; 79(4): 1104-1111.
71. McCammon R, Schefter TE, Gaspar LE, et al. Observation of a dose-control relationship for lung and liver tumors after stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys.* 2009; 73(1): 112-118.
72. Norihisa Y, Nagata Y, Takayama K, et al. Stereotactic body radiotherapy for oligometastatic lung tumors. *Int J Radiat Oncol Biol Phys.* 2008; 72(2): 398-403.
73. Okunieff P, Petersen AL, Philip A, et al. Stereotactic body radiation therapy (SBRT) for lung metastases. *Acta Oncol.* 2006; 45(7): 808-817.
74. Olsen JR, Robinson CG, El Naqa I, et al. Dose-response for stereotactic body radiotherapy in early-stage non-small cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2011; 81(4): e299-303.
75. Onishi H, Shirato H, Nagata Y, et al. Stereotactic body radiotherapy (SBRT) for operable stage I non-small cell lung cancer: can SBRT by comparable to surgery? *Int J Radiat Oncol Biol Phys.* 2011; 81(5): 1352-1358.
76. Pennathur A, Luketick J, Heron D, et al. Stereotactic radiosurgery for the treatment of lung neoplasm: experience in 100 consecutive patients. *Ann Thorac Surg.* 2009; 88: 1594-1600.
77. Rusthoven KE, Kavanagh BD, Burri SH, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for lung metastases. *J Clin Oncol.* 2009; 27(10): 1579-1584.
78. Salazar OM, Sandhu TS, Lattin PB, et al. Once-weekly, high-dose stereotactic body radiotherapy for lung cancer: 6-year analysis of 60 early-stage, 42 locally advanced, and 7 metastatic lung cancers. *Int J Radiat Oncol Biol Phys.* 2008; 72(3): 707-715.
79. Scorsetti M, Navarria P, Facoetti A, et al. Effectiveness of stereotactic body radiotherapy in the treatment of inoperable early-stage lung cancer. *Anticancer Res.* 2007; 27(5B): 3615-3619.
80. Senan S, Lagerwaard F. Stereotactic radiotherapy for stage I lung cancer: Current results and new developments. *Cancer Radiother.* 2010; 14(20: 115-118.
81. Siva S, ManManus M, Ball D. Stereotactic radiotherapy for pulmonary oligometastases: a systematic review. *J Thorac Oncol.* 2010; 5(7): 1091-1099.
82. Stephans KL, Djemil T, Reddy CA, et al. A comparison of two stereotactic body radiation fractionation schedules for medically inoperable stage I non-small cell lung cancer: the Cleveland Clinic experience. *J Thorac Oncol.* 2009; 4(8): 976-982.
83. Takeda A, Kunieda E, Ohashi T, et al. Stereotactic body radiotherapy (SBRT) for oligometastatic lung tumors from colorectal cancer and other primary cancers in comparison with primary lung cancer. *Radiother Oncol.* 2011; 101(2): 255-259.
84. Takeda A, Sanuki N, Kunieda E, et al. Stereotactic body radiotherapy for primary lung cancer at a dose of 50 Gy total in five fractions to the periphery of the planning target volume calculated using a superposition algorithm. *Int J Radiat Oncol Biol Phys.* 2009; 73(2): 442-448.
85. Taremi M, Hope A, Dahele M, et al. Stereotactic body radiotherapy for medically inoperable lung cancer: prospective, single-center study of 108 consecutive patients. *Int J Radiat Oncol Biol Phys*. 2012; 82(2):967-973
86. Verstegen NE, Lagerwaard FJ, Haasbeek CJ, et al. Outcomes of stereotactic ablative radiotherapy following a clinical diagnosis of stage I NSCLC: comparison with contemporaneous cohort with pathologically proven disease. *Radiother Oncol.* 2011; 101(2) 250-254.
87. Zimmermann F, Wulf J, Lax I, et al. Stereotactic Body Radiation Therapy for Early Non-Small Cell Lung Cancer. *Front Radiat Ther Oncol.* 2010; 42: 94-114.

Pancreas

88. Chang DT, Schellenberg D, Shen J, et al. Stereotactic radiotherapy for unresectable adenocarcinoma of the pancreas. *Cancer.* 2009; 115(3): 665-672.
89. Didolkar MS, Coleman CW, Brenner MJ, et al. Image-guided stereotactic radiosurgery for locally advanced pancreatic adenocarcinoma: results of first 85 patients. *J Gastrointestin Surgery.* 2010; 14:1547-1559.
90. Goyal K, Einstein D, Ibarra RA, et al. Stereotactic body radiation therapy for nonresectable tumors of the pancreas. *J Syrg Res*. 2012; 174(2): 319-325.
91. Mahadevan A, Jain S, Goldstein M, et al. Stereotactic Body Radiotherapy and Gemcitabine for Locally Advanced Pancreatic Cancer. *Int J Radiat Oncol Biol Phys.* 2010; 78(3): 735-742.
92. Rwigema J, Parihk S, Heron D, et al. Stereotactic body radiotherapy in the treatment of advanced adenocarcinoma of the pancreas. *Am J Clin Oncol.* 2011; 34(1): 63-69.
93. Seo Y, Kim MS, Yoo S, et al. Stereotactic body radiation therapy boost in locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys.* 2009; 75(5): 1556-1461.
94. Schellenberg D, Goodman KA, Lee F, et al. Gemcitabine chemotherapy and single-fraction stereotactic body radiotherapy for locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys.* 2008; 72: 678-686.

Pelvic, Non-prostate

95. Choi C, Cho C, Yoo S, et al. Image-guided Stereotactic Body Radiation Therapy in Patients with Isolated Para-aortic Lymph Node Metastases from Uterine Cervical and Corpus Cancer. *Int J Radiat Oncol Biol Phys.* 2009; 74(1): 147-153.
96. Kim MS, Choi C, Yoo S, et al. Stereotactic body radiation therapy in patients with pelvic recurrence from rectal carcinoma. *Jpn J Clin Oncol.* 2008; 38(10): 695-700.

Prostate

97. Buyyounouski MK, Price RA, Harris EER, et al. Stereotactic body radiotherapy for primary management of early-stage, low-to intermediate-risk prostate cancer: Report of the American Society for Therapeutic Radiology and Oncology Emerging Technology Committee. *Int J Radiat Oncol Biol Phys.* 2010; 76(5): 1297-1304.
98. Freeman DF, King CR. Stereotactic body radiation for low-risk prostate cancer: five year outcomes. *Radiat Oncol.* 2011; 6:3.
99. Ishiyama H, Teh BS, Lo SS, et al. Stereotactic body radiation therapy for prostate cancer. *Future Oncol.* 2011; 7(9): 1077-1086.
100. 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(1):118.
101. 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(2): 877-882.
102. King CR, Brooks JD, Gill H, et al. Stereotactic body radiotherapy for localized prostate cancer: interim results of a prospective phase II clinical trial. *Int J Radiat Oncol Biol Phys.* 2009; 73(4): 1043-1048.
103. 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): 939-945.
104. Madsen BL, Hsi RA, Pham HT, et al. Stereotactic hypofractionated accurate radiotherapy of the prostate (SHARP), 33.5 Gy in five fractions for localized disease: first clinical trial results. *Int J Radiat Oncol Biol Phys.* 2007; 67(4): 1099-1105.
105. Parthan A, Pruttivarasin N, Davies D, et al. Comparative cost-effectiveness of stereotactic body radiation therapy versus intensity-modulated and proton radiation therapy for localized prostate cancer. *Front Oncol.* 2012; 2: 81.
106. Townsend NC, Huth BJ, Ding W, et al. Acute toxicity after Cyberknife-delivered hypofractionated radiotherapy for treatment of prostate cancer. *Amer J Clin Oncol.* 2011; 34(1): 6-10.

Washington State Health Care Authority

Submit competed petition to: shtap@hca.wa.gov; **or**
Atten: Health Technology Assessment
PO Box 42712, Olympia, Washington 98504-2712; **or**
FAX (360) 586-8827

Petition for technology review or re-review

Your name:	Berit Madsen, Md
Mailing address:	19917 Seventh ave, Poulsbo WA 98370
E-mail address:	bmadsen@seattlecca.org
Telephone number:	360 697-8000

Note: Not all questions will apply to all technologies. For assistance email the HTA program at the address above, or phone (360) 725-5126 (TTY 711).

Technology topic SBRT specifically for prostate cancer

If this topic has been reviewed by the health technology assessment program in the past, skip to question 7, below. See technologies HTCC has previously reviewed.

1. Background information

- Does this technology have FDA approval? ☐ Yes ☐ No
- When was this technology approved?
- For what indications has FDA approved this technology?
- Why do you believe this technology merits consideration for assessment?
- Proposed research questions.

Click here to enter text.

2. Potential patient harm(s) or safety concerns

- What is the potential for patient harm, related to use of this technology?
- What are the likelihood and severity of the potential harms or adverse outcomes that may result from recommended use of this technology?
- Are there significant potential harms associated with this technology compared to alternatives?

Click here to enter text.

3. Therapeutic efficacy, effectiveness or diagnostic accuracy

- What is the potential effectiveness of this technology on the indicated clinical condition? (e.g., prevent/reduce mortality; increase quality of life)
- How are indicated conditions diagnosed? Is there a consensus on diagnosis?

- For diagnostic technologies: Is this technology compared to a "gold standard" technology?
- What is the diagnostic accuracy or utility?
- What published, peer-reviewed literature documents the efficacy of this technology or the science that underlies it? Please enclose publications or bibliography.

Click here to enter text.

4. Estimated total cost per year

- What are the direct health care costs of this technology (annual or lifetime)?
- What is the potential cost-effectiveness of this new technology compared with other alternatives?
- Which private insurers reimburse for use of this technology? Please provide contact information and phone numbers.

Click here to enter text.

5. Secondary considerations

- **Number of persons affected** - What are the numbers of people affected by this technology in the State of Washington?
- **Severity of condition(s)** - What is the severity of the condition treated by this technology? Does it result in premature death; short or long term disability? How would this technology increase the quality of care for the State of Washington?
- **Policy-related urgency -** Is there a particular urgency related to this technology? Is it new and rapidly diffusing? How long has this technology been in use? Is there a standard of care? Is this technology or proposed use(s) controversial?
- **Potential or observed variation** - What is the observed or potential for under, or overuse of this technology? Are there any variations in use or outcomes by region or other characteristics?
- **Special populations and ethical concerns** - Is use limited to small populations; what characteristics are present (e.g., race, ethnicity, religion, rare condition, socioeconomic status) that may impact policy decision?

Click here to enter text.

6. References

- List other organizations that have completed technology assessments on this topic (please provide date of technology assessments and links).
- Cite any Center for Medicare and Medicaid Services (CMS) national coverage decision on this topic and the date issued.
- Provide list of key references used in preparing this petition.

- Have any relevant medical organizations (e.g., American Medical Association) expressed an opinion on this technology? If so, please provide verification documents and contact names, numbers and links.
- Bibliography or reference list of requestor attached: ☐ Yes ☐ No

Click here to enter text.

7. For re-review petitions only

Re-review of a technology requires new evidence that could change a previous decision. What new evidence should be considered? Please provide specific publication information and/ or references.

The HTA has declined to review stereotactic body radiotherapy (SBRT) in general and concluded that there was no basis to change the HTA coverage recommendations from 2012. I don't know if the committee would reconsider the approval of Stereotactic Radiotherapy for low risk prostate cancer in isolation from the other indications for SBRT but I would like to make the case that SBRT for prostate cancer should be an approved indication. SBRT for low risk prostate cancer has been the subject of numerous prospective trials and reviews as the 2018 HTA literature search (see page 12 of recent HTA appendix, with 1472 participants) found all indicating better outcomes in the SBRT comparator groups (EBRT, IMRT, Brachytherapy, and prostatectomy). No RCTs are published due to the very difficult nature of performing RCTs on this disease with very different treatment modalities and longstanding turf battles (Urology vs Radiation Oncology), not to mention the extremely long follow up needed due to long natural disease progession times. Futhermore, as the HTA report notes, SBRT for low risk prostate cancer is covered by Medicare, and Cigna, Aetna, and Regence. It is also an appropriate 2A treatment recommendation per NCCN. Moreover, the economic rationale is very good with a superior cost utility compared to both IMRT and brachytherapy. Based on the HTA's own 2018 analysis, SBRT should be an approved treatment modality for low risk proatate cancer.

Washington State Health Care Authority

Submit competed petition to: shtap@hca.wa.gov; **or**
Atten: Health Technology Assessment
PO Box 42712, Olympia, Washington 98504-2712; **or**
FAX (360) 586-8827

Petition for technology review or re-review

Your name:	Simon S. Lo, MB, ChB, FACR, FASTRO
Mailing address:	University of Washington Medical Center, 1959 NE Pacific St, Box 356043, Seattle, WA 98195
E-mail address:	simonsmlo@gmail.com
Telephone number:	773-983-0470

Note: Not all questions will apply to all technologies. For assistance email the HTA program at the address above, or phone (360) 725-5126 (TTY 711).

Technology topic Click here to enter text.

If this topic has been reviewed by the health technology assessment program in the past, skip to question 7, below. See technologies HTCC has previously reviewed.

1. Background information

- Does this technology have FDA approval? ☐ Yes ☐ No
- When was this technology approved?
- For what indications has FDA approved this technology?
- Why do you believe this technology merits consideration for assessment?
- Proposed research questions.

Click here to enter text.

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- What are the likelihood and severity of the potential harms or adverse outcomes that may result from recommended use of this technology?
- Are there significant potential harms associated with this technology compared to alternatives?

Click here to enter text.

3. Therapeutic efficacy, effectiveness or diagnostic accuracy

- What is the potential effectiveness of this technology on the indicated clinical condition? (e.g., prevent/reduce mortality; increase quality of life)
- How are indicated conditions diagnosed? Is there a consensus on diagnosis?

- For diagnostic technologies: Is this technology compared to a "gold standard" technology?
- What is the diagnostic accuracy or utility?
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Click here to enter text.

4. Estimated total cost per year

- What are the direct health care costs of this technology (annual or lifetime)?
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- Which private insurers reimburse for use of this technology? Please provide contact information and phone numbers.

Click here to enter text.

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- **Severity of condition(s)** - What is the severity of the condition treated by this technology? Does it result in premature death; short or long term disability? How would this technology increase the quality of care for the State of Washington?
- **Policy-related urgency -** Is there a particular urgency related to this technology? Is it new and rapidly diffusing? How long has this technology been in use? Is there a standard of care? Is this technology or proposed use(s) controversial?
- **Potential or observed variation** - What is the observed or potential for under, or overuse of this technology? Are there any variations in use or outcomes by region or other characteristics?
- **Special populations and ethical concerns** - Is use limited to small populations; what characteristics are present (e.g., race, ethnicity, religion, rare condition, socioeconomic status) that may impact policy decision?

Click here to enter text.

6. References

- List other organizations that have completed technology assessments on this topic (please provide date of technology assessments and links).
- Cite any Center for Medicare and Medicaid Services (CMS) national coverage decision on this topic and the date issued.
- Provide list of key references used in preparing this petition.

- Have any relevant medical organizations (e.g., American Medical Association) expressed an opinion on this technology? If so, please provide verification documents and contact names, numbers and links.
- Bibliography or reference list of requestor attached: ☐ Yes ☐ No

Click here to enter text.

7. For re-review petitions only

Re-review of a technology requires new evidence that could change a previous decision. What new evidence should be considered? Please provide specific publication information and/ or references.

Since the last review in 2012, there has been abundant literature documenting the efficacy and safety of SBRT for the treatment of different disease entities, yielding more favorable or non-inferior outcomes while shortening the treatment course.

I am requesting a re-review of the below disease entities:

Oligometastasis

This document has omitted some important studies of oligometastasis including the phase 2 randomized trial of consolidative therapy for limited non-small cell lung cancer from M.D. Anderson Cancer Center and the SABR-COMET randomized phase 2 trial from London, Ontario.

For the M.D. Anderson trial, patients with stage IV NSCLC and three or fewer metastatic disease lesions after first-line systemic therapy were randomized to SABR for the oligometastatic lesions +/- maintenance therapy or maintenance therapy/ observation. A total of 74 patients were enrolled during initial systemic therapy and 49 patients were randomized.In the initial publication in Lancet Oncology in 2016, SABR was associated with an improved median progression-free survival (PFS) of 11.93 months vs. 3.9 months (p = 0.005). The 1-year PFS was 48% (SABR) vs 20% (control) [1]. The median overall survival (OS) were not reached in both arms. The toxicities were similar between the two arms. The group updated and presented the data at the American Society for Radiation Oncology Meeting in 2018. The median OS was improved from 17 to 41.2 months with SABR (https://www.astro.org/ASTRO/media/ASTRO/News%20and%20Publications/Press%20Kits/PDFs/BriefingSlides_Gomez.pdf).

The results of the SABR-COMET trial were presented at the American Society for Radiation Oncology Meeting in 2018 and it has been accepted for publication, with the paper in the press currently. This phase 2 randomized trial compared SABR (66 patients) and conventional care (33 patients) in patients with 1-5 metastases (oligometastases). SABR led to improvement of both PFS and OS (https://www.astro.org/ASTRO/media/ASTRO/News%20and%20Publications/Press%20Kits/PDFs/Palma_NewsBriefingslides.pdf). There was no decreased quality of life.

Recently, Ost et al. from Belgium published their phase 2 randomized trial comparing surveillance with 3 monthly PSA and metastasis-directed therapy (SABR or surgery) for prostate cancer patients with oligometastases (1-3 metastases). Quality if life was similar between the 2 arms. With a median follow up of 3 years, the androgen deprivation therapy-free survival was longer in the metastasis-directed

therapy arm (21 months vs 13 months)[2].

References:

1. Gomez DR, Blumenschein GR Jr, Lee JJ, Hernandez M, Ye R, Camidge DR, Doebele RC, Skoulidis F, Gaspar LE, Gibbons DL, Karam JA, Kavanagh BD, Tang C, Komaki R, Louie AV, Palma DA, Tsao AS, Sepesi B, William WN, Zhang J, Shi Q, Wang XS, Swisher SG, Heymach JV.Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. Lancet Oncol. 2016 Dec;17(12):1672-1682. doi: 10.1016/S1470-2045(16)30532-0. Epub 2016 Oct 24.

2. Ost P, Reynders D, Decaestecker K, Fonteyne V, Lumen N, De Bruycker A, Lambert B, Delrue L, Bultijnck R, Claeys T, Goetghebeur E, Villeirs G, De Man K, Ameye F, Billiet I, Joniau S, Vanhaverbeke F, De Meerleer G. Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial.J Clin Oncol. 2018 Feb 10;36(5):446-453. doi: 10.1200/JCO.2017.75.4853. Epub 2017 Dec 14.

Primary renal cell carcinoma/ kidney cancer

The standard treatment for primary renal cell carcinoma (RCC) is nephrectomy. In patients who are poor surgical candidates, the option is ablative therapy (e.g. RFA). However, in some patients who have large tumors or tumors in some locations of the kidney, ablative therapy may not be feasible. SABR has emerged as a non-invasive therapy for these RCC patients and have been practiced worldwide.

In 2018 and 2019, two important multi-institutional studies were published. Both studies came from International Radiosurgery Oncology Consortium for Kidney (IROCK) group. In the first study, a pooled analysis of 223 patients who underwent SABR for renal cell carcinoma was performed. This represents the largest series in the world. Patients were pulled from USA, Canada, Australia, Japan, and Germany. The 4-year local control, cancer-specifc survival, overall survival, and progression-free survival were 97.8%, 91.9%. 70.7%. and 65.4%, respectively. The toxicity rate was very low. Of note, based on this study, the Japanese Ministry of Health approved SABR as one of the treatment options for RCCs <5 cm for their 125 million citizens (personal communication with Professor Hiroshi Onishi, Chairman of Radiation Oncology, University of Yamanashi, Japan) as of April 1, 2018.

The second study looked at SABR for renal cell carcinoma in solitary kidney using the IROCK database. 81 patients with a solitary kidney were compared with 138 patients with both kidneys. There were no significant difference in oncologic outcomes or renal function between the single vs double kidnedy cohort. No solitary kidney patients required dialysis. Local control, progression-free survival, cancer-specific survival, and overall survival in the solitary cohort were 98.0%, 77.5%, 98.2% and 81.5% at 2 years, respectively [3]. In this particular group of patients, SABR yielded acceptable impact on renal function and achieved excellent oncological outcomes, similar to those in patients with bilateral kidneys.

References:

1. Siva S, Louie AV, Warner A, Muacevic A, Gandhidasan S, Ponsky L, Ellis R, Kaplan I, Mahadevan A, Chu W, Swaminath A, Onishi H, Teh B, Correa RJ, Lo SS, Staehler M. Pooled analysis of stereotactic ablative

radiotherapy for primary renal cell carcinoma: A report from the International Radiosurgery Oncology Consortium for Kidney (IROCK). Cancer. 2018 Mar 1;124(5):934-942. doi: 10.1002/cncr.31156. Epub 2017 Dec 20. PMID: 29266183

2. Correa RJM, Louie AV, Staehler M, Warner A, Gandhidasan S, Ponsky L, Ellis R, Kaplan I, Mahadevan A, Chu W, Swaminath A, Onishi H, Teh BS, Lo SS, Muacevic A, Siva S. Stereotactic radiotherapy as a treatment option for renal tumours in the solitary kidney: a multicenter analysis from the International Radiosurgery Oncology Consortium for Kidney (IROCK).
J Urol. 2019 Feb 5. doi: 10.1097/JU.0000000000000111. [Epub ahead of print]

[redacted]

From: Melissa <Melissa@bogardjohnson.com>
Sent: Wednesday, March 27, 2019 2:59 PM
To: HCA ST Health Tech Assessment Prog
Cc: Paul Diaz
Subject: tinnitus review

Good afternoon,

On behalf of the Washington Speech-Language-Hearing Association (WSLHA), I am providing comments on the topic non-pharmaceutical treatments for tinnitus.

The American Speech-Language-Hearing Association (ASHA) has a Practice Portal page that provides an overview of tinnitus. There are a variety of treatment options for management of tinnitus that are individualized on a case by case basis. However, there is no cure.

https://www.asha.org/Practice-Portal/Clinical-Topics/Tinnitus-and-Hyperacusis/

We also suggest resources on the American Tinnitus Association website https://www.ata.org/

Please use WSLHA and ASHA as a resource, should the Health Technology Assessment program choose tinnitus to review.

Thanks,
Melissa
--
Melissa Johnson
Bogard & Johnson
200 Union Ave SE
Olympia, WA 98501
360.280.6429 cell
melissa@bogardjohnson.com

LivaNova

Health innovation that matters

March 27, 2019

Washington State Health Care Authority
PO Box 42712, Olympia, Washington 98504-2712
Attention: Health Technology Assessment

RE: LivaNova Comments on 2019 Prospective HTA technology topics: Re-review of Vagus Nerve Stimulation (VNS) Therapy for Epilepsy and Depression

Dear Health Technology Assessment Committee,

The Vagus Nerve Stimulation (VNS) Therapy for Epilepsy and Depression was last reviewed in August 2009. At the end of the review, the Health Technology Clinical Committee (HTCC) concluded there was sufficient evidence to cover the use of VNS Therapy for Epilepsy, but not the use of VNS Therapy for Depression.

The published 2019 Prospective HTA technology topics indicate that new evidence and expanded indications for new populations support re-review at this time. As the manufacturer of the Vagus Nerve Therapy (VNS) system, LivaNova, Inc. concurs with this statement and is in support of the re-review of VNS Therapy.

Since the time of the review, a significant body of new evidence has emerged about treatment resistant depression and the role of VNS Therapy in its treatment. Standards of care have evolved, including the APA updating its Practice Guideline for the Treatment of Patients with Major Depressive Disorder in October 2010 to include recommendations of several potential strategies for depression that is non-responsive to treatment, including VNS Therapy. And, it should be noted in February 15, 2019 the Centers for Medicare & Medicaid Services (CMS) modified the NCD for VNS Therapy for TRD, initiating coverage for Medicare beneficiaries through CED when offered in a CMS-approved clinical trial, as well as the coverage of VNS Therapy device replacement. We believe this new evidence and evolving standards of care support reconsideration of VNS Therapy for TRD as reasonable and necessary.

Relative to the VNS Therapy indication for Epilepsy, at the time of the last review VNS Therapy was FDA approved for patients ages 12 and older. In June 2017, LivaNova received FDA approval of its VNS Therapy system in patients as young as four years of age with partial onset seizures that are refractory to antiepileptic medications. This expansion of the FDA indication for use in Epilepsy supports re-review of the HCA coverage policy with respect to expanding coverage for patients with medically refractive Epilepsy to age four and above.

LivaNova welcomes the opportunity to provide this new evidence to the HTCC in support of the re-review of VNS Therapy.

Sincerely,

Cindy Zajac

Cynthia Zajac, MA, BSEd, RN, LPC

Director of Market Access & Payer Relations

LivaNova USA, Inc.

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LivaNova USA, Inc.
100 Cyberonics Blvd
Houston, TX 77058

March 27, 2018

Sue Birch
Director
Washington State Health Care Authority
Cherry Street Plaza
626 8th Avenue SE
Olympia, WA 98501

Dear Director Birch:

Mental Health America (MHA) respectfully requests the Washington State Health Care Authority re-review coverage for Vagus Nerve Stimulation (VNS) for Treatment-Resistant Depression (TRD).

MHA – founded in 1909 – is the nation's leading community-based nonprofit dedicated to addressing the needs of those living with mental illness and to promoting the overall mental health of all Americans. Our work is driven by our commitment to promote mental health as a critical part of overall wellness, including prevention services for all, early identification and intervention for those at risk, integrated care, services, and supports for those who need it, with recovery as the goal. While depression is one of the greatest contributors to disability in the United States, individuals with TRD experience worse quality of life, greater risk of suicide attempts, and higher health care utilization and costs than their remitted counterparts.

MHA believes that individuals should have access to the full range of effective treatment options for their mental health conditions, and this is especially the case for individuals with TRD, for whom many common treatment options have failed. Additional evidence published since the last Health Technology Clinical Committee review merits re-review of coverage for VNS for TRD by the Washington State Health Care Authority.

MHA looks forward to working with Washington State Health Care Authority on ensuring that patients have access to effective care that meets their needs, and please do not hesitate to contact Nathaniel Z. Counts, J.D., Associate Vice President of Policy for MHA, at ncounts@mentalhealthamerica.net for follow-up or questions.

Sincerely,

Nathaniel Z Counts, J.D.
Associate VP of Policy
Mental Health America
ncounts@mentalhealthamerica.net

American Association of Neurological Surgeons

Congress of Neurological Surgeons

WSANS Washington State Association of Neurological Surgeons

March 27, 2019

Josiah Morse, MPH, Program Director
Washington State Health Care Authority
Health Technology Assessment Program
P.O. Box 42712
Olympia, WA 98504-2712

Via e-mail: shtap@hca.wa.gov

Subject: Washington State Health Care Authority Proposal for Re-review of Vagus Nerve Stimulation (VNS) for Epilepsy and Depression

Dear Mr. Morse:

On behalf of the American Association of Neurological Surgeons (AANS), the Congress of Neurological Surgeons (CNS), the American Society for Stereotactic and Functional Neurosurgery (ASSFN) and the Washington State Association of Neurological Surgeons (WSANS), we wish to express our support for the inclusion of vagus nerve stimulation (VNS) for epilepsy and treatment-resistant depression (TRD) on the list of procedures for re-review by the Washington State Health Care Authority (HCA) Health Technology Assessment (HTA) program in 2019. We agree with the HCA that new evidence has become available since the HTA program decision in 2009 not to cover VNS for depression.

Despite decades of research, patients with treatment-resistant depression (TRD) continue to have very limited options. We are pleased to see that the Washington State HTA program has recognized that additional evidence exists for VNS for TRD and we hope the review will result in a policy that will permit more patients in the state of Washington to have access to this important treatment option for their TRD. We believe the current literature is robust and shows clear evidence of efficacy and cost-benefit for VNS for TRD. As part of the Food and Drug Administration (FDA) approval process in 2005 and since that time, a strong body of evidence has been developed for VNS for TRD. With suicide continuing to be among the top ten causes of death in the United States, we urge the HCA to make this potentially life-saving procedure available to appropriately selected patients without undue burden on the patient or the treating surgeon.

Organized neurosurgery has been active in reviewing, commenting on and attending meetings regarding procedures under consideration by the HCA HTA program for over a decade. We share a common dedication to safe and effective treatments, and nothing is more important to our members than the well-being of their patients. We are pleased the HCA has recognized the existence of new data and will review and consider reversing its 2009 decision not to cover VNS for depression. We note that the Centers for Medicare & Medicaid Services (CMS) has recently changed its non-coverage policy to permit coverage for patients enrolled in a clinical trial. While we agree that coverage for study patients is better than no coverage at all, we do not believe that requiring a prospective randomized controlled trial that will duplicate pivotal studies that have already shown VNS for TRD to be safe and effective is necessary. We would, therefore, urge the HCA to cover VNS for TRD and to consider less onerous options for further evidence development, such as participation in clinical registries. Gathering real-world

experience outside of the study setting would be more useful than restricting coverage to study populations.

Thank you for considering our recommendations and for including a reconsideration of the 2009 non-coverage policy for VNS for TRD on the list of policies for review in 2019. If you have any questions or need additional information, please do not hesitate to contact us.

Sincerely,

[redacted]

Shelly D. Timmons, MD, PhD, FAANS, President
American Association of Neurological Surgeons

[redacted]

Ganesh Rao, MD, FAANS, President
Congress of Neurological Surgeons

[redacted]

Robert E. Gross, MD, PhD. FAANS, President
American Society for Functional and Stereotactic Neurosurgery

[redacted]

Jean-Christophe Leveque, MD, President
Washington State Association of Neurological Surgeons

Staff Contact:

Catherine Jeakle Hill
Senior Manager, Regulatory Affairs
AANS/CNS Washington Office
25 Massachusetts Avenue, NW, Suite 610
Washington, DC 20001
Phone: 202-446-2026
E-mail: chill@neurosurgery.org

[redacted]

From: Telles, Mark <mark.telles@abbott.com>
Sent: Friday, March 29, 2019 9:24 AM
To: HCA ST Health Tech Assessment Prog
Subject: WA – Health Technology Assessment / Prospective HTA technology topics (new & re-review)
Attachments: ACCURATE Deer 2017.pdf; NACC_Appropriate Use of DRG Stim_Deer_2018.pdf; Deer 2019 Safety analysis of DRG stimulation chronic pain.pdf

In the recent announcement regarding prospective HTA's, including Topics considered but not proposed - we reviewed and while our area of interest is not considered we wanted to make sure that you have most updated clinical data - please find attached data regarding Dorsal Root Ganglion

Topics considered, not proposed Technology

1 Dorsal root ganglion stimulation
2 Non-invasive testing: fibrosis for patients with chronic Hepatitis C
3 Balloon tubuloplasty for eustachian tube dysfunction
4 Percutaneous heart pump

Abbott

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Research Paper

PAIN

OPEN

Dorsal root ganglion stimulation yielded higher treatment success rate for complex regional pain syndrome and causalgia at 3 and 12 months: a randomized comparative trial

Timothy R. Deer[a,*], Robert M. Levy[b], Jeffery Kramer[c], Lawrence Poree[d], Kasra Amirdelfan[e], Eric Grigsby[f], Peter Staats[g], Allen W. Burton[h], Abram H. Burgher[i], Jon Obray[j], James Scowcroft[k], Stan Golovac[l], Leonardo Kapural[m], Richard Paicius[n], Christopher Kim[a], Jason Pope[a], Thomas Yearwood[o], Sam Samuel[p], W. Porter McRoberts[q], Hazmer Cassim[r], Mark Netherton[s], Nathan Miller[t], Michael Schaufele[u], Edward Tavel[v], Timothy Davis[w], Kristina Davis[c], Linda Johnson[c], Nagy Mekhail[p]

Abstract

Animal and human studies indicate that electrical stimulation of dorsal root ganglion (DRG) neurons may modulate neuropathic pain signals. ACCURATE, a pivotal, prospective, multicenter, randomized comparative effectiveness trial, was conducted in 152 subjects diagnosed with complex regional pain syndrome or causalgia in the lower extremities. Subjects received neurostimulation of the DRG or dorsal column (spinal cord stimulation, SCS). The primary end point was a composite of safety and efficacy at 3 months, and subjects were assessed through 12 months for long-term outcomes and adverse events. The predefined primary composite end point of treatment success was met for subjects with a permanent implant who reported 50% or greater decrease in visual analog scale score from preimplant baseline and who did not report any stimulation-related neurological deficits. No subjects reported stimulation-related neurological deficits. The percentage of subjects receiving ≥50% pain relief and treatment success was greater in the DRG arm (81.2%) than in the SCS arm (55.7%, $P < 0.001$) at 3 months. Device-related and serious adverse events were not different between the 2 groups. Dorsal root ganglion stimulation also demonstrated greater improvements in quality of life and psychological disposition. Finally, subjects using DRG stimulation reported less postural variation in paresthesia ($P < 0.001$) and reduced extraneous stimulation in nonpainful areas ($P = 0.014$), indicating DRG stimulation provided more targeted therapy to painful parts of the lower extremities. As the largest prospective, randomized comparative effectiveness trial to date, the results show that DRG stimulation provided a higher rate of treatment success with less postural variation in paresthesia intensity compared to SCS.

Keywords: Chronic pain, Neurostimulation, Complex regional pain syndrome, Causalgia, Dorsal root ganglion stimulation

1. Introduction

The prevalence of neuropathic pain refractory to the current standard of care has been estimated to be 1.5% of the general population.[26] Spinal cord stimulation (SCS), for which electrodes are placed into the dorsal epidural space, is an available treatment of a variety of chronic neuropathic pain conditions such as failed back surgery syndrome and complex regional pain syndrome (CRPS).[8]

Specific challenges for SCS remain, especially for pain conditions such as CRPS I and causalgia that differ by etiology and symptom profile from other chronic pain syndromes. An estimated 40% to 50% of CRPS subjects achieved clinically meaningful pain relief with SCS.[11,14] Similar rates of successful pain relief are reported for heterogeneous populations that contain a significant CRPS population.[23] Less than optimal

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results for some patients may be due to limitations of the selective targeting capabilities of SCS, unpleasant paresthesia, or from different mechanisms of action.

Lack of precision with SCS is attributed to shunting of energy by the cerebral spinal fluid, positional variations in stimulation, segmentation of spinal sensory input, and lead migrations postimplantation.[18] In some cases, these challenges can be addressed with improved surgical techniques and device programming, but pain related to CRPS and causalgia remains difficult to treat; many SCS patients do not achieve high-level pain relief, despite efforts to improve techniques and programming.[14]

The dorsal root ganglion (DRG) plays a key role in the development and maintenance of neuropathic pain.[13] The DRG, located between every spinal nerve and the spinal cord on the posterior root, houses the somas of the primary sensory neurons. These somas process and transmit sensory information from the periphery to the central nervous system. Animal models of chronic pain have shown that pathophysiologic changes occur in the DRG, including altered electrophysiological membrane properties, altered expression of integral membrane proteins, and altered expression of various genes that contribute to the hyperexcitability of neurons.[15] The combination of the DRG's sensory function and accessibility through familiar epidural approaches make it an ideal target for neurostimulation. Pain therapies targeting the DRG included radiofrequency frequency ablation, steroid injections, and ganglionectomy.[8]

Initial evidence with 8 CRPS patients suggested that DRG stimulation may be successful in a larger proportion of subjects than SCS (71% vs 50%).[28] Thus, the ACCURATE study, a randomized, controlled, multicenter trial, evaluated DRG stimulation compared to SCS stimulation for the treatment of chronic, intractable pain of the lower limbs attributed to CRPS or causalgia.

2. Methods

Under an Investigational Device Exemption, the ACCURATE study was designed as a prospective, randomized, controlled, multicenter study to evaluate the safety and efficacy of the DRG stimulation compared to traditional SCS for subjects with CRPS or causalgia (ClinicalTrials.gov: NCT01923285). The study was conducted in 22 US sites. Prior to any study initiation, all sites obtained approval from the institutional review board, and subjects were enrolled only after informed consent was obtained.

2.1. Patient selection

Subjects who had chronic, intractable neuropathic pain of the lower limbs associated with a diagnosis of CRPS or causalgia were screened and determined to be eligible according to the inclusion or exclusion criteria of the study (**Table 1**). Patients were diagnosed with CRPS type 1 based on the Budapest criteria.[12] Causalgia was defined as a painful condition arising from damage to a nerve resulting in chronic pain, generally restricted to the innervation pattern of the damaged nerve or nerves, which may or may not have secondary symptoms.[25] The diagnosis, in every case, was confirmed by an experienced medical monitor (N.M.) for strict adherence to these diagnostic criteria. Briefly, eligible subjects were naive to stimulation, had chronic, intractable pain for at least 6 months, tried and failed at least 2 prior pharmacologic treatments from 2 different drug classes, had stable neurologic function 30 days prior to screening, and were free from psychological pathology that contraindicated an implantable device. Subjects with changing or escalating pain condition or unstable use of pain medication 30 days prior to enrollment were not considered eligible to participate in the study. All subjects' medical, psychological, and imaging records were evaluated by an independent medical monitor to ensure appropriate patient selection.

2.2. Study design

After signing informed consent, subjects underwent a baseline evaluation to determine enrollment eligibility. After enrollment, subjects were randomized to either DRG stimulation (DRG group) or traditional SCS (SCS group) in a 1:1 ratio. Randomization was based on random, permuted blocks and stratified by study center. The study's centralized electronic data collection system provided the subjects' randomized group assignments after subjects were enrolled. Subjects, investigators, and study site staff were not blinded to subjects' assigned therapy. Subjects proceeded to a temporary trial stimulation phase (ranging from 3 to 30 days based on each site's standard of care), using the device type stipulated by their randomization. The average trial stimulation phase in the DRG group was 5.8 (SD 2.8) days and 5.8 (SD 5.1) days for the SCS group ($P = 0.206$, Wilcoxon test).

Successful trial stimulation was determined by the subject achieving at least a 50% lower limb pain relief during the trial phase and expressing a desire to go on to a permanent implant. Subjects who were successful during the trial phase were eligible to continue on to permanent implantation. Subjects who failed the trial stimulation phase were exited from the study. However, data from the trial failures were included as treatment failures for the composite treatment success end point at 3 months and at subsequent time points through 12 months. Subjects in both arms, who achieved a successful outcome during the trial phase, were implanted with a permanent device and were followed for 12 months, with follow-ups at 3, 6, 9, and 12 months postimplant. Subjects were not allowed to change the maximum daily dose of their prescribed chronic lower limb pain medications from baseline to the 3-month follow-up visit at which time the primary and secondary end points were ascertained. Postoperative reprogramming to optimize therapy was allowed for both groups at any time during the study, per standard of care for neuromodulation devices. Programming occurred by respective companies (Medtronic and Spinal Modulation) under the guidance of appropriate clinical and technical industry personnel.

2.3. Description of devices and implant procedures

Dorsal root ganglion stimulation was delivered by the AXIUM Neurostimulator System (Spinal Modulation; LLC, Menlo Park, CA, a wholly owned subsidiary of St Jude Medical), which was recently approved by the US Food and Drug Administration for spinal column stimulation via epidural and intraspinal lead access to the DRG as an aid in the management of moderate to severe chronic intractable pain of the lower limbs in adult patients with CRPS type I and causalgia. The system is composed of percutaneous leads designed to stimulate the DRG, an external trial pulse generator, and an implantable pulse generator.

Traditional SCS was delivered with a commercially available system (RestoreUltra and RestoreSensor; Medtronic, Minneapolis, MN) indicated for a number of chronic pain conditions including CRPS I and causalgia. Both devices were programmed by separate technicians for each arm such that the programming was performed by experienced personnel for the specific device to achieve optimal analgesia. See **Table 2** for a summary of programming parameters used during the study for both devices.

Table 1

Inclusion or exclusion criteria.

Inclusion criteria	Exclusion criteria
1. Subject is male or female between the ages of 22 and 75 y	1. Back pain is the greatest region of pain as measured on the baseline VAS
2. Subject is able and willing to comply with the follow-up schedule and protocol	2. Female subject of childbearing potential is pregnant or nursing, plans to become pregnant, or is unwilling to use approved birth control
3. Subject has chronic, intractable pain of the lower limb(s) for at least 6 mo	3. Subject has exhibited escalating or changing pain condition within the past 30 d as evidenced by investigator examination
4. Subjects are diagnosed with complex regional pain syndrome and/or peripheral causalgia	4. Subject is currently involved in medically related litigation, including workers compensation
5. Subjects have a minimum VAS >60 mm in the area of greatest pain in the lower limbs	5. Subject has had corticosteroid therapy at an intended site of stimulation within the past 30 d
6. Subject has failed to achieve adequate pain relief from at least 2 prior pharmacologic treatments from at least 2 different drugs classes	6. Subject's pain medication(s) dosage(s) is not stable for at least 30 d
7. Subject has had stable neurologic function in the past 30 d	7. Subject has had radiofrequency treatment of an intended target DRG within the past 3 mo
8. In the opinion of the investigator, the subject is psychologically appropriate for the implantation of an active implantable medical device	8. Subject has previously failed spinal cord stimulation therapy
9. Subject is able to provide written informed consent	9. Subject currently has an active implantable device including ICD, pacemaker, spinal cord stimulator, or intrathecal drug pump or subject requires MRI or diathermy
	10. Subject has pain only within a cervical distribution
	11. Subject has cognitive, physical, or sensory impairment that, in the opinion of the investigator, may limit their ability to operate the device
	12. Subject currently has an indwelling device that may pose an increased risk of infection
	13. Subject currently has an active systemic infection
	14. Subject has, in the opinion of the investigator, a medical comorbidity that contraindicates placement of an active medical device
	15. Subject has participated in another clinical investigation within 30 d
	16. Subject has a coagulation disorder or uses anticoagulants that, in the opinion of the investigator, precludes participation
	17. Subject has been diagnosed with cancer in the past 2 y
	18. Imaging (MRI, computed tomography, and x-ray) findings within the last 12 mo that, in the investigator's opinion, contraindicates lead placement
	19. Subject is a prisoner

DRG, dorsal root ganglion; ICD, implantable cardioverter defibrillator; MRI, magnetic resonance imaging; VAS, visual analog scale.

Standard procedures for trial and permanent implantations were used in the study. Dorsal root ganglion leads were placed in the lateral epidural space near the target DRG at levels from T10 to S2, depending on the dermatomal target corresponding to the subject's primary region of pain. Spinal cord stimulation leads were placed in the medial or paramedial epidural space such that the caudal-most electrical contact was not caudal to the top of the L1 vertebral body on an anterior–posterior fluoroscopic view. Depending on the anatomical target, up to 16 contacts were placed for both study arms. Intraoperative testing to determine stimulation overlap with subjects' painful areas was conducted during implantation. **Figure 1** shows the lead placements for both groups. **Table 3** summarizes the number and placement of leads for subjects in the study.

2.4. Sample size calculation and analysis populations

Sample size was determined based on the planned noninferiority test for the composite safety and effectiveness primary end point of treatment success. Treatment success was defined as ≥50% reduction in the visual analog scale (VAS) score in the primary area of pain during both trial and the 3-month visits with no incidence of stimulation-induced neurological deficits. Pilot data with 8 CRPS subjects and 22 causalgia subjects indicated that the success rate of DRG, defined as a 50% reduction in pain intensity, was 87% for CRPS subjects and 77% for causalgia subjects. Thus, an observed success rate at of least 15% above the 50% rate reported for SCS subjects was expected.[14,28] Accounting for 15% attrition, an estimated 152 subjects (76 subjects in each arm) would provide greater than 85% power to test the primary end point hypothesis with a noninferiority margin of 10%.

The primary, secondary, and tertiary effectiveness analyses were based on the modified intention-to-treat (MITT) population including all randomized subjects who participated in the trial procedure (73 in each group). The MITT population was based on standard intention-to-treat principles, wherein subjects were analyzed based on their initial randomized treatments. The binary composite end points for success included subjects who failed the trial evaluation and exited the study as treatment failures.

Table 2

Programming settings.

	3 mo		6 mo		9 mo		12 mo	
	DRG	SCS	DRG	SCS	DRG	SCS	DRG	SCS
No. of subjects with available data	59	54	59	52	55	49	55	50
Frequency or rate range, Hz								
Mean (±SD)	20.8 (7.1)	65.5 (111.2)	20.0 (6.8)	63.6 (54.3)	19.0 (5.5)	72.0 (102.1)	19.0 (5.1)	63.6 (48.7)
Min, max	10.0, 48.0	10.0, 1200.0	10.0, 48.0	10.0, 500.0	8.0, 40.0	15.0, 1000.0	10.0, 36.0	2.0, 3600.0
Pulse width, μs								
Mean (±SD)	306.4 (148.1)	408.2 (191.0)	315.4 (166.0)	432.5 (183.0)	295.6 (140.7)	432.6 (193.9)	289.8 (133.8)	417.1 (172.7)
Min, max	30.0, 1000.0	60.0, 1000.0	60.0, 1000.0	90.0, 1000.0	90.0, 1000.0	60.0, 1000.0	90.0, 1000.0	60.0, 1000.0
Amplitude, μA								
Mean (±SD)	915.4 (822.0)	3288.8 (2255.2)	822.3 (724.0)	3590.4 (1912.6)	764.6 (630.9)	3304.1 (1848.8)	827.4 (657.1)	2929.7 (2024.3)
Min, max	75.0, 6000.0	0.0, 9533.1	1.0, 4600.0	0.0, 10,076.3	100.0, 3950.0	0.0, 13,380.1	75.0, 4000.0	0.0, 12,659.8

DRG, dorsal root ganglion; SCS, spinal cord stimulation.

Safety data tabulations are based on the intention-to-treat analysis set including all randomized subjects (76 in each group).

2.5. Data collection and general statistical methods

Patient demographics and medical history were collected at baseline. At baseline and at each study visit, physical and neurological examinations, along with medication utilization, were recorded by study staff. Pain intensity was measured at baseline and at each study visit using the 100-mm visual analog scale (VAS), ranging from 0 (no pain) to 100 (worst imaginable pain) where higher scores represent greater pain severity. At baseline and each study visit, assessments of quality of life, psychological disposition, and experiential factors (measures described in detail below) were completed. All adverse events (AEs) through 12 months were reported and the occurrence of any stimulation-related neurological deficits was documented.

Descriptive statistics are presented as number of subjects, mean, SD, median, and range for all continuous variables and the number and percentage of subjects for categorical variables. As stipulated by the protocol and with the exception of the primary end point analysis, DRG stimulation and SCS were compared using a 2-sample *t* test (or Wilcoxon rank-sum test) for continuous outcomes and Pearson χ^2 test (or Fisher exact test) for categorical outcomes. Choice of parametric or alternative tests was based on the data distributions for each measure, and the test used is reported in the results. Two-sided confidence intervals are also provided for certain outcome measures of interest to assess differences between the treatment arm and the control arm.

2.6. Primary composite end point

The predefined primary composite end point of the study was treatment success rates for the DRG subjects compared to the SCS subjects. To be considered a treatment success (1) a subject had a successful trial reporting ≥50% reduction in VAS score from baseline to the end of the trial phase, (2) reported a VAS

Table 3

Summary of permanent leads implanted.

	DRG	SCS
No. of leads implanted per subject, n/N (%)		
0	3/61 (4.9)	0/54 (0.0)
1	12/61 (19.7)	4/54 (7.4)
2	37/61 (60.7)	50/54 (92.6)
3	4/61 (6.6)	—
4	5/61 (8.2)	—
Lead location, n/N (%)*		
T7	—	1/54 (1.9)
T8	—	4/54 (7.4)
T9	—	10/54 (18.5)
T10	0/0 (0)	15/54 (27.8)
T11	1/61 (1.6)	12/54 (22.2)
T12	3/61 (4.9)	20/54 (37.0)
L1	11/61 (18.0)	—
L2	15/61 (24.6)	—
L3	13/61 (21.3)	—
L4	28/61 (45.9)	—
L5	32/61 (52.5)	—
S1	1/61 (1.6)	—
S2	0/0 (0)	—

* Subjects could have up to 4 leads in the DRG group and 2 leads in the SCS group. Leads were placed to target the subject's painful areas at one or multiple levels; spinal level categories are not mutually exclusive.
DRG, dorsal root ganglion; SCS, spinal cord stimulation.

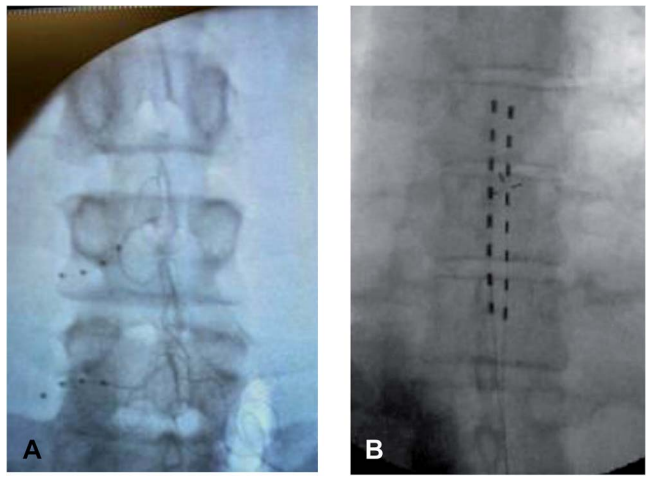

Figure 1. Lead placement. The lead for dorsal root ganglion (DRG) stimulation is specialized to provide percutaneous entry through the epidural space, exiting through the foramen, and resting around the DRG. As shown in panel A, DRG leads were placed in the lateral epidural space near the target DRG. For the SCS arm (panel B), leads were placed in the medial or paramedial epidural space such that the caudal-most electrical contact was not caudal to the top of the L1 vertebral body on an anterior–posterior fluoroscopic view. Depending on the anatomical target, up to 16 contacts were placed for both study arms. Intraoperative testing to determine paresthesia overlap over pain areas was conducted during trial evaluation period.

score at 3 months that was reduced from preimplant baseline by ≥50%, and (3) did not experience a stimulation-related neurological deficit during either the trial phase or after permanent implant. A stimulation neurological deficit, different from AEs, was defined as a measurable 2-point worsening on the in-clinic sensory and motor neurological examination, within the appropriate concordant anatomy, that was induced by stimulation and subsided in the absence of stimulation for at least 24 hours. Sensory and motor examinations were conducted by the physician and rated as 2 (normal function), 1 (decreased function), or 0 (abnormal function); a score of 0 would indicate neurological deficit. No neurological deficits, as defined, were recorded for any subjects in either arm of the study. In addition, if a subject withdrew from the study due to a device-, procedure-, or stimulation-related AE, the subject was treated as a failure in the primary end point analysis.

As prespecified, the primary end point analyzed the success rate between the two treatment arms using Blackwelder methods for testing noninferiority between 2 proportions at a one-sided significance of 0.05.[3] The noninferiority margin was set at 10%. If noninferiority of the primary end point was achieved, a superiority test was performed at a one-sided significance level of 0.025.

2.7. Secondary end point

2.7.1. Positional effects on paresthesia intensity

Paresthesia intensity, a prespecified secondary end point, was assessed at 3 months. Paresthesia intensity was rated by subjects using a previously published paresthesia intensity rating scale.[16] Subjects rated the intensity of their perception of paresthesia, while upright and supine, on an 11-point numeric rating scale from 0 representing "No feeling" to 10 "Very intense." Perceived paresthesia intensity difference between supine and upright positions was calculated and averaged across each group This end point was evaluated at a 2-sided significance level of 0.05.

2.8. Other end points

2.8.1. Short-Form-36

The Short-Form-36 (SF-36) is a self-reported health-related quality-of-life scale with 36 questions that yield scores on 8 dimensions of quality of life including physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health.[27,29] These 8 dimensions also are combined to provide 2 summary scales for physical health (Physical Component Summary) and mental health (Mental Component Summary). Improvements on the SF-36 scale are represented by increased scores. Within- and between-group improvements were examined using the calculated change from baseline for each subscale or summary scales.

2.8.2. Profile of mood states

The profile of mood states (POMS) scale is a 65-item, 5-point Likert scale that measures mood states overall (total mood disturbance) as well as for 6 domains: tension, depression, anger, vigor, fatigue, and confusion. Higher scores indicate more negative mood states except for the vigor domain where higher scores indicate increased vigor.[6] Within- and between-group improvements were examined using the calculated change from baseline for each domain and the total POMS score.

2.8.3. Brief pain inventory

The brief pain inventory (BPI) measures pain severity in the last 24 hours on a numeric pain rating scale from 0 "No pain" to 10 "Pain as bad as you can imagine," and interference due to pain from 0 "Does not interfere" to 10 "Completely interferes."[5] The interference score was calculated as the mean of the interference items, and 2 subscales for the activity dimension and the affective dimensions of interference were tabulated. Within- and between-group improvements were examined using the calculated change from baseline for the pain and interference scales and for each interference subscale.

2.8.4. Subject satisfaction

Subjects completed a satisfaction scale at the end of trial phase and at 3, 6, and 12 months. Subjects rated satisfaction with pain relief and the therapy in general on an 11-point numeric rating scale with 0 indicating "Not Satisfied" and 10 indicating "Very Satisfied." Subjects rated the likelihood of undergoing the therapy again on an 11-point numeric rating scale with 0 indicating "Not Likely" and 10 indicating "Very Likely." Finally subjects rated the their subjective change in pain since baseline on a 7 point scale ranging from "Much Worse" to "Much Better." Ratings were treated as interval data and summarized with descriptive statistics of central tendency.

2.8.5. Stimulation specificity

Stimulation specificity was evaluated to determine the extent to which paresthesia was felt by subjects in anatomical regions that were not painful at baseline. The pain and paresthesia diagram forms had identical diagrams of the human body on which subjects marked where they felt pain and paresthesia. The baseline pain diagrams completed by the subjects were compared to the subjects' paresthesia maps completed at the end of trial phase and at 3 months postimplant. Subjects were categorized based on the presence or absence of one or more paresthesia areas at follow-up that were not coincident with a pain area at baseline.

2.8.6. Percentage change in visual analog scale

The percentage of change in VAS score from baseline to each scheduled follow-up was computed for each subject and inspected using descriptive statistics and confidence intervals. Missing data were not imputed for this analysis; only subjects with VAS scores at baseline and follow-up were included in the analysis.

2.9. Safety analysis

Adverse events were collected and tabulated at all scheduled or unscheduled visits during the study. An AE was defined as any unfavorable and/or unintended sign, symptom or disease temporarily associated with the use of the implanted device, whether or not related to the device. A serious adverse event (SAE) was defined as any AE that is immediately life threatening; results in significant, persistent, or permanent disability; necessitates invasive intervention to prevent permanent impairment or death; results in the need for a 24-hour hospital stay or prolongation of a hospital stay; or results in death. Adverse event and SAE rates are expressed as the number of patients divided by the population at risk for each group (n = 76) through the 12-month study visit. All AEs reported were reviewed by an

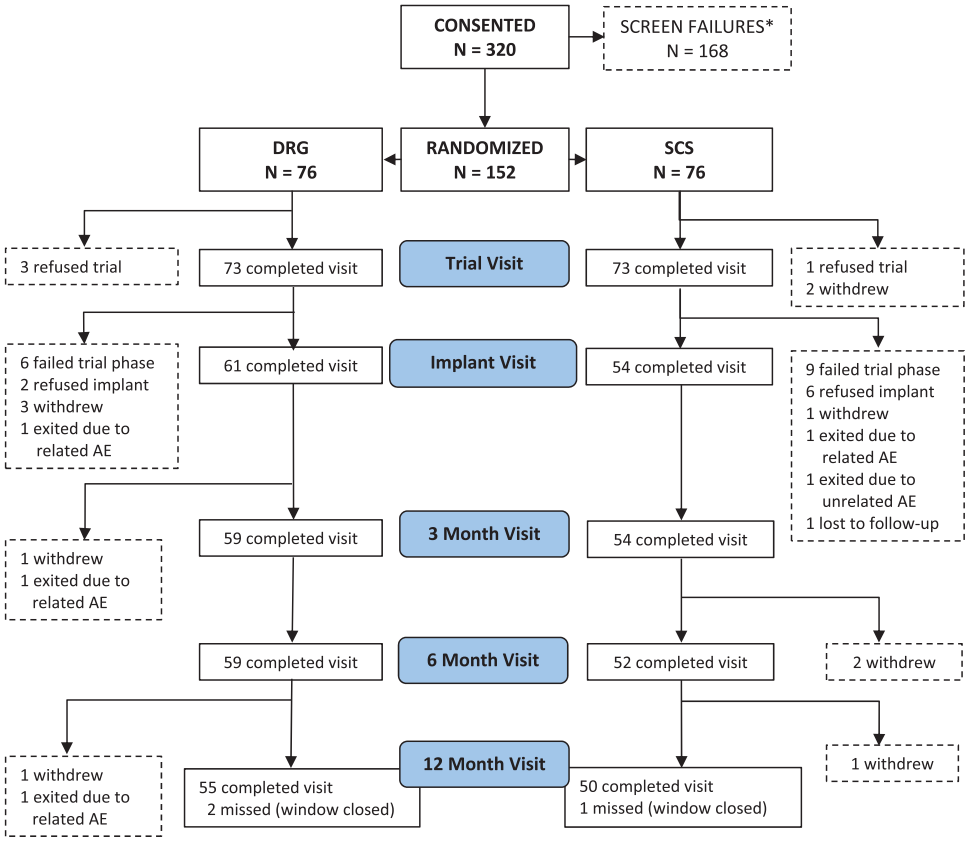

Figure 2. CONSORT diagram. *Subjects were enrolled if they met the inclusion criteria for the study. After consent, subjects were screened per exclusion criteria and exited if violations were revealed. AE, adverse event; DRG, dorsal root ganglion; SCS, spinal cord stimulation.

independent event committee that coded and adjudicated each event with regard to seriousness and relatedness to the implant procedure, device, and/or stimulation therapy.

3. Results

3.1. Patient accounting

See CONSORT diagram for full accounting (**Fig. 2**). Briefly, 320 subjects were consented and enrolled in the study from 22 investigational sites. Of these subjects, 168 were excluded for screen failures because they failed to meet the study's inclusion or exclusion criteria with the majority failing to meet the diagnostic criteria for inclusion. The remaining 152 subjects were enrolled and randomized to either the DRG or the SCS arm (76 in each arm). After randomization, 3 subjects from each group did not continue to the trial evaluation phase. Subjects who failed the success criterion at the end of the trial phase were exited from the study and considered treatment failures for composite end point analyses. A total of 61 DRG subjects and 54 SCS subjects met the success criteria at the end of their trial phase and continued to permanent implant. By the 12-month visit, 55 DRG subjects and 50 SCS subjects had evaluable data.

On average, each active study site randomized 3 subjects (range 0, 9) to each arm of the study. At any one site, the maximum number of randomized subjects was 11% (17/152) of the MITT population.

3.2. Baseline characteristics

The average age of subjects was 52.4 years in the DRG stimulation arm and 52.5 years in the SCS arm. There were slightly more females than males in both arms (51.3% for both arms). Race was predominantly white (94.7% and 92.1% for DRG and SCS, respectively). Average body mass index was 30.5 for DRG and 28.9 for SCS. The average duration of chronic lower limb pain was 7.5 years for the DRG arm and 6.8 years for the SCS arm. Comorbidities and medications taken for subject conditions were similar in both arms. Overall, no statistically significant differences were found among the baseline characteristics between treatment arms. See **Table 4** for a detailed summary of baseline characteristics.

Similar distribution of CRPS (DRG: 44/76 [57.9%]; SCS: 43/76 [56.6%]) and causalgia (DRG: 32/76 [42.1%]; SCS: 33/76 [43.4%]) was reported between the arms. All CRPS subjects had sensory symptoms, 82/87 (94.3%) had motor trophic symptoms, 57/87 (65.5%) had vasomotor symptoms, and 58/87 (66.7%) had sudomotor or edema symptoms. A total of 79 of the 87 CRPS subjects had at least one symptom in each of 3 symptom categories documented at baseline; 8 CRPS subjects (3 in the DRG group and 5 in the SCS group) had one symptom in each of 2 symptom categories documented at the time of the baseline evaluation (sensory and motor). In the 8 subjects with only 2 secondary symptoms (sensory and motor) at enrollment, the medical monitor indicated that the reason that sudomotor or edema and vasomotor symptoms were not present at enrollment was a manifestation typically evident in the acute or early phase of the disease. The 8 patients who were enrolled in the study with only 2 symptoms documented had a range of 3 to 11 years

Table 4

Baseline demographics and characteristics.

	DRG	SCS
Age, y		
Mean (±SD)	52.4 (12.7)	52.5 (11.5)
Median (min, max)	53.2 (23.9, 75.8)	53.0 (25.4, 75.9)
Sex, n (%)		
Female	39/76 (51.3)	39/76 (51.3)
Race (not mutually exclusive), n/N (%)		
American Indian or Alaska Native	0/76 (0.0)	1/76 (1.3)
Asian	0/76 (0.0)	0/76 (0.0)
Black or African American	2/76 (2.6)	3/76 (3.9)
Native Hawaiian or Other Pacific Islander	1/76 (1.3)	0/76 (0.0)
White	72/76 (94.7)	70/76 (92.1)
Other	1/76 (1.3)	2/76 (2.6)
Ethnicity, n/N (%)		
Hispanic or Latino	4/76 (5.3)	8/76 (10.5)
Not Hispanic or Latino	72/76 (94.7)	68/76 (89.5)
BMI, kg/m^2		
Mean (±SD)	30.5 (7.2)	28.9 (6.0)
Median (min, max)	29.9 (16.9, 54.0)	27.9 (17.4, 44.6)
Primary region of pain, n/N (%)		
Right groin	4/76 (5.3)	2/76 (2.6)
Left groin	4/76 (5.3)	7/76 (9.2)
Right buttock	1/76 (1.3)	2/76 (2.6)
Left buttock	2/76 (2.6)	2/76 (2.6)
Right leg	14/76 (18.4)	16/76 (21.1)
Left leg	8/76 (10.5)	11/76 (14.5)
Right foot	21/76 (27.6)	19/76 (25.0)
Left foot	22/76 (28.9)	17/76 (22.4)

BMI, body mass index; DRG, dorsal root ganglion; SCS, spinal cord stimulation.

Table 5

Injured nerves for causalgia subjects.

Injured nerve, n/N (%)	DRG	SCS	Total
Digital	—	2/33 (6.0)	2/65 (3.1)
Femoral	4/32 (12.5)	3/33 (9.0)	7/65 (10.8)
Femoral and saphenous	—	1/33 (3.0)	1/65 (1.5)
Femoral and sciatic	1/32 (3.1)	1/33 (3.0)	2/65 (3.1)
Fibular and L5 spinal	—	1/33 (3.0)	1/65 (3.1)
Pudendal and ilioinguinal	1/32 (3.1)	—	1/65 (3.1)
Genitofemoral and ilioinguinal	—	1/33 (3.0)	1/65 (3.1)
Ilioinguinal	4/32 (12.5)	7/33 (21.2)	11/65 (17.0)
Ilioinguinal and testicular plexus	—	1/33 (3.0)	1/65 (3.1)
Infrapatellar and saphenous	1/32 (3.1)	—	1/65 (3.1)
Peroneal	6/32 (18.8)	7/33 (21.2)	13/65 (20)
Peroneal and plantar	2/32 (6.3)	2/65 (3.1)	—
Peroneal and saphenous	2/32 (6.3)	2/65 (3.1)	—
Peroneal and superficial	—	1/33 (3.0)	1/65 (3.1)
Peroneal and sural	—	1/33 (3.0)	1/65 (3.1)
Plantar	4/32 (12.5)	1/33 (3.0)	5/65 (7.7)
Plantar and tibial	1/32 (3.1)	—	1/65 (3.1)
Sciatic	2/32 (6.3)	3/33 (9.0)	5/65 (7.7)
Sciatic saphenous	—	1/33 (3.0)	1/65 (3.1)
Sural	1/32 (3.1)	2/33 (6.0)	3/65 (4.6)
Tibial	3/32 (9.4)	—	3/65 (4.6)
Grand total	32/32 (100)	33/33 (100)	65/65 (100)

DRG, dorsal root ganglion; SCS, spinal cord stimulation.

of history of CRPS before enrollment. For subjects diagnosed with causalgia the injured nerves are documented in **Table 5**.

3.3. Primary composite end point

Figure 3 summarizes the primary composite end point results at 3 months, when the primary end point was ascertained, as well as over time through 12 months. No neurological deficits were reported during the study, so the rates of success at each time point include those subjects with a permanent implant who reported at least a 50% reduction in VAS from preimplant levels. Randomized subjects who did not proceed to permanent implant were considered treatment failures for this end point at each study visit. The proportion of subjects who achieved treatment success at 3 months in the DRG arm (81.2%; 56/69) was statistically greater than the SCS arm (55.7%; 39/70). The results demonstrated that DRG stimulation met not only noninferiority ($P < 0.0001$) but also statistical superiority ($P < 0.0004$). Long term, the proportion of subjects who achieved treatment success at 12 months in the DRG arm (74.2%; 49/66) also was greater than that in the SCS arm (53.0%; 35/66); these results demonstrated both noninferiority ($P < 0.0001$) and superiority ($P < 0.0004$) at the long-term follow-up.

Similar results were observed at 3 months when the primary end point was stratified by primary diagnoses. For CRPS, a greater proportion of DRG subjects (82.5%) met the primary end point at 3 months than SCS subjects (57.5%) (noninferiority, $P < 0.001$; superiority, $P = 0.006$). For causalgia, the proportion of subjects who met the primary end point was higher for DRG (79.3%) than for SCS (53.3%) (noninferiority, $P = 0.001$; superiority, $P = 0.014$).

3.4. Secondary end point

On average, DRG subjects experienced significantly less postural variation in perceived paresthesia intensity than the SCS subjects ($P < 0.001$) at 3 months. Dorsal root ganglion subjects reported a mean difference between supine and upright paresthesia intensity rating of -0.1 ± 1.6, and SCS subjects had a mean difference of 1.8 ± 3.0. These results persisted throughout the study (**Fig. 4**).

3.5. Other end points

3.5.1. Short-Form-36

Table 6 summarizes the SF-36 results. Both the DRG stimulation and SCS groups experienced improvements in SF-36 scores from baseline to 3 months ($P < 0.05$) and 12 months, with the one exception that the General Health scale was not significantly improved at 12 months in the SCS group ($P > 0.05$).

At 3 months, the change in the mental health dimension was statistically better for DRG stimulation subjects compared to SCS subjects ($P = 0.0295$). At 12 months, DRG subjects had statistically greater improvement on 3 scales: overall change in the physical component score ($P = 0.04$), general health ($P = 0.03$), and social functioning ($P = 0.03$) when compared to SCS subjects.

3.5.2. Profile of mood states

Both groups experienced improvements in all domains of the POMS from baseline to 3 months ($P < 0.05$). At 12 months, DRG subjects had statistically significant improvements in all scales

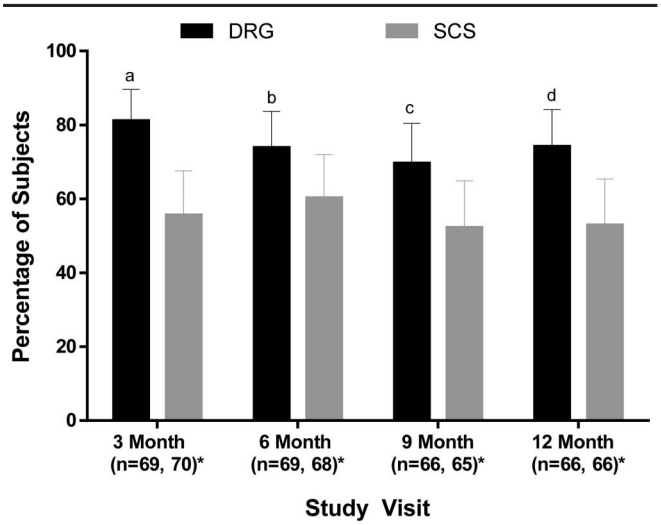

Figure 3. Proportion of subjects in each group who met the primary end point. The proportion of subjects who met the composite end point of success defined as 50% or greater pain reduction at both the trial phase and the indicated follow-up visit without a stimulation-related neurological deficit in the modified intent-to-treat population is shown. Subjects who exited the study after randomization were considered treatment failures. At all study visits, the proportion of subjects in the DRG stimulation group with successful therapy was noninferior to SCS (Blackwelder test of 2 proportions, all $P < 0.01$). Superiority was also established at each time point. [a]$P < 0.001$, [b]$P = 0.04$, [c]$P = 0.02$, and [d]$P = 0.005$. Error bars represent 95% confidence interval. *n for the DRG and SCS groups, respectively. DRG, dorsal root ganglion; SCS, spinal cord stimulation.

($P < 0.05$), and the SCS subjects had statistically significant improvements ($P < 0.05$) in all scales except for the depression and confusion scales compared to baseline.

Figure 5 presents the change in POMS scores through the 12-month visit. The changes in POMS scores from baseline to 3 months were statistically greater for DRG subjects than for SCS subjects for the Total Mood Disturbance scale ($P = 0.0466$) and the tension domain ($P = 0.0430$). Specifically, the Total Mood Disturbance at 3 months improved by a magnitude of 20.4 points (29.0 at baseline to 8.6 at 3 months) for DRG subjects, and only a magnitude of 14.7 points (25.6 at baseline to 10.9 at 3 months) for SCS subjects. These improvements in the Total Mood

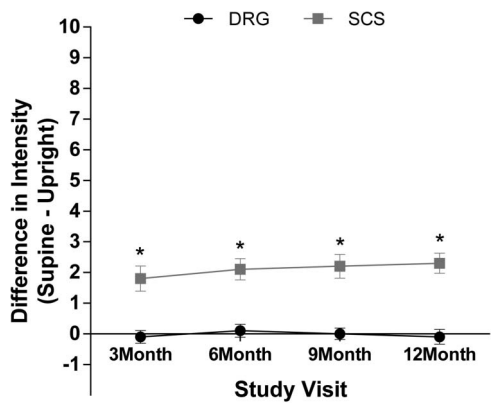

Figure 4. Postural variation in paresthesia intensity. Variation in the intensity of paresthesia was calculated as the difference in intensity during supine and upright positions, rated on an 11-point numerical rating scale. Wilcoxon test indicated that subjects using DRG stimulation had significantly less postural variation in paresthesia intensity than SCS subjects. *$P < 0.001$. DRG, dorsal root ganglion; SCS, spinal cord stimulation.

Disturbance and tension domain score for DRG subjects persisted to 12 months ($P = 0.021$ and $P = 0.004$, respectively). In addition, at 12 months, the depression ($P = 0.004$) and confusion ($P = 0.020$) domains also demonstrated statistically greater magnitudes of improvement for DRG subjects compared to the improvements for SCS subjects.

3.5.3. Brief pain inventory

As shown in **Table 7**, both groups experienced improvements in all of the BPI scales from baseline to 3 months ($P < 0.05$) and 12 months ($P < 0.05$). Between the 2 groups, improvements from baseline on the interference scale (treatment 4.2, control 3.0), the activity scale (treatment 4.5, control 3.4), and the affective scale (treatment 3.8, control 2.5) were statistically greater ($P < 0.05$) for DRG subjects compared to SCS subjects at 3 months. These results persisted to 12 months.

3.5.4. Subject satisfaction

The majority of patients in both groups reported high degrees of satisfaction (**Table 8**) for all 4 satisfaction items. However, no statistical significance was found between the groups for all items assessed ($P > 0.05$).

3.5.5. Stimulation specificity

At 3 months, SCS subjects were 2.3 times more likely to report feeling paresthesia in one or more nonpainful areas as DRG subjects (35.2% vs 15.3%, $P = 0.0142$). At 12 months postimplant, SCS subjects were 7.1 times more likely to report feeling paresthesia in one or more nonpainful areas as DRG subjects (38.8% vs 5.5%, $P < 0001$). The percent of subjects who reported that they felt paresthesia in only their painful region(s) at 3 and 12 months was 84.7% and 94.5% in the DRG group, and 64.8% and 61.2% in the SCS group.

3.5.6. Percentage change in visual analog scale

As shown in **Table 9**, DRG stimulation demonstrated a greater mean percent reduction in VAS scores than SCS (84.1% vs 70.9%, respectively) with the significant reduction persisting to 6 months and 12 months. Subjects using DRG reported mean VAS of 80.6 mm at baseline, which reduced to 13.1 mm at 3 months and remained low, at 15.0 mm, at 12 months. The subjects using SCS reported a baseline mean VAS of 80.7, 3-month mean VAS of 23.8 mm, and 12-month mean VAS of 26.5 mm.

3.6. Safety analysis

A total of 21 SAEs occurred in 19 subjects (8 DRG subjects and 11 SCS subjects). The rates of SAEs were 10.5% (8/76) in the DRG arm and 14.5% (11/76) in the SCS arm. The difference in the rate of SAEs between groups was not statistically different ($P = 0.62$). Two of the SAEs in the control group were adjudicated as definitely related to the implant procedure. Both events were infections that required device explant. There were no unanticipated SAEs or stimulation-induced neurological deficits at any time during the study. None of the subjects died.

Table 10 presents the rates of related AEs. Fifty two procedure-related events were reported by 35 patients (46.1%) in the DRG arm, and 29 procedure-related events were reported by 20 patients (26.3%) in the SCS arm, yielding a statistically significant difference between the groups ($P = 0.018$). Possible

Table 6

Change in Short-Form-36 scores from baseline through 12 months.

	3 mo		6 mo		9 mo		12 mo	
	DRG	SCS	DRG	SCS	DRG	SCS	DRG	SCS
No. of subjects*	59	54	59	52	55	49	55	50
Physical Component Summary								
Mean (SD)	11.8 (7.7)	9.4 (9.5)	11.1 (8.0)	8.6 (8.4)	10.7 (8.0)	8.6 (8.9)	11.5 (9.4)	8.0 (9.0)
Median	11.0	9.0	11.7	8.1	8.8	7.2	9.5	6.6
Difference between mean and 95% CI	2.5 (−0.7 to 5.7)		2.5 (−0.6 to 5.6)		2.1 (−1.2 to 5.4)		3.5 (−0.1 to 7.1)	
Mental Component Summary								
Mean (SD)	8.3 (11.2)	4.8 (10.2)	6.6 (13.2)	4.1 (10.2)	6.8 (13.7)	3.8 (11.1)	6.2 (12.3)	3.6 (11.1)
Median	9.4	4.2	6.4	3.5	6.5	1.9	4.7	2.6
Difference between mean and 95% CI	3.5 (−0.5 to 7.5)		2.5 (−2.0 to 7.0)		3.0 (−1.9 to 7.9)		2.6 (−1.9 to 7.1)	
Physical functioning								
Mean (SD)	27.1 (22.1)	19.5 (24.1)	26.2 (23.0)	19.0 (23.9)	26.7 (21.9)	20.8 (23.7)	26.6 (26.0)	17.7 (24.0)
Median	25.0	20.0	25.0	20.0	25.0	20.0	20.0	15.0
Difference between mean and 95% CI	7.6 (−1.2 to 16.4)		7.2 (−1.8 to 16.2)		6.0 (−3.1 to 15.0)		9.0 (−1.0 to 18.9)	
Role-physical								
Mean (SD)	38.9 (24.2)	28.6 (29.1)	33.9 (25.8)	28.1 (28.4)	33.9 (25.0)	27.1 (28.0)	30.4 (27.3)	24.6 (30.0)
Median	37.5	25.0	31.3	25.0	31.3	21.9	31.3	18.8
Difference between mean and 95% CI	10.3 (−0.7 to 21.3)		5.7 (−5.5 to 16.9)		6.9 (−4.5 to 18.2)		5.8 (−6.4 to 18.1)	
Bodily pain								
Mean (SD)	32.7 (20.7)	29.0 (22.8)	27.4 (20.6)	26.2 (25.2)	24.6 (20.9)	22.3 (24.1)	27.4 (24.0)	23.1 (25.5)
Median	30.0	29.0	29.0	29.0	21.0	19.0	29.0	19.0
Difference between mean and 95% CI	3.7 (−5.2 to 12.6)		1.2 (−8.2 to 10.7)		2.3 (−7.2 to 11.9)		4.2 (−6.2 to 14.7)	
General health								
Mean (SD)	10.9 (18.0)	6.3 (14.8)	11.7 (20.6)	2.3 (17.2)	9.5 (20.7)	3.3 (16.6)	13.0 (21.5)	2.9 (18.2)
Median	10.0	5.0	10.0	3.0	5.0	5.0	10.0	5.0
Difference between mean and 95% CI	4.6 (−1.6 to 10.8)		9.4 (2.2 to 16.6)‡		6.2 (−1.2 to 13.6)		10.1 (2.3 to 17.9)‡	
Vitality								
Mean (SD)	21.3 (21.9)	14.5 (18.2)	17.5 (20.2)	12.0 (18.5)	18.9 (22.0)	10.4 (16.8)	17.8 (24.2)	10.0 (20.3)
Median	21.9	12.5	18.8	12.5	18.8	12.5	18.8	12.5
Difference between mean and 95% CI	6.9 (−0.9 to 14.6)		5.5 (−2.0 to 13.1)		8.5† (0.7 to 16.3)		7.8 (−1.1 to 16.8)	
Social functioning								
Mean (SD)	28.9 (29.6)	19.8 (25.1)	24.5 (29.3)	18.3 (25.6)	25.3 (30.9)	16.9 (26.8)	23.0 (29.1)	13.1 (27.4)
Median	37.5	25.0	25.0	12.5	25.0	12.5	25.0	12.5
Difference between mean and 95% CI	9.1 (−1.9 to 20.1)		6.2 (−4.9 to 17.3)		8.4 (−3.6 to 20.4)		9.9 (−1.8 to 21.6)	
Role-emotional								
Mean (SD)	17.0 (28.2)	15.2 (28.4)	14.7 (33.6)	12.6 (27.2)	14.8 (34.1)	11.8 (32.4)	14.9 (32.2)	11.0 (30.7)
Median	12.5	8.3	12.5	8.3	12.5	4.2	12.5	0.0
Difference between mean and 95% CI	1.8 (−9.3 to 12.9)		2.2 (−10.0 to 14.3)		3.0 (−10.6 to 16.6)		3.9 (−8.9 to 16.8)	
Mental health								
Mean (SD)	15.5 (18.5)	8.1 (17.3)	11.9 (21.3)	6.7 (17.6)	12.6 (20.8)	8.3 (18.1)	13.7 (20.3)	8.6 (20.1)
Median	15.0	10.0	10.0	5.0	10.0	10.0	10.0	7.5
Difference between mean and 95% CI	7.5 (0.8 to 14.2)†		5.1 (−2.3 to 12.5)		4.4 (−3.3 to 12.0)		5.1 (−2.7 to 12.9)	

* Subjects with evaluable data; missing data not imputed.
† *t* test, $P < 0.05$.
‡ Wilcoxon test, $P < 0.05$.
CI, confidence interval; DRG, dorsal root ganglion; SCS, spinal cord stimulation.

contributors to the differential rate of procedure-related AEs are the procedure times and number of leads. Procedure times for permanent implant averaged 107.2 minutes (±51.2) for DRG subjects and 75.7 minutes (±32.2) for SCS subjects. In addition, 16.4% (10/61) of DRG subjects were implanted with 3 or 4 leads, while all SCS subjects had 1 or 2 leads implanted. For both groups, the most frequently occurring procedure-related AE was pain at the incision sites with 7 events reported by 6 patients (7.9%) in the DRG arm and 5 events reported by 5 patients (6.6%) in the SCS arm.

For device-related AEs, 39 events were reported by 28 patients (36.8%) in the DRG arm and 24 events were reported by 20 patients (26.3%) in the SCS arm. No statistical difference was found between the groups ($P = 0.22$). The most frequently occurring device-related AE in the DRG arm was implantable pulse generator (IPG) pocket pain with 10 events reported by 10 patients (13.2%). On the other hand, the most frequently occurring device-related AE in the SCS arm was loss of stimulation due to lead migration with 8 events reported by 8 (10.5%) patients.

There was also no statistical difference between the groups for stimulation-related AEs ($P = 0.8025$). Ten events were reported by 8 patients (10.5%) in the DRG arm, and 10 events were reported by 10 patients (13.2%) in the SCS arm. The most frequently occurring stimulation-related AE for both groups was overstimulation with 3 events reported by 3 patients (3.9%) in the DRG arm and 5 events reported by 5 patients (6.6%) in the SCS arm.

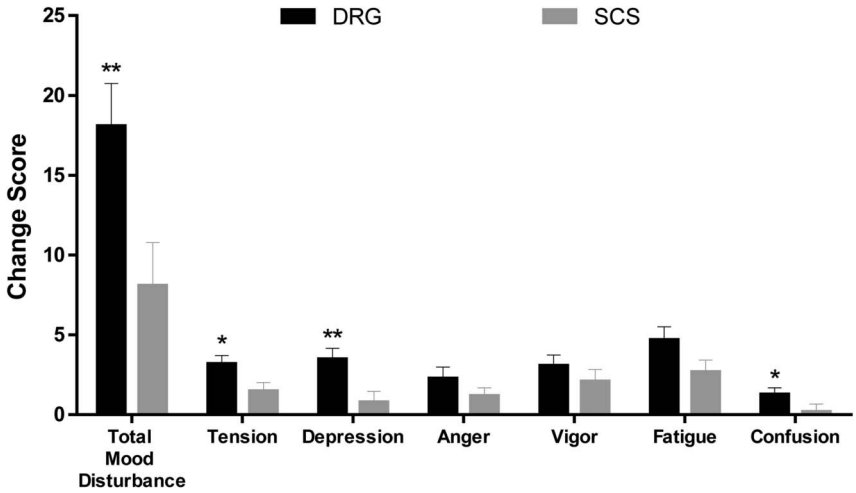

Figure 5. Change in profile of mood states (POMS) at 12 months. Change from baseline scores was calculated for each patient on each domain and the total score for the POMS. Mean change scores from baseline to 12 months are represented for both the DRG stimulation and the SCS groups. Error bars represent standard error of the mean. *Significant between-group difference with $P < 0.05$. **Significant between-group difference with $P < 0.001$. DRG, dorsal root ganglion; SCS, spinal cord stimulation.

4. Discussion

This study represents the largest randomized controlled trial assessing DRG stimulation for the treatment of chronic, intractable pain associated with the diagnoses of CRPS or causalgia. Analysis of the primary end point revealed that subjects using DRG stimulation had a higher rate of treatment success (81.2%) compared with the treatment success rate for traditional SCS (56.7%). Furthermore, pain relief persisted through 12 months of follow-up and remained significantly lower for DRG subjects than for those using SCS. Subjects using DRG reported significantly less postural-related changes in paresthesia and showed larger improvements on measures of quality of life, functional status, and psychological disposition than subjects using SCS. The safety profile of the DRG stimulation device was similar to traditional SCS devices, with the exception of the rate of procedural events.

These results for DRG stimulation as a treatment of chronic neuropathic pain associated with CRPS and causalgia must be interpreted within the context of previous neurostimulation studies for this population. Treatment of chronic reflex sympathetic dystrophy with SCS, in combination with physical therapy, reduced pain to a greater degree than physical therapy alone[14]; mean VAS scores for implanted patients reduced to 3.5 cm on a 10-cm VAS scale after 6 months of SCS. A retrospective analysis of SCS for the treatment of CRPS reported a mean VAS of 5.6 cm over a mean follow-up time of 88 months.[19] Mean VAS scores during SCS therapy in both these previous studies were higher, by a clinically meaningful margin[10] than the VAS score of 13.1 mm and 15 mm reported by subjects treated with DRG stimulation in our study at 3 and 12 months. Similarly, Geurts et al.[11] reported only a 50% pain reduction in an observational trial of SCS for CRPS.

Table 7

Change from baseline in brief pain inventory through 12 months.

Score	1 mo		3 mo		6 mo		9 mo		12 mo	
	DRG	SCS	DRG	SCS	DRG	SCS	DRG	SCS	DRG	SCS
No. of subjects*	61	54	59	54	59	52	55	49	55	50
Severity score†										
Mean (±SD)	3.8 (2.6)	4.0 (2.5)	4.2 (2.4)	3.8 (2.6)	3.8 (2.1)	3.6 (2.3)	4.0 (2.4)	3.5 (2.4)	3.8 (2.7)	3.3 (2.9)
Difference between mean and 95% CI	−0.2 (−1.1 to 0.8)		0.4 (−0.5 to 1.4)		0.2 (−0.7 to 1.0)		0.4 (−0.5 to 1.4)		0.5 (−0.6 to 1.6)	
Interference score†										
Mean (±SD)	3.7 (3.0)	3.1 (2.9)	4.2 (2.6)	3.0 (2.6)	3.8 (2.6)	3.1 (2.5)	4.2 (2.5)	2.8 (2.6)	3.9 (2.8)	2.6 (2.6)
Difference between mean and 95% CI	0.6 (−0.5 to 1.7)		1.1 (0.2 to 2.1)‡		0.8 (−0.2 to 1.7)		1.4 (0.4 to 2.4)		1.3 (0.2 to 2.3)‡	
Activity dimension of interference§										
Mean (±SD)	3.8 (2.8)	3.4 (3.2)	4.5 (2.5)	3.4 (2.9)	4.1 (2.6)	3.4 (2.8)	4.6 (2.4)	3.1 (2.9)	4.1 (2.9)	2.9 (2.9)
Difference between mean and 95% CI	0.4 (−0.7 to 1.5)		1.0 (0.0 to 2.0)‡		0.7 (−0.3 to 1.7)		1.5 (0.4 to 2.5)		1.3 (0.1 to 2.4)‡	
Affective dimension of interference#										
Mean (±SD)	3.5 (3.3)	2.7 (3.0)	3.8 (3.1)	2.5 (2.7)	3.5 (3.0)	2.6 (2.7)	3.8 (3.0)	2.4 (2.7)	3.5 (3.1)	2.2 (2.7)
Difference between mean and 95% CI	0.8 (−0.4 to 2.0)		1.3 (0.2 to 2.4)¶		0.9 (−0.2 to 2.0)		1.4 (0.3 to 2.5)		1.3 (0.1 to 2.4)¶	

* Only subjects with evaluable data; missing data not imputed.
† Per the user manual, subject-level scores were calculated as the mean of all severity or intensity items on the scale.
‡ *t* test, $P < 0.05$.
§ Subject-level scores comprised the mean of enjoyment of life, mood, and relations with others items.
¶ Wilcoxon test, $P < 0.05$.
# Significance is $P < 0.05$.
CI, confidence interval; DRG, dorsal root ganglion; SCS, spinal cord stimulation.

Table 8

Subject satisfaction through 12 months.

Score	3 mo		6 mo		12 mo	
	DRG	SCS	DRG	SCS	DRG	SCS
No. of subjects	59	54	59	52	55	50
Satisfaction with the pain relief provided by the stimulation*						
Mean (±SD)	8.4 (2.0)	7.9 (3.0)	8.3 (2.5)	8.1 (2.7)	8.4 (2.3)	8.0 (2.8)
Min, max	3.0, 10.0	0.0, 10.0	0.0, 10.0	0.0, 10.0	1.0, 10.0	0.0, 10.0
Difference between mean and 95% CI	0.5 (−0.5 to 1.5)		0.2 (−0.8 to 1.2)		0.4 (−0.6 to 1.4)	
Satisfaction with the therapy in general*						
Mean (±SD)	8.8 (1.9)	8.3 (2.9)	8.6 (2.4)	8.2 (2.7)	8.7 (2.1)	8.3 (2.7)
Min, max	2.0, 10.0	0.0, 10.0	0.0, 10.0	0.0, 10.0	0.0, 10.0	0.0, 10.0
Difference between mean and 95% CI	0.5 (−0.4 to 1.5)		0.5 (−0.5 to 1.4)		0.5 (−0.4 to 1.4)	
How likely you would undergo the therapy again†						
Mean (±SD)	9.0 (2.0)	9.1 (2.3)	8.7 (2.6)	8.7 (2.5)	8.9 (2.4)	8.5 (2.6)
Min, max	1.0, 10.0	0.0, 10.0	0.0, 10.0	0.0, 10.0	0.0, 10.0	0.0, 10.0
Difference between mean and 95% CI	−0.1 (−0.9 to 0.7)		0.0 (−0.9 to 1.0)		0.4 (−0.6 to 1.4)	
Change in your pain compared to before the device was implanted, n/N (%)						
Much worse	0/59 (0.0)	0/54 (0.0)	0/59 (0.0)	0/52 (0.0)	0/55 (0.0)	1/48 (2.1)
Worse	0/59 (0.0)	1/54 (1.9)	1/59 (1.7)	0/52 (0.0)	1/55 (1.8)	0/48 (0.0)
A little worse	1/59 (1.7)	1/54 (1.9)	0/59 (0.0)	1/52 (1.9)	0/55 (0.0)	0/48 (0.0)
No change	0/59 (0.0)	2/54 (3.7)	3/59 (5.1)	3/5 (5.8)	2/55 (3.6)	2/48 (4.2)
A little better	4/59 (6.8)	6/54 (11.1)	4/59 (6.8)	5/52 (9.6)	2/55 (3.6)	6/48 (12.5)
Better	16/59 (27.1)	8/54 (14.8)	12/59 (20.3)	10/5 (19.2)	14/55 (25.5)	10/48 (20.8)
Much better	38/59 (64.4)	36/54 (66.7)	39/59 (66.1)	33/52 (63.5)	36/55 (65.5)	29/48 (60.4)

* Scale 0 to 10 (0 = not satisfied, 10 = very satisfied).
† Scale 0 to 10 (0 = not likely, 10 = very likely).
CI, confidence interval; DRG, dorsal root ganglion; SCS, spinal cord stimulation.

A study using a heterogeneous population, including subjects with CRPS, reported that 68.4% of subjects were able to achieve ≥50% leg pain relief, and 60% of subjects achieved ≥50% pain relief for overall pain.[21] A published case series of CRPS subjects reported that 71.4% of subjects achieved ≥50% pain relief after 6 months of DRG stimulation.[28] In addition, a randomized trial comparing SCS to physical therapy for subjects with CRPS reported that 50% of subjects achieved at least 50% reduction in pain intensity.[14] Here, we report an 84% reduction in pain for patients treated with DRG stimulation and that 81% of subjects achieved ≥50% pain relief. Furthermore, the optimal programming for DRG stimulation is still being developed; **Table 2** shows that SCS and DRG parameters were quite different. Additional developments in optimized programming for DRG should improve clinical outcomes over time for this therapy. Taken together, we conclude that DRG stimulation provides better pain relief than traditional SCS.

Patients with CRPS and causalgia are difficult to treat with symptoms for 20% to 80% of CRPS I patients persisting for 1 year, even when treatment was considered successful.[2] Surgical interventions such as joint denervation or neurolysis also have variable outcomes; approximately 20% of patients failed to report low pain intensity and improved activities of daily living 2 years after surgery.[9] For patients with CRPS I or causalgia who do not achieve adequate pain management with conservative therapies, SCS provides an additional and reversible treatment option. Furthermore, DRG stimulation augments the patient experience by

Table 9

Percent change from baseline in visual analog scale scores through 12 months.

	3 mo		6 mo		9 mo		12 mo	
	DRG	SCS	DRG	SCS	DRG	SCS	DRG	SCS
No. of subjects*	59	54	59	52	55	49	55	50
Primary region of pain								
Mean	84.1	70.9	80.2	71.7	79.8	67.9	81.4	66.5
SD	22.9	32.7	26.4	32.8	26.6	35.4	26.4	37.5
Difference between mean and 95% CI	13.2 (2.6 to 23.8)		8.6 (−2.6 to 19.7)		11.9 (−0.5 to 24.2)		14.8 (2.1 to 27.5)	
Overall lower limb								
Mean	80.9	67.5	74.6	69.7	77.0	66.1	69.4	60.5
SD	23.8	35.2	26.6	34.5	27.5	36.9	43.1	39.9
Difference between mean and 95% CI	13.4 (2.1 to 24.8)		4.9 (−6.6 to 16.4)		10.9 (−1.9 to 23.7)		8.9 (−7.3 to 25.0)	

* Only subjects reporting visual analog scale scores at baseline and each study visit; missing data not imputed.
CI, confidence interval; DRG, dorsal root ganglion; SCS, spinal cord stimulation.

Table 10

Rates of related adverse events.

Adverse event characteristics	DRG (N = 76 subjects)		SCS (N = 76 subjects)	
	Events, n	Subjects, n/N (%)	Events, n	Subjects, n/N (%)
Relatedness to neurostimulator system or device	39	28/76 (36.8)	24	20/76 (26.3)
Relatedness to implant procedure	52	35/76 (46.1)	29	20/76 (26.3)
Relatedness to stimulation therapy	10	8/76 (10.5)	10	10/76 (13.2)

DRG, dorsal root ganglion; SCS, spinal cord stimulation.

providing a therapy that is adaptable to each patient's individual pain profile through more precise anatomical targeting.

The pathways for sensory afferents into the central nervous system via the DRG are well documented.[4,13] Anatomically, peripheral inputs associated with pain symptoms can be traced to relevant DRG at one or more spinal levels. Stimulation of the relevant DRG modifies pain signaling from the periphery for only the affected dermatomes. By contrast, SCS targets large dermatomal areas through stimulation of the dorsal column at anatomically defined spinal levels, and, as such, modifies ascending pathways for pain while also modulating collateral afferents in or near the medial lemniscus. Modulating pain signals from distal appendages with SCS typically requires that multiple dermatomes be captured–with paresthesias in the entire region. Our results showed that subjects treated with DRG stimulation had significantly less perceived stimulation sensation in nonpainful areas than subjects using SCS, while reporting better pain relief. This may indicate more precision targeting by virtue of the greater anatomical specificity with DRG stimulation.

The differences in collateral paresthesia may also be influenced by differences in programming parameters. Programming parameters were individualized for each subject's optimal experience. The resulting parameters were quite different between the 2 therapies (**Table 2**) with much lower amplitudes for DRG programming. This was expected from pilot work[7] and because diffusion of energy by the cerebrospinal fluid is less influential at the DRG. The between-subjects design of this study prohibits a real comparison of the relationship between targeting, programming, and pain relief; more research is needed.

Chronic pain conditions, in general, are associated with disturbances in mood and physical and social functioning.[1,22,24] The targeted pain relief provided by DRG stimulation in the ACCURATE study was also associated with additional benefits. After 3 months, subjects using DRG stimulation reported significantly greater improvements in total mood disturbance, as measured by the POMS, as well as larger improvements pain interference, affective disruption, and activity, as measured by the BPI. Moreover, by 12 months, subjects treated with DRG stimulation reported significantly larger improvements than SCS subjects for physical function, general health, and social function, as measured by the SF-36.

Despite the differences reported for treatment success, pain relief, and affective or functional outcomes, the majority of subjects were satisfied with their respective therapy, regardless of treatment group. While subjects using DRG stimulation reported a larger magnitude of change and there was a greater proportion of successful subjects with DRG stimulation, SCS subjects, as a group, did report significant improvements from baseline in all measured domains. The satisfaction results reported here reflect the improvements from preimplant baseline experienced by subjects.

The rate of AEs for DRG stimulation, through 12 months postimplant, was similar to that seen for the SCS-treated subjects in this study and in previous reports.[17,20] Only 2 subjects had procedure-related SAEs; 2 infections in the SCS group that required explant. It is notable that the rate of nonserious procedure-related events was higher for the DRG stimulation group (46%) compared with the SCS group (26%). The higher rate of procedure-related events may be attributed to the differences in average procedure time and a greater number of leads placed for DRG some subjects, which may increase exposure to risk. It is expected that additional experience with DRG implantation will result in shorter procedure times and fewer procedure-related events.

There are limitations to this study that may affect the interpretation of the results. The calculated success rate was contingent upon subjects not only achieving 50% pain relief but also continuing in the study (dropouts were counted as failures). Therefore, the success rate could be influenced by factors associated with the lack of blinded treatments (eg, SCS subjects were less motivated to stay in the trial, uncontrolled differences in health care provider interactions). In addition, subjects were required to maintain a stable regimen of pain medications through 3 months only, and the long-term results after 3 months may be affected by medication changes. The SCS device also had limitations placed on the programming of the device so that the comparison between the devices was not confounded by unique SCS device programming features. In particular, the accelerometer function in the SCS device was disabled. If the accelerometer was enabled, the SCS group may have had less postural changes in perceived paresthesia intensity. In addition, the analysis of subjects who did and did not experience paresthesia when stimulation was on was confounded by the fact that the SCS device instruction for use requires the device to be programmed for subjects to receive paresthesia. In addition, the number of subjects who did not have paresthesia is very small, and this end point was not adequately powered to detect the difference in pain relief for subjects who reported feeling vs not feeling paresthesia.

In conclusion, CRPS I and causalgia, in their chronic forms, are difficult to treat with variable outcomes with conservative symptom management. Neuromodulation techniques, like SCS, may benefit many patients who have exhausted other therapy options. SCS, however, often has a limited ability to target discrete focal anatomical regions of pain, as is common in CRPS and causalgia. Dorsal root ganglion stimulation provides an effective alternative that provides precision stimulation targeting and improved patient outcomes.

Conflict of interest statement

All authors were paid by Spinal Modulation & St Jude Medical as investigators for the clinical trial. T. R. Deer is a consultant for Axonics, Bioness, Flowonix, Medtronic, Jazz, Nevro, St. Jude, and Saluda and has consulting or equity for Axonics and Bioness. T. R. Deer formerly had equity in Spinal Modulation and Nevro.

R. M. Levy has served as a consultant for Bioness, BlueWind Medical, Boston Scientific, Flowonix, Medtronic, Microtransponder, Nevro, Saluda, Spinal Modulation, and St Jude Medical. R. M. Levy is or has been a minority shareholder in Saluda, Spinal Modulation, Bioness, Vertos, and Nevro. N. Mekhail formerly had a consultation agreement with spinal modulation to serve as medical monitor of the ACCURATE study. Currently, he is a consultant for St Jude Medical, Saluda medical, Stimwave, Medtronic neurological, and Flowonix inc. K. Amirdelfan is a consultant for St. Jude Medical, Nevro, Saluda, Nalu, and Biotronik. J. Pope is a consultant for Medtronic, NEVRO, St Jude, Flowonix, Jazz Pharmaceuticals, and Suture Concepts. T. Yearwood is a consultant for St Jude Medical, Boston Scientific, Nevro, Flowonix, and Neuronano; he serves as an officer for Meghan Medical. W. P. McRoberts serves or has served as a consultant for St Jude Medical, Medtronic, Nevro, Boston Scientific, Bioness, Vertiflex, and SPR. T. Davis has conducted research for Spinal Modulation, Vertiflex, Medtronic, Axsome, Nature Cell, and Halyard Health; has received fees for consulting, education, or speaking from St Jude Medical, Medtronic Restorative Therapies, Stryker, Vertiflex, DrChrono, and Tenex Health; and has ownership interests in Paradigm Spine <1%, LDR Holdings <1%, Alpha Diagnostics Neuromonitoring, and Broadway Surgical Institute. J. Scowcroft has served as a consultant for Boston Scientific. L. Kapural is a consultant for St Jude Medical, Nevro, Neuros, SPR Therapeutics, and Saluda. R. Paicius is a consultant for St Jude Medical, Nevro, and Boston Scientific. J. Kramer, Burton, Johnson, and Kristina Davis are employees of St. Jude Medical. The remaining authors have no conflicts of interest to declare.

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References

[1] Banks SM, Kerns RD. Explaining high rates of depression in chronic pain: a diathesis-stress framework. Psychol Bull 1996;119:95–110.
[2] Bean DJ, Johnson MH, Kydd RR. The outcome of complex regional pain syndrome type 1: a systematic review. J Pain 2014;15:677–90.
[3] Blackwelder WC. Proving the null hypothesis in clinical trials. Controlled Clin Trials 1982;3:345–53.
[4] Caspary T, Anderson KV. Patterning cell types in the dorsal spinal cord: what the mouse mutants say. Nature reviews. Neuroscience 2003;4:289–97.
[5] Cleeland CS, Ryan KM. Pain assessment: global use of the brief pain inventory. Ann Acad Med 1994;23:129–38.
[6] Curran S, Andrykowaski M, Studts J. Short form of the profile of mood states (POMS-SF): psychometric information. Psychol Assess 1995; 7:80–3.
[7] Deer TR, Grigsby E, Weiner RL, Wilcosky B, Kramer JM. A prospective study of dorsal root ganglion stimulation for the relief of chronic pain. Neuromodulation 2013;16:67–72.
[8] Deer T, Mekhail N, Provenzano D, Pope J, Krames E, Leong M, Levy R, Abejon D, Buchser E, Burton A, Buvanendran A, Candido K, Caraway D, Cousins M, DeJongste M, Diwan S, Eldabe S, Gatzinsky K, Foreman R, Hayek S, Kim P, Kinfe T, Kloth D, Kumar K, Rizvi S, Lad S, Liem L, Linderoth B, Mackey S, McDowell G, McRoberts P, Poree L, Prager J, Raso Lou, Rauck R, Russo M, Simpson B, Slavin K, Staats P, Stanton-Hicks M, Verrills P, Wellington J, Williams K, North R. The appropriate use of neurostimulation of the spinal cord and the peripheral nervous system for the treatment of chronic pain and ischemic diseases: the neuromodulation appropriateness consensus committee. Neuromodulation 2014;17:515–50.
[9] Dellon AL, Adonian E, Rosson GD. CRPS of the upper or lower extremity: surgical treatment outcomes. J Brachial Plex Peripher Nerve Inj 2009;4:1–6.
[10] Dworkin R, Turk D, McDermott M, Peirce-Sandner S, Burke L, Cowan P, Farrar J, Hertz S, Raja S, Rappaport B, Rauschkolb C, Sampaio C. Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. PAIN 2009;146:238–44.
[11] Geurts JA, Smits H, Kemler MA, Brunner F, kessles AG, van Kleef M. Spinal cord stimulation for complex regional pain syndrome type I: a prospective cohort study with long-term follow-up. Neuromodulation 2013;16:523–9.
[12] Harden RN, Bruehl S, Stanton-Hicks M, Wilson PR. Proposed new diagnostic criteria for complex regional pain syndrome. Pain Med 2007;8: 326–31.
[13] Hogan QH. Labat lecture: the primary sensory neuron: where it is, what it does, and why it matters. Reg Anesth Pain Med 2010;35:306–11.
[14] Kemler MA, Barendse GA, van Kleef M, de Vet HC, Rijks CP, Furnee CA, van den Wildenberg FA. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. N Engl J Med 2000;343:618–24.
[15] Koopmeiners AS, Mueller S, Kramer J, Hogan QH. Effect of electrical field stimulation on dorsal root ganglion neuronal function. Neuromodulation 2013;16:304–11.
[16] Kramer J, Liem L, Russo M, Smet I, Van Buyten JP, Huygen F. Lack of body positional effects on paresthesias when stimulating the dorsal root ganglion (DRG) in the treatment of chronic pain. Neuromodulation 2015; 18:50–7.
[17] Krishna K, Buchser E, Linderoth B, Meglio M, Van Buyten JP. Avoiding complications from spinal cord stimulation: practical recommendations from an international panel of experts. Neuromodulation 2007;10: 24–33.
[18] Kumar K, Caraway DL, Rizvi S, Bishop S. Current challenges in spinal cord stimulation. Neuromodulation 2014;17:22–35.
[19] Kumar K, Rizvi S, Bnurs S. Spinal cord stimulation is effective in management of complex regional pain syndrome I: fact or fiction. Neurosurgery 2011;69:566–80.
[20] Kumar K, Wilson J, Taylor R, Gupta S. Complications of spinal cord stimulation, suggestions to improve outcome, and financial impact. J Neurosurg Spine 2006;5:191–203.
[21] Liem L, Russo M, Huygen FJ, Van Buyten JP, Smet I, Verrills P, Cousins M, Brooker C, Levy R, Deer T, Kramer J. One-year outcomes of spinal cord stimulation of the dorsal root ganglion in the treatment of chronic neuropathic pain. Neuromodulation 2015;2015:41–9.
[22] Modovan AR, Onac IA, Vantu M, Szntagotai A, Onac I. Emotional distress, pain catastrophizing an expectancies in patients with low back pain. J Cogn Behav Psychother 2009;9:83–93.
[23] Oakley JC, Krames ES, Prager JP, Stamatos J, Foster AM, Weiner R, Rashbaum RR, Henderson J. A new spinal cord stimulation system effectively relieves chronic, intractable pain: a multicenter prospective clinical study. 2007;10:262–78.
[24] Robinson ME, Riley JL. The role of emotion in pain. In: Gatchel RJ, Turk DC, editors. Psychosocial factors in pain: clinical perspectives. New York: Guilford Press, 1999. pp. 74–88.
[25] Schott GD. Mechanisms of causalgia and related clinical conditions. The role of the central and of the sympathetic nervous systems. Brain 1986; 109:717–38.
[26] Taylor RS. Epidemiology of refractory neuropathic pain. Pain Pract 2006; 6:22–6.
[27] User's manual for the SF-36v2 health survey. 2nd ed. Lincoln, RI: Quality Metric Inc, 2007.
[28] Van Buyten JP, Smet I, Liem L, Russo M, Huygen F. Stimulation of dorsal root Ganglia for the management of complex regional pain syndrome: a prospective case series. Pain Pract 2015;15:208–16.
[29] Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30: 473–83.

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The Neuromodulation Appropriateness Consensus Committee on Best Practices for Dorsal Root Ganglion Stimulation

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Introduction: The Neuromodulation Appropriateness Consensus Committee (NACC) is dedicated to improving the safety and efficacy of neuromodulation and thus improving the lives of patients undergoing neuromodulation therapies. With continued innovations in neuromodulation comes the need for evolving reviews of best practices. Dorsal root ganglion (DRG) stimulation has significantly improved the treatment of complex regional pain syndrome (CRPS), among other conditions. Through funding and organizational leadership by the International Neuromodulation Society (INS), the NACC reconvened to develop the best practices consensus document for the selection, implantation and use of DRG stimulation for the treatment of chronic pain syndromes.

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Methods: The NACC performed a comprehensive literature search of articles about DRG published from 1995 through June, 2017. A total of 2538 article abstracts were then reviewed, and selected articles graded for strength of evidence based on scoring criteria established by the US Preventive Services Task Force. Graded evidence was considered along with clinical experience to create the best practices consensus and recommendations.

Results: The NACC achieved consensus based on peer-reviewed literature and experience to create consensus points to improve patient selection, guide surgical methods, improve post-operative care, and make recommendations for management of patients treated with DRG stimulation.

Conclusion: The NACC recommendations are intended to improve patient care in the use of this evolving therapy for chronic pain. Clinicians who choose to follow these recommendations may improve outcomes.

Keywords: chronic pain, complex regional pain syndrome, dorsal root ganglion, spinal stimulation

Conflict of Interest: Dr. Deer is a consultant for Abbott, Axonics, Bioness, Flowonix, Jazz Pharm, Saluda Medical, Vertos, SpineThera, Nalu, and Vertiflex. Dr. Deer is a member of the advisory board for Abbott, Flowonix, Jazz Pharm, Nalu, and Vertiflex. Dr. Deer has equity options in Bioness, Vertiflex, Axonic, Vertos, SpineThera, Saluda Medical, Nalu, Cornerloc and Flowonix. He is research consultant for Abbott, Mainstay Medical, Saluda, and Vertiflex. Dr. Deer formerly had equity positions in Spinal Modulation and Nevro. Dr. Deer has a patent pending for the DRG paddle lead with Abbott. Dr. Pope has management/advisory and consulting relationships with Abbott Neuromodulation, Jazz Pharmaceuticals, Saluda Medical, Flowonix Medical Inc., VertiFlex Inc., and SPR Therapeutics. Dr. Lamer has no disclosures. Dr. Grider has no disclosures. Dr. Provenzano has consulted for Halyard Health, Boston Scientific Corp., Abbott Neuromodualtion, Bioness Inc., Nevro Corp., and Medtronic Inc. Dr. Lubenow is a consultant for Medtronic Inc., Abbott Neuromodulation, Boston Scientific Corp., Halyard Health, and Flowonix Medical Inc. Dr. FitzGerald has no disclosures. Dr. Hunter is a consultant for Abbott Neuromodulation. Dr. Falowski is a consultant and advisor for Abbott Neuromodulation. Dr. Sayed is a consultant for Abbott Neuromodulation. Dr. Baranidharan is a consultant for Abbott Neuromodulation, Nevro Corp., and Boston Scientific Corp. He is also an advisor for Spinal Modulation Inc., and Abbott Neuromodulation. Dr. Patel has no disclosures. Dr. Davis has no disclosures. Dr. Green is an advisor for Abbott Neuromodulation and a consultant for Renishaw. He has also received travel and accommodation fees from Abbott Neuromodulation, Boston Scientific Corp., and Medtronic Inc. Dr. Pajuelo has no disclosures. Dr. Epstein has no disclosures. Dr. Harned is a consultant for Abbott, and Medtronic Inc. Dr. Liem has no disclosures. Dr. Christo has no disclosures. Dr. Chakravarthy is a consultant for Abbott. Dr. Gilmore receives speaking fees from Abbott. Prof. Huygen is a consultant for Abbott, Medtronic Inc., and Grünenthal. Dr. Lee has no disclosures. Dr. Mehta has no disclosures. Dr. Nijhuis is a consultant for Saluda Medical. He also has an advisory and consulting relationship with Abbott. He has stock options with Spinal Modulation and holds a patent for an L2 DRG stimulation device. Dr. Patterson is a consultant for Abbott. Dr. Petersen is a consultant for Abbott, Medtronic Inc., and Boston Scientific Corp. Dr. Pilitsis is a shareholder and has an advisory relationship with Centauri Therapeutics and Karuna Pharmaceuticals. She receives grant support from Medtronic Inc., Boston Scientific Corp., Abbott, Nevro Corp., NIH, and Jazz Pharmaceuticals PLC. She is also a consultant for Medtronic Inc., Boston Scientific Corp., Abbott, Jazz Pharmaceuticals PLC, Neurobridge Therapeutics Inc., and Nevro Corp. Dr. Rowe has no disclosures. Dr. Rupert is a consultant for Abbott. Dr. Skaribas has consulting relationships with Abbott and Vertiflex Inc. Dr. Sweet has no disclosures. Dr. Verrills has advisory and consulting relationships with Nevro Corp., Abbott, and Nalu Medical Inc. Dr. Wilson is a consultant for Abbott. Dr. Levy is a consultant for Abbott, Saluda Medical, Nuvectra Corp., and Nalu Medical Inc. He has stock options in Nalu Medical Inc., Bioness Inc., Vertos Medical Inc., and Nevro Corp. Dr. Mekhail has no disclosures.

INTRODUCTION

Neurostimulation involves the delivery of electricity to the nervous system to elicit a desired therapeutic response. Spinal cord stimulation (SCS), one of the most commonly utilized forms of neurostimulation, has been an established therapeutic option for a variety of neurologic conditions, including treatment of chronic pain syndromes. In the United States, the total cost of chronic pain is estimated at $560–$635 billion (1). Direct health care costs range from $261 to $300 billion, while the productivity loss ranges from $299 to $334 billion. The goal of neuromodulation therapy in the setting of chronic pain is to improve function and quality of life, decreasing the cost of the health care burden on society and reducing the opioid burden on the world population. Despite the successful use of SCS to treat many chronic pain syndromes, there are cases where SCS fails to produce initial or lasting relief (2). Dorsal root ganglion (DRG) stimulation is an option to improve outcomes in certain conditions that have challenged the efficacy of other forms of spinal stimulation and may, in fact, be the first choice of neuromodulation therapies for certain disorders.

Recent guidelines have established SCS as a safe and cost-effective treatment that helps improve function and decrease pain (3–9). Despite the overall success of SCS in treating many neuropathic pain conditions, focal pain conditions such as complex regional pain syndrome (CRPS), phantom limb pain, and injury or disease of the peripheral nervous system have created challenges to SCS efficacy. Focal areas of pain such as the trunk, groin, knee, foot, hand, and sacral areas have not always been captured reliably, resulting in unwanted paresthesias or failure to provide relief. Spinal cord architecture and the somatotropic distribution of the dorsal columns may result in poor delivery of stimulation to target fibers deep within the cord. There is also growing concern that excessive energy delivery to the spinal cord may lead to increased tolerance and habituation to therapy.

Literature reviews have reported a rate of SCS system removal as high as 23.5% (10–12). One analysis of a more than five-year span from 2007 to 2012 revealed a lower 9.2% explant rate (13). Recent reviews of explant data also examined the potential reasons for device explantation. Pope and colleagues in their retrospective review of 352 SCS cases found that 43.9% (152/346) of

explants occurred due to failure or lack of efficacy (14), and Van Buyten et al. in a study of more than 900 patients, found that 50% of the devices were explanted due to therapeutic failure (2). These failures of device may suggest the need for different approaches, specifically with traditionally difficult pain patterns and regions.

Advancements in technology and identification of new targets amenable to neuromodulation have led to development of a device to stimulate the DRG. This device was approved for clinical use in Europe in 2011 and in the United States in 2016 (15). This new therapy has increased the number of potential patients and conditions that may respond to neurostimulation. The DRG is a prime structural target for treating neuropathic pain because, as a coalition of sensory cell bodies, the DRG transmits input from the peripheral nervous system to the central neural system. The DRG lies within the epidural space and is bathed in a minimal volume of cerebrospinal fluid (CSF), making it amenable to epidural access techniques.

The DRG as a target was first explored in 1991 in animal models to treat pain and inflammation (16). By 2006, novel DRG stimulation systems were being designed and a few years later first implanted in humans. This was followed by the feasibility study by Deer and colleagues in 2009 that showed a novel DRG device could be placed and create safe and effective energy delivery to this structure (17). In this proof-of-concept study there were no device-related adverse events (AEs) and an efficacy of 70% was achieved. A larger scale international study to evaluate safety and efficacy built on this initial work. Liem et al. evaluated the first fully implantable device in Holland in 2011, as part of an international prospective study on the relief of chronic pain (18). This landmark study demonstrated the efficacy of DRG stimulation for many focal nerve-related pain syndromes. A total of 32 patients were followed for six months, with no unexpected device-related AEs and only minor AEs overall. The decrease in back, leg, and foot pain was statistically significant compared to baseline, and there were minimal issues with stimulating lead migration. This study also showed that paresthesia intensity did not vary with change in patient position. The results were reproducible in Australian and European centers. In addition to these developmental studies, approval of DRG therapy in those two continents led to post-market research on DRG stimulation for specific conditions such as groin pain, axial back pain (19), leg, and foot pain (18), CRPS (20), chest wall pain (21), and post-amputation pain (22) syndromes. Further clinical studies have reported DRG stimulation for a variety of conditions (23,24), including one randomized controlled trial (RCT) comparing DRG to SCS in treating CRPS type I or type II of the lower extremity (23).

As with new therapy, adoption often outpaces the evaluation of best practices. Our goal with this article is to describe DRG stimulation best practices guidelines based on available peer-reviewed literature, clinical evidence, clinical experience, and expert opinion. It is our hope that this will ensure the highest level of patient care.

DRG stimulation for chronic pain has the potential benefits of achieving pain relief in focal neuropathic pain syndromes, including in regions that are typically difficult to target or maintain with SCS over time (25). As clinical practice and research matures, DRG stimulation outcomes have continued to improve and indications for DRG stimulation are being refined. Safe and vigilant use of DRG stimulation will hopefully lead to long-term improvement in outcomes of this promising therapy.

METHODS

Development Process

The International Neuromodulation Society (INS) created a process to evaluate the level of current evidence in the peer-reviewed literature pertaining to neuromodulation (neurostimulation and intraspinal drug administration). The original publication, the Polyanalgesic Consensus Committee (PACC) 2000, represented the first guideline published using this process (26). A similar process was used to create the first neurostimulation guidelines published in 2014 (3–6) by the Neurostimulation Appropriateness Consensus Committee (NACC). These are living documents, subject to revision based upon new literature and changes in practice; as such, both the NACC (7–9) and PACC documents (27–32) have been regularly updated. This consensus guideline for DRG stimulation adds to the NACC family of guidance manuscripts and for the first time incorporates a systematic literature review.

An international multidisciplinary panel of experts, including anesthesiologists, neurosurgeons and pain medicine specialists, was selected by the executive committee of the INS to create this best practices guideline. Selection criteria for the expert panel included experience with DRG, publications, research, impact on the field, diversity, specialty, and practice setting. Authors' financial relationships were disclosed and managed prior to the start of the guideline development process.

It has become standard practice to use systematic reviews and meta-analyses to guide clinical practice, however, it should be recognized that there are many clinical scenarios where the literature is insufficient to render an evidence-based recommendation. For example, new techniques, applications of existing therapies to new disease states, modifications in technique or approach or 'new to market' innovations often move the clinical state of the art forward faster than RCT or large observational study data can be produced. It is in these instances that clinical consensus statements, based upon the available literature and coupled with clinical best practice by recognized experts, is used to fill the void. Given that DRG stimulation is a relatively new therapy, the goal of the NACC was to utilize the systematic review process to the fullest extent and create consensus guidelines to help shape the application of this rapidly developing treatment modality with the goal of improving patient outcomes by sharing the global body of expertise contained within the authorship. The following methods describe the literature search process and give an overview of the systematic review process and consensus creation and grading process.

Literature Search Methods

A comprehensive literature search protocol was used to identify the relevant studies to be included in guideline development. Searches were performed in the following databases: Scopus, Web of Science, EMBASE, Cochrane Central Registry of Controlled Trials, and Ovid Medline with a search timeline of 1995 through week 24 of 2017. The following search terms were used in addition to a search using expert author names: DRG stimulation, dorsal root ganglion stimulation, DRG neuromodulation, DRG stimulator, neuromodulation, neurostimulation, nerve root stimulation, nerve root stimulator, nerve root neuromodulation, ganglionic field stimulation, and analgesia/pain/neuropathy. Authors also performed independent literature searches to identify

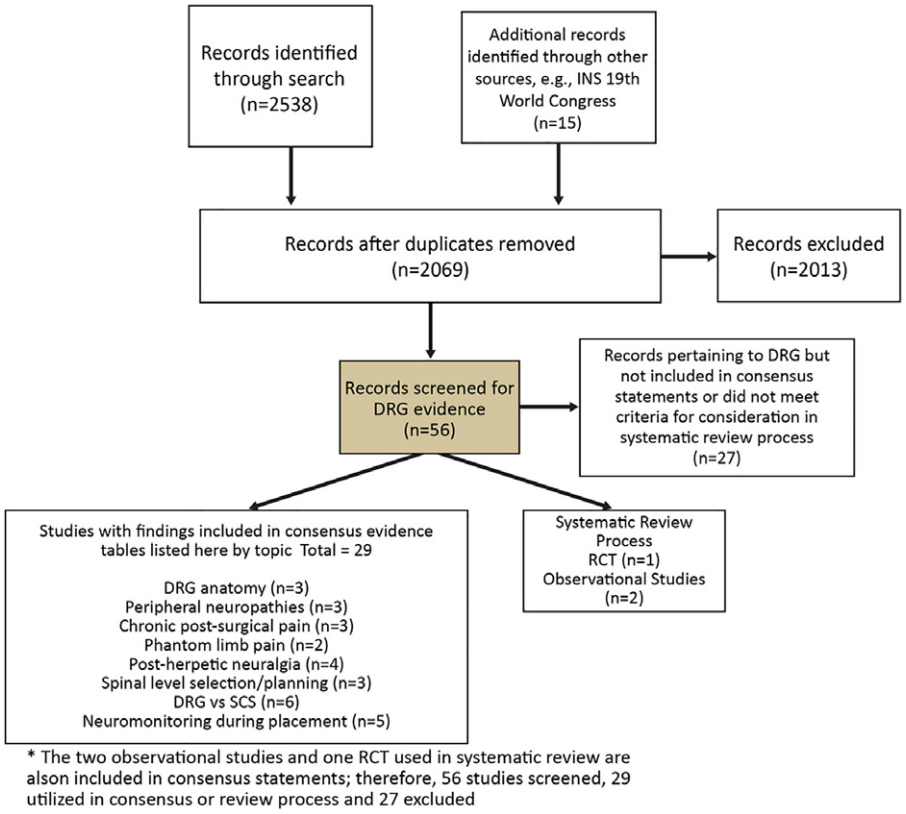

Figure 1. This diagram was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Criteria are available at http://prisma-statement.org. [Color figure can be viewed at wileyonlinelibrary.com]

literature that may not have been identified in the formal search. Manuscript types included for the initial search were RCTs, observational studies, case reports, systematic reviews, and conference abstracts, and all languages were allowed.

Systematic Evaluation of Evidence

A total of 2538 studies were identified with the initial search. Abstracts of each study were reviewed independently by two reviewers to identify studies for full review. Numerous studies were identified that the consensus group felt were of value to influence clinical reasoning and these are identified in the flow diagram (Fig. 1). These studies were not evaluated in a systematic fashion as they did not meet the selection criteria as outlined below, however, given the emerging body of literature with regard to DRG, the committee did feel these manuscripts were of value to help shape consensus. Ten studies were identified for full review and again were reviewed by two independent reviewers, with three articles identified for inclusion in the systematic review portion of the project. Inclusion criteria for systematic review were prospective trials (RCT and observational prospective trials) with at least 10 subjects who were not part of a larger or previously reported cohort or trial. In studies where the cohort was unclear (i.e., the manuscript may have been part of a larger trial), the manuscript was excluded as a separate entity and instead considered in totality of the data presented. Studies excluded were either retrospective, contained fewer than 10 subjects, or were in abstract form and not yet published.

One RCT and two large prospective trials were reviewed in systematic fashion using QAREL (33), Cochrane (34) and IMP-QRB (35) criteria that have been validated (Appendix A). Evidence was given a final grading using modified *Pain Physician* criteria (Table 1) and US Preventive Services Task Force (USPSTF) criteria (Table 2).

Analysis of Evidence

Using modified *Pain Physician* criteria, the evidence for DRG stimulation is Level 2 based upon one moderate quality (Level 2) RCT and two observational studies that are relevant but of lesser quality (Levels 3,4). Using the USPSTF criteria, one RCT was considered Level 1 and two observational studies were considered Level II-2.

Recommendation

The literature selected by the systematic review process strongly suggests that DRG stimulation is recommended as an option for patients with CRPS type I and type II and likely has significant benefit in those with other neuropathic pain syndromes. Due to the burgeoning nature of DRG stimulation, it is recommended that clinical situations and practice not covered in this systematic review be guided by consensus at present.

Consensus Best Practices Development

Previous INS consensus best practices guidelines adopted levels of evidence and grades of recommendation based upon the methodology of the USPSTF (Table 2 and Table 3) (36). Table 2 categorizes the hierarchy of studies, and Table 3 summarizes of the degrees of recommendation used in this methodology. *A*, signifies the highest degree of recommendation, *D*, the lowest degree, and *I*, signifies that insufficient evidence exists to make a

Table 1. Qualified Modified Approach to Grading of Evidence.

Level I	Strong	Evidence obtained from two or more relevant high quality randomized controlled trials for effectiveness. or Evidence obtained from four or more relevant high quality observational studies or large case series for assessment of preventive measures, adverse consequences, and effectiveness of other measures.
Level II	Moderate	Evidence obtained from at least one relevant high quality randomized controlled trial (Level 2 or greater) or multiple relevant moderate or low quality randomized controlled trials. or Evidence obtained from at least two high quality relevant observational studies or large case series for assessment of preventive measures, adverse consequences, and effectiveness of other measures.
Level III	Fair	Evidence obtained from at least one relevant high quality nonrandomized trial (Level 2 or greater) or observational study with multiple moderate or low quality observational studies. or At least one high quality relevant observational study or large case series for assessment of preventive measures, adverse consequences, effectiveness of other measures.
Level IV	Limited	Evidence obtained from multiple moderate or low quality relevant observational studies. or Evidence obtained from moderate quality observational studies or large case series for assessment of preventive measures, adverse consequences, and effectiveness of other measures.
Level V	Consensus based	Opinion or consensus of a large group of clinicians and/or scientists for effectiveness as well as to assess preventive measures, adverse consequences, effectiveness of other measures.

Modified from Ref. (35).

recommendation. The patients studied were adults aged 18 years and older with intractable neuropathic pain of greater than six months duration and who failed extensive trials of conservative therapy, such as physical therapy, systemic medications, and injection/nerve block therapy. The majority of patients had CRPS type I or II as a contributing diagnosis. The primary outcome measure was pain relief via a validated pain measurement scale (numerical pain scale or NPS, visual analogue scale or VAS). Secondary outcome measures included functional improvement, pain medication reduction and complications.

Multiple panel members were assigned to one or more work groups with each group compiling evidence tables (Table 4). Both face-to-face meetings and conference calls were convened to discuss the evidence. Expert consensus was used when higher level evidence was not available. Table 5 summarizes the key points and consensus recommendations made by the NACC regarding DRG stimulation therapy.

Table 2. Hierarchy of Studies by the Type of Design (U.S. Preventive Services Task Force).

Evidence level	Study type
I	At least one controlled and randomized clinical trial, properly designed
II-1	Well-designed, controlled, non-randomized clinical trials
II-2	Cohort or case studies and well designed-controls, preferably multicenter
II-3	Multiple series compared over time, with or without intervention, and dramatic results in noncontrolled experiences
III	Clinical experience-based opinions, descriptive studies, clinical observations or reports of expert committees.

ARCHITECTURE OF THE DORSAL ROOT GANGLION

DRG Anatomy and Physiology

The DRG is an integral structure for pain transmission and modulation. Previously, it was thought to function merely as a relay station between the peripheral nervous system and the central nervous system, but the DRG serves as a dynamic structure that plays a key role in up- and down-regulation processing in the pain pathway. DRG cells develop from the neural crest at about four weeks postconception and immediately begin to migrate ventrally. In six to seven weeks postconception embryos, DRGs are composed of loosely packed and randomly oriented cells with wide intercellular spaces and scattered processes (37) (Fig. 2). Newly formed neurons and their DRGs increase in density from six weeks postconception to 28–36 weeks postconception. They then remain stable from 36 weeks postconception until four months of age (38).

The DRG consists of paired pseudo-unipolar axons. Distal and proximal processes act as a single axon, with the cell body connected as an "off-shoot" in the shape of a T-stem (the T-junction) (39,40). This T-junction plays a vital role in the propagation of action potentials from a nociceptor to the dorsal root entry zone, acting as either an impediment to block a signal, an aid in propagation, or a low-pass filter to select in or out electrical information from the periphery (41).

The DRG is identified on radiologic imaging as lying at the caudal aspect of the neuroforamen between the pedicles on the anterior–posterior (AP) view and posterior to the posterior portion of the vertebral body on the lateral view. Yabuki et al. reported that DRGs are divided into two types, proximally situated and distally situated (42).

Table 3. Meaning of Recommendation Degrees (U.S. Preventive Services Task Force).

Degree of recommendation	Meaning
A	Extremely recommendable (good evidence that the measure is effective and benefits outweigh the harms)
B	Recommendable (at least, moderate evidence that the measure is effective and benefits exceed harms)
C	Neither recommendable nor inadvisable (at least moderate evidence that the measure is effective, but benefits are similar to harms and a general recommendation cannot be justified)
D	Inadvisable (at least moderate evidence that the measure is ineffective or that the harms exceed the benefits)
I	Insufficient, low quality or contradictory evidence; the balance between benefit and harms cannot be determined.

The positions are determined according to a line that bisects the center of each pedicle. If the proximal end of DRG was located medially or proximally to this line it was classified as proximal. If it was distal or lateral to this line then it was classified as distally located.

Sacral anatomy of the DRG location is somewhat different, as the DRGs reside either within the spinal canal or the neuroforamen, depending on sacral level. S1 DRGs are located in the intraforaminal region in 55–60% of individuals and in the intra-canalar region in 40–45%. S2 DRGs are within the intra-foraminal region in 15–50% of individuals and in the intra-canalar region in 50–85%. All of the S3 and S4 DRGs are located in the intra-canalar region. Further, no DRG was identified outside the foraminae (43). Tables 6 and 7 describe characteristics of DRG anatomy in the cervical and sacral spine.

The DRG is comprised entirely of afferent neurons with a combination of somatic and sympathetic fibers (Fig. 3). The somatic afferents located within the DRG derive from a predictable region conforming to their corresponding dermatome. The sympathetic afferents, on the other hand, include information from outside the dermatome. The white communicating rami contain fibers from the analogous gray communicating rami, roughly approximating the region proximal to the somatic afferents, as well as those fibers traveling through the sympathetic chain. This amalgamation of afferents suggests that each DRG possesses fibers from a diverse region superseding that of a simple dermatome.

The DRG has been considered a collection of neuronal cell bodies where stimuli from the periphery coalesce via sensory neurons along the afferent pathway before entering the spinal cord. At this site, however, there is also a collection of neuronal cells that are active and continue to fire once the stimulation threshold is reached. The T-junction is a bifurcation of sensory neuron axons within the DRG, which allows modulation of incoming and outgoing signals, and acts as a low-pass filter, regulating the number of action potentials that reach the dorsal horn of the spinal cord (45–47).

Filtering is achieved by both anatomic and neurophysiologic impedance barriers (45). Within the DRG, the difference between the diameters of the peripheral and central branches critically affects the ability of the T-junction to filter action potentials. DRG cell bodies create action potentials themselves (48,49). These action potentials occur within the cell body, feed into the T-junction, and augment or dampen the painful inputs. The resultant action potentials regulate the signals coming from the sensory nerves and can increase or decrease the signal propagated along the spinal cord (50). Therefore, instead of merely being a gate, the DRG acts like a series of locks, pooling stimuli from the periphery until a critical activation level is reached, and then opening up, sending a processed action potential to the spinal cord and subsequently up through the central nervous system.

Further, the DRG has a somatosensory distribution, allowing it to receive and process input from discrete regions of the body. Injury or stimuli to a peripheral nerve initiates a cascade of events, with increased discharge from the primary sensory neurons leading to an increase in the release of excitatory amino acids, ATP, nitric oxide, and neuropeptides (51), which activate the surrounding glia, initiating the release of pro-inflammatory cytokines and the development of membrane excitability (45,52,53) and reduced firing threshold.

Neurotransmitters, such as neuropeptides, play an important role in signal transmission. It has been shown that neuropeptide Y (NPY) in pain modulation has specific Y1 receptor antagonists directly in the DRG (54). The activation of these receptors leads to astrocyte activation within the dorsal horn, along with satellite cell activation in the DRG proximal to painful stimuli. This activation is reduced after Y2 receptor antagonist application. These findings indicate an important link between pain-related behavior and neuroimmune activation by NPY through its Y2 receptor (54).

Table 4. Recommendations With Supporting Evidence, Levels of Evidence and Recommendation Strength.
DRG Best Practices: _____.
Author: _____.
Topic:_____.

Key statements (2–5 total)	Supporting references List the references that support the key statement.	Levels of evidence Determine the level of evidence for each reference that supports a key statement.	Recommendation strength Assign a degree of recommendation to each key statement based on the supporting evidence.
1.			
2.			

Table 5. Consensus Recommendations Regarding Dorsal Root Ganglion (DRG) Stimulation From the Neuromodulation Appropriateness Consensus Committee (NACC).

Consensus point 1. The NACC recommends that DRG be considered primarily for patients who have focal neuropathic pain syndromes with identified pathology. Level I, Grade A, Consensus Strong

Consensus point 2. The NACC recommends DRG stimulation as an effective therapy in CRPS type I or type II of the lower extremity. Level I, Grade A, Consensus Strong

Consensus point 3. DRG stimulation of the upper extremity for treatment of CRPS type I or type II requires more study. Level II-2, Grade A, Consensus Strong

Consensus point 4. DRG stimulation in diabetic peripheral neuropathy (DPN) may be effective based on limited data. There is good evidence for SCS in this condition, and, therefore, at present the NACC recommends that the use of DRG stimulation rather than SCS should be carefully justified in individual cases. Level III, Grade C, Consensus Strong

Consensus point 5. The NACC appreciates that the current evidence for non-diabetic peripheral neuropathy is limited. More robust prospective trials are needed to determine if the efficacy seen in the diabetic population can be extrapolated to other populations. The NACC recommends these patients be treated on a case-by-case basis, and that if the pain is neuropathic in nature there is a good likelihood of response. Level III, Grade B, Consensus Moderate

Consensus point 6. The NACC recommends the use of DRG stimulation in patients with chronic postoperative surgical pain. As data are emerging, decisions need to be made on a case-by-case basis. Level III, Grade C, Consensus Moderate

Consensus point 7. At this time, the treatment of pelvic pain with DRG should occur using strict selection criteria, including the identification of the mechanism of injury (surgical or trauma-related) and related pathology, along with the designation of visceral or somatic. Currently, it is suggested that proceeding with DRG stimulation should be a team effort, combining specialists in gynecology, urology, and psychology. Patients with significant psychological issues should be excluded or treated prior to consideration of DRG stimulation. A history of sexual abuse or significant psychologic comorbidity should be considered a relative contraindication until proper counseling can be established and the therapist feels that an implant is indicated. Level III, Grade I, Consensus Moderate

Consensus point 8. The NACC recommends DRG stimulation for the treatment of neuropathic groin pain. Level II-2, Grade B, Consensus Strong

Consensus point 9. The NACC acknowledges that DRG stimulation in phantom limb pain may be considered in select patients. Further study is needed. Level III, Grade I, Consensus Moderate

Consensus point 10. Mapping of the appropriate DRG with sensory stimulation may be helpful in proper lead placement in specific patients with phantom limb pain. Further study is needed. Level III, Grade I, Consensus Moderate

Consensus point 11. The NACC recommends that the DRG(s) targeted should be those corresponding to the location of the phantom sensation. If there is significant pain in the stump itself, a further lead can be added to cover the relevant dermatome. Further study is needed. Level III, Grade I, Consensus Moderate

Consensus point 12. DRG stimulator leads are currently approved by the Food and Drug Administration (FDA) in the United States with the most rostral spinal level of T10. Off-label placement above T10 is common and appears safe. The use of DRG stimulation is common from C5 downward in Europe and Australia, and safety profiles appear similar in the United States. Based on the current body of literature and experience, the NACC recommends that DRG leads should not be placed above the C5 level, and the epidural needle entry should be at C6 or lower. Level II, Grade C, Consensus Moderate

Consensus point 13. Safe epidural needle placement for DRG stimulation requires satisfactory spinal and epidural anatomy. The NACC recommends that appropriate neuroimaging should be personally reviewed by the implanting physician. Epidural needle placement should not be attempted at a level of moderate or severe central or lateral spinal stenosis. In cases where the implanting doctor is unsure of the anatomical limitations, a consultation with a radiologist or other physician experienced in the local anatomy surrounding the DRG is indicated. Level III, Grade 1, Consensus Strong

Consensus point 14. DRG sheath and lead placement necessitates satisfactory lateral recess and foraminal anatomy for safe placement. The NACC recommends that appropriate neuroimaging be personally reviewed by the implanting physician and that percutaneous lead placement should not be attempted in the setting of severe lateral recess or foraminal stenosis. Level III, Grade I, Consensus Moderate

Consensus point 15. Epidural needle placement should not be attempted at the level of previous spinal surgery, and percutaneous DRG sheath and lead placement should not be attempted at the level of previous spinal surgery. Level III, Grade I, Consensus Strong

Consensus point 16. The NACC recognizes the number of leads implanted for unilateral and bilateral complaints may differ, based on pain coverage and anatomic considerations, with the maximum of four leads per implantable pulse generator (IPG). Level I, Grade A, Consensus Strong

Consensus point 17. The NACC recommends a trialing methodology that attempts to treat the painful areas with coverage of bilateral complaints bilaterally. Unilateral coverage trialing strategies in patients with bilateral complaints are not recommended. Level II-1, Grade B, Consensus Strong

Consensus point 18. The NACC recommends considering the potential risks and benefits when employing the guidewire/sheath introductory method compared to the lead/sheath introductory method. Preloading the sheath with the guidewire may allow for more maneuverability of the sheath system, but the increased rigidity may increase the likelihood of nerve irritation. Utilizing the sheath loaded with the lead system may increase procedural time. Level III, Grade I, Consensus Low

Consensus point 19. The proper position of the needle within the midline of the interlaminar epidural space is a major factor in entering the foramen at the superior aspect with the sheath. If the needle is not in the recommended position, attention should be given to repositioning the needle prior to attempting lead or guidewire placement. Level III, Grade I, Consensus Strong

Consensus point 20. The anchoring method is at the discretion of the implanter. If anchoring is to be used, the NACC suggests securing the lead with a loosely tied anchoring suture, either employing the provided plastic anchor or directly to the lead. Level III, Grade I, Consensus Low

Consensus point 21. Intra-epidural curve creation with an S-shaped strain-relief curve seems imperative to reduce migration. The NACC recommends creating such well-developed inferior and superior curves. Additional configurations may also be useful, but additional studies are needed. Level III, Grade C, Consensus Strong

Consensus point 22. In settings where the ability to create sufficient epidural strain-relief curves may be limited, such as in some sacral or cervical settings, additional extra-spinal anchoring is recommended. This may require undermining the tissue to allow for a 1–2 cm loop in the lead wound. Level III, Grade I, Consensus Moderate

Consensus point 23. The NACC recommends careful preoperative planning for tunneling from the lead placement incisions to the IPG, with central lead consolidation when many leads are implanted. Level III, Grade B, Consensus Strong

Table 5. *Continued*

Consensus point 24. The NACC recommends the dissection and creation of the IPG pocket in the posterior lateral flank or buttock ipsilateral to the needle skin entrance for DRG lead placement. Level III, Grade B, Consensus Moderate

Consensus point 25. DRG stimulation is superior to standard tonic SCS for unilateral focal pain caused by CRPS type I or type II in the lower extremity. Level I, Grade A, Consensus Strong

Consensus point 26. For other indications there is presently no firm basis on which a recommendation can be made for DRG stimulation over SCS.

Neurons in the DRG are surrounded by a cradle of satellite glial cells (SGCs), which carry receptors for numerous transmitters and can therefore receive signals from other cells and respond to external input. Activation of SGCs might, in turn, influence neighboring neurons, and thus SGCs may participate in signal processing and transmission in sensory ganglia (53). Damage to the axons of sensory ganglia contributes to neuropathic pain. Such damage may also affect SGCs, so these cells may have a role in the pathological changes that occur in the ganglia.

Given all the possible factors that affect the transmission of pain signals from the periphery to the central nervous system, the DRG becomes a plausible target for modulating pain. Specifically, DRG treatments may reduce response to nociceptive, neuropathic, and mechanical stimuli, perhaps by reducing sympathetic sprouting in the DRG (50–53), and decrease satellite glia activation in the DRG and microglia activation in the spinal cord, which occurs after injury (52,54). These findings provide support for the idea that localized inflammation at the level of the DRG is an important component in neuropathic pain development. These physiologic and anatomic factors suggest that the mechanism of action of DRG stimulation involves electrical modulation of neural processing at the T-cell junction.

Dorsal Root Ganglion Map

DRG neuroanatomy and physiology allow for therapeutic exploitation by allowing for adjacent level device placement with reliable preferential stimulation of the reduced firing threshold of hyper-excitable neuropathic pain fibers. Furthermore, the consistent anatomic location relative to surrogate bony anatomy makes lead placement reliable for stimulation of the DRG via fluoroscopy. Interestingly, when DRG target location to treat CRPS was determined for the ACCURATE study (23), it was based on maps of dermatomal sensory coverage (Fig. 4).

Due to the complexity of the afferents contained within a particular DRG, selecting the correct target for stimulation may require more than simply relying on a dermatomal map. In cases like post-amputation pain (PAP), maladaptive changes occur within the central nervous system (55–57) such that a lead placed over the L5 DRG may not correspond to the phantom foot due to deafferentation and central sensitization (57–60). Currently there is debate whether phantom limb pain is a top-down phenomenon due to loss of sensory input and caused by maladaptive cortical plasticity or a bottom-up phenomenon due to exaggerated input in the primary afferent neurons in the DRG innervating that limb (61). In cases of bottom-up processing, stimulation of the DRG may improve pain control. Neuroplastic maladaptation is not unique to PAP and may occur in a number of chronic, neuropathic conditions (62). It has been suggested that one may percutaneously apply sensory mapping stimulation to an individual DRG preoperatively to predict which potential targets most closely correlate with the area(s) of pain (62,63).

In 2017, Hunter and Sayed reported on a 217-patient registry tracking the results of DRG stimulation trials (64). In this registry, the authors compared lead locations to the areas of pain in an attempt to "map" which DRG should be targeted for a given pain

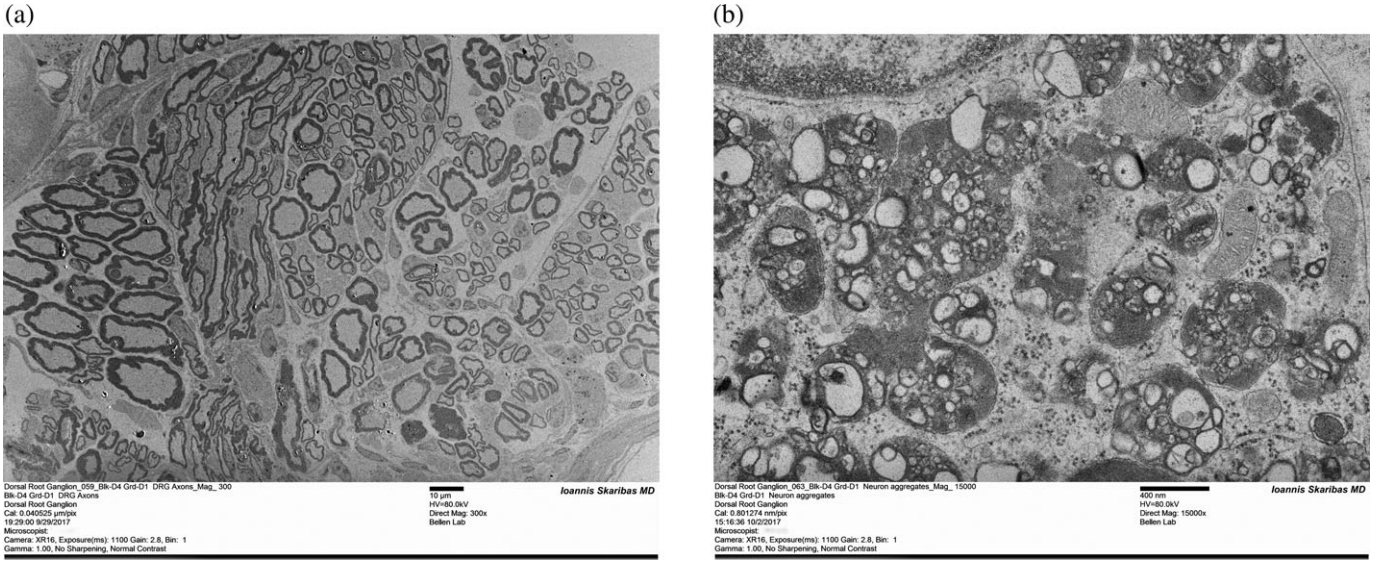

Figure 2. a. Electron microscopic image of dorsal root ganglion (DRG) axons (300 × magnification). b. Electron microscopic image of DRG neuron aggregates (15,000 × magnification).

Table 6. Evidence for DRG Cervical Anatomy.

Key statements	Supporting references	Levels of evidence	Recommendation strength	Consensus strength
The average distance between the takeoff point of nerve root from the thecal sac and the proximal end of the dorsal root ganglia increases in the cervical spine from 4.3 cm at C4 to 7.1 cm at C8.	Yabuki et al. 1996 (42)	II-3	A	Strong

complaint. Among their 125 subjects the most common diagnoses were CRPS (45.3%), post-knee replacement syndrome (9.4%), and post-herniorrhaphy neuralgia (6%). Greater pain reduction occurred in patients trialed with more rather than fewer leads, and areas of pain that spanned ≥3 dermatomes were less likely to be relived than smaller painful areas.

Physiology of Dorsal Root Ganglion in Normal Pain Processing

The DRG was previously thought to be a support structure whose main purpose was the transmission of sensory information and nociceptive pain (65,66) with no involvement in the initiation, development or maintenance of acute or chronic neuropathic pain (67). Contemporary research, however, indicates that the DRG does more than just facilitate communication between the central and peripheral nervous systems and assist in metabolic support of the long proximal and distal axons. The DRG plays an active role in the signal processing of nociception through the detection and manufacturing of relevant molecules that modulate the process (68).

Physiology of the Dorsal Root Ganglion and Implications in Chronic Pain

Evidence suggests that the DRG acts directly in the development of neuropathic pain through hyper-excitability (69) and the spontaneous, ectopic firing (67) of the cell bodies following peripheral nerve injury. These processes are known contributors of central sensitization and clinical allodynia (70) – the hallmark of CRPS and peripheral nerve pain. An injury to a peripheral afferent fiber causes numerous changes within the DRG (Table 8).

Considering the host of changes occurring in the DRG following a peripheral nerve injury, stimulation of the DRG for the treatment of chronic pain seems logical. DRG stimulation is believed to alter these changes via the mechanisms described in Table 9 and illustrated in Figure 5 (83–85).

PATIENT SELECTION

Using DRG stimulation for patients with focal neuropathic pain syndromes has been supported by the literature since the approval of DRG therapy. In certain patient subgroups this selection process can be further expanded and may be supported by more recent literature (19). The groups for which there is the highest level of evidence are those patients with CRPS type 1, and those with focal neuropathic pain secondary to peripheral nerve injury or disease (23).

Consensus point 1 The NACC recommends that DRG be considered primarily for patients who have focal neuropathic pain syndromes with identified pathology. Level I, Grade A, Consensus Strong.

General Considerations

The patient selection for DRG stimulation is very well defined in the literature based on specific medical conditions. In addition, the NACC recommends that best practices also make selection based on commonly practiced principles for other forms of neurostimulation (3). The patient should:

1. Be psychologically stable.
2. Have a defined pathology.
3. Have any issues with addiction under control.
4. Have optimal anticoagulant management that allows for the safe placement of an epidural lead.
5. Have no unaddressed or poorly controlled medical conditions that may impact the outcome of the procedure, such as those relating to infection risk, diabetes or other systemic diseases.
6. Be properly educated on the device and treatment, have a chance to ask questions, and be given options.

Table 7. Evidence for DRG Sacral Anatomy.

Key statements	Supporting references	Levels of evidence	Recommendation strength	Consensus strength
S1 DRGs are located in the intra-foraminal region in 55–60% of people and in the intra-canalar region in 40–45%. S2 DRGs are in the intra-foraminal region in 15–50% and in the intracanalar region in 50–85%. All of the S3 and S4 DRGs are located in the intracanalar region.	Ebraheim et al. 1998 (43)	III	B	Moderate
The shape of the sacral ganglion is usually olive-like.	Ebraheim et al. 1998 (43)	III	B	Moderate
None of the sacral DRGs is located in the extra-foraminal region	Ebraheim et al. 1998 (43)	III	B	Moderate
All the S3 and S4 DRGs are located in the intracanalar region.	Ebraheim et al. 1998 (43)	III	B	Moderate
The DRGs are located in the intervertebral foramina, except for the sacral DRGs, which are located inside the vertebral canal, and the coccygeal DRGs, which are intradural.	Vialle et al. 2015 (44)	III	B	Moderate

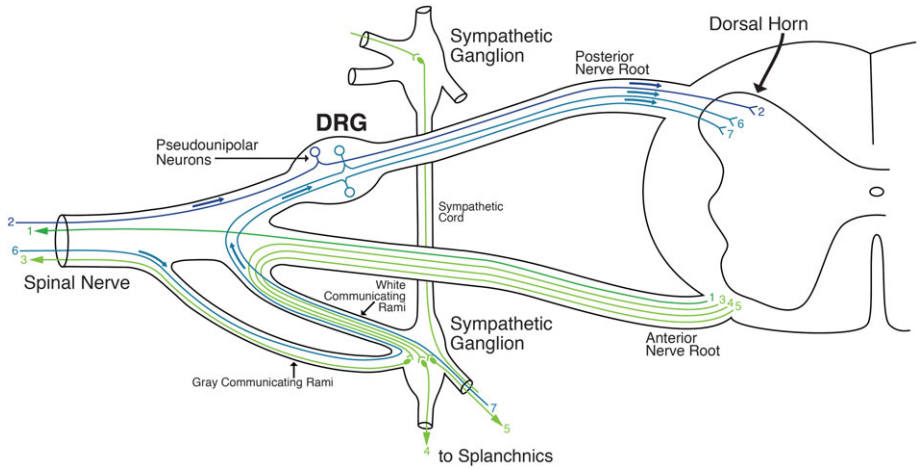

Figure 3. Control of electrical impulses that reach the dorsal horn. The dorsal root ganglion (DRG) acts to either block, propagate, or filter potentials from the periphery. 1) Somatic efferent fibers; 2) Somatic afferent fibers; 3,4,5) Sympathetic efferent fibers; 6,7) Sympathetic afferent fibers. [Color figure can be viewed at wileyonlinelibrary.com]

Disease-based treatment with DRG stimulation can be a critical part of treatment algorithms, and the choice of patients should be based on the currently available evidence.

Complex Regional Pain Syndrome

The use of DRG stimulation in CRPS is supported by high-level evidence and by consensus (Table 10). The European and Australian experience (18) shaped the design of the American multisite, pivotal ACCURATE study (23). It is the first and, at present, the only RCT evaluating DRG stimulation. Subjects meeting inclusion criteria with a confirmed diagnosis of CRPS were randomized in a 1:1 ratio to either DRG or tonic SCS (tSCS). Subjects were evaluated at three, six, nine and twelve months using primary end points of ≥50% reduction in VAS and monitored for any adverse events. Secondary end points were the degree of positional changes in stimulation effects, differences in outcome between treatments based on SF-36, Profile of Mood States, Brief Pain Inventory (BPI), subject satisfaction and change in VAS. After screening, randomization, and stimulation trials, 61 subjects went to implant in the DRG group and 54 in the tSCS group. The cohorts were similar demographically, had a homogenous diagnosis, and were followed at three-month intervals for one year. Additional data were collected at 18 months in a voluntary follow-up study.

The primary end point of ≥50% pain reduction was achieved in 81.2% of subjects receiving DRG therapy and 55.7% receiving tSCS. DRG stimulation also demonstrated greater improvement in quality of life and psychological disposition with less postural interference from stimulation or unwanted paresthesia compared to tSCS. It should be noted that tSCS also experienced treatment success for CRPS type I and type II consistent with previously reported studies, however, DRG stimulation achieved significantly better outcomes in this head-to-head trial (23).

Treatment of CRPS with DRG stimulation is illustrated in Figure 6.

Consensus point 2 The NACC recommends DRG stimulation as an effective therapy for the treatment of CRPS type I or type II of the lower extremity. Level I, Grade A, Consensus Strong.

Consensus point 3 DRG stimulation of the upper extremity for treatment of CRPS type I or type II requires more study. Level II-2, Grade A, Consensus Strong.

Diabetic Peripheral Neuropathy

Two small retrospective case series of DRG stimulation in diabetic peripheral neuropathy (DPN) have been reported (Table 11). The first series (86) included seven patients, five of whom were treated for lower extremity pain with leads at L5, one for upper extremity pain, and one for both lower and upper extremity pain. The mean pain VAS was 94.4 mm pre-treatment, and 47.1 mm at last follow-up (mean follow-up 12.4 months). Follow-up longer than 12 months was available for four patients who all continued to benefit from stimulation.

The second series (87) included ten patients, all men and all treated for lower extremity pain with leads between L2 and L5. Mean pre-trial VAS was 79.6 mm. A permanent implant was only placed if a trial yielded a ≥ 50% VAS reduction. Three patients failed to find relief during the trial. Among the seven who received a permanent implant, the mean VAS reduction postimplantation was 68.3%, and at six months was 58.4%.

There is much stronger evidence for the efficacy of SCS in DPN (Level I, Recommendation A). Two multicenter RCTs comparing SCS vs. medical management (89,90) reported responder rates (defined as 50% or greater reduction in pain VAS) of 59 and 60% in the SCS arms, while responder rates in the control arms were, respectively, 7 and 5%. These were both highly significant results, based on six months follow-up data with an intention-to-treat analysis.

Consensus point 4 DRG stimulation in DPN may be effective based on limited data. There is good evidence for SCS in this condition, and, therefore, at present the NACC recommends that the use of DRG stimulation rather than SCS should be carefully justified in individual cases. Level III, Grade C, Consensus Strong.

Other Peripheral Neuropathies

Several other types of peripheral neuropathy are associated with severe pain. Prominent among these are idiopathic peripheral neuropathy, chemotherapy-induced peripheral neuropathy and HIV-related neuropathy. A case series investigated the efficacy of DRG stimulation for the treatment of pain related to general peripheral neuropathy in the lower extremities (n = 8) (88). This multicenter retrospective analysis provided evidence that painful symptoms of general peripheral neuropathy in the lower extremities can be effectively managed by DRG stimulation at the L4/L5/S1 spinal levels. There is no high-level evidence for the use

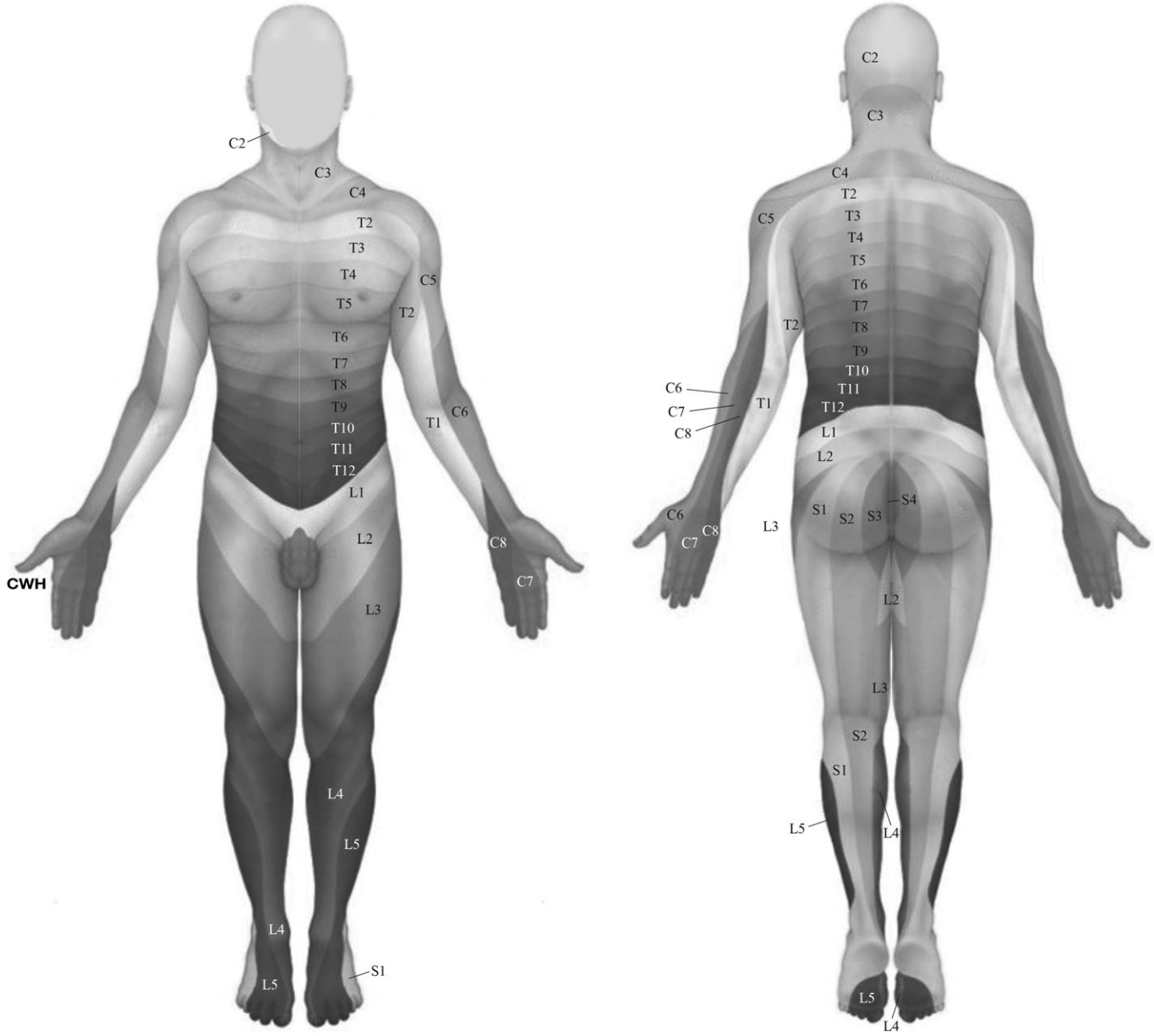

Figure 4. Dermatomal map. The general pattern of dermatomes is similar in all people, but the precise areas of innervation are unique to each individual. Illustrated by Corey Hunter.

of DRG stimulation in any of these conditions, although the NACC feels that the focal nature of the neuropathic pain syndromes would be likely to respond to DRG stimulation.

Consensus point 5 The NACC appreciates that the current evidence for non-diabetic peripheral neuropathy is limited. More robust prospective trials are needed to determine if the efficacy seen in the diabetic population can be extrapolated to other populations. The NACC recommends these patients be treated on a case-by-case basis, and that if the pain is neuropathic in nature there is a good likelihood of response. Level III, Grade B, Consensus Moderate.

Postsurgical Pain

The use of DRG stimulation for the treatment of postsurgical pain is supported in the literature (Table 12). The ACCURATE study had a large subgroup of subjects (nearly 40%) with pain in the groin, knee, and foot secondary to surgical nerve trauma and the development of CRPS type II (23). This group did extremely well, with improvements in pain and many secondary variables, and was statistically better than the comparative group. In addition to this Level 1 study, the evidence for other postsurgical nerve injuries has been demonstrated in multiple small studies. Indications have included post-knee surgery pain, post-hip surgery pain, post-thoracotomy pain, postmastectomy pain, postherniorrhaphy pain, and other nerve injuries.

Chronic postoperative pain after thoracic or breast surgery is a common occurrence (21,94). Pain lasting longer than six months following thoracotomy occurs in as many as 57% of patients (21). Persistent pain after mastectomy occurs in as many as 60% of patients (94). In these cases, postoperative pain is frequently segmental, with pain primarily spanning one to three thoracic dermatomes.

Table 8. DRG Changes Resulting From Peripheral Nerve Injury.

- Schwann cells and satellite glial cells contained within the DRG release a slew of pro-inflammatory mediators and cytokines including TNF-α, interleukins, nerve growth factors, interferons and chemokines (71–74)
- Spontaneous discharge and ectopic firing of DRG A-neurons leads to central sensitization (67,70,73)
- Activation of support cells within the DRG produces mediators that sensitize and lower the threshold of glial cells to firing from action potentials—thus leading to peripheral and central sensitization (75,76)
- Changes in gene expression occur leading to alterations in ion channels, receptors and signal transduction (77)
- Upregulation of certain Na^+ channels (TTX-R and TTX-S) results in a lower threshold for firing, leading to hyperexcitability (78)
- Downregulation of K^+ channels alters the resting membrane potential for neurons (79)
- Decreased Ca^{++} currents (80) lead to hyperexcitability (81) and the release of glutamate, substance P and calcitonin gene-related peptide (CGRP) (82)

The DRG has been suggested as a therapeutic target for treatment of chronic postthoracotomy or postmastectomy pain. Thoracic ganglionectomy, a nonreversible procedure, has been reported to be effective in treating segmental postsurgical pain (95). Radiofrequency lesioning of the DRG has also been shown to be temporarily effective and superior to lesioning of the intercostal nerves (21,24).

Stimulation of the DRG for treatment of chronic postoperative surgical pain (CPSP), has been evaluated in a prospective, noncontrolled study. Espinet et al. (91) reported on 18 patients with CPSP: "At six months, six patients (85.7%) had >50% pain relief and three (42.9%) had >80% pain relief." In a similarly noncontrolled prospective study, Liem et al. (92) reported that 29 of 36 patients trialed (80.6%) received a permanent implant. At three months, overall pain relief and segmental pain relief were 64.0 ± 8.3% ($N = 16$) and 76.4% ± 7.4% ($N = 24$), respectively. Significant improvement in the EQ-5D index score was also observed (0.722 ± 0.070 at three months vs. 0.364 ± 0.036 at baseline, $p < 0.0005$). Thus, data from prospective studies suggest that stimulation of the DRG may be an effective intervention for CPSP.

Table 9. Processes Altered by DRG Stimulation.

- Upstream and downstream effects causing stabilization of peripheral nociceptor sensitization, vasodilation, activation of wide-dynamic range (WDR) neurons and the release of neuromodulators in the dorsal horn aimed at decreasing excitability and excess neuronal firing
- Down-regulation of abnormal Na^+ channels, up-regulation of K^+ channels and restoration of normal Ca^{++} currents/flow—resulting in decreased hyper-excitability of the neurons within the DRG
- Activation of supra-spinal centers, deactivation of hyper-excitability of dorsal horn WDR neurons, and increase in membrane firing thresholds
- Stabilization of the microglia and satellite glial cells resulting in decreased release of pro-inflammatory mediators and cytokines
- Normalization in gene expression
- Reactivation or augmentation of DRG low-pass filter at the T-junction, thus reducing the propagation of action potentials to the dorsal horn

Similarly, in another prospective noncontrolled study, Breel et al. (93) reported on 30 subjects with chronic postsurgical neuropathic pain (13 with pain located in trunk/abdomen/groin, nine in the lower limb; eight in the upper limb) who underwent trial stimulation. With these, 26 subjects (87%) proceeded to permanent implantation. At baseline, mean VAS at the primary site of pain was 78.8 mm (± 2.1; $n = 23$). After six months of treatment, VAS decreased to 43.2 (± 6.7; $p < 0.05$), a 45% reduction, and 53% of subjects reported greater than 50% pain relief. Similarly, mean Brief Pain Inventory scores rating severity decreased from 7.1 (± 0.23) at baseline to 4.2 (± 0.52) at six months ($p < 0.05$). Additionally, 83% of subjects reported that they had pain relief in the areas of their normal pain, although only 50% of subjects reported paresthesias in these areas while using DRG stimulation. Subjects' quality of life and sleep improved (EQ-5D index scores increased from 0.360 [± 0.0.051] to 0.612 [± 0.071; $p < 0.05$], and the proportion of subjects rating their quality of sleep as excellent or good increased from 9 to 27%, respectively). The median satisfaction rating with the overall therapy was 8.0 out of 10.0. Of note, the authors reported that 50% of patients had paresthesias associated with stimulation, implying they may have been overstimulated. Thus, adjusting the stimulation to subthreshold levels could have achieved better-than-reported outcomes.

Each of these studies included patients with postthoracotomy or postmastectomy pain and, when specified, reported good relief in that category. In summary, chronic postthoracotomy and postmastectomy pain are common, and the DRG is an effective target for treating that pain.

Consensus point 6 The NACC recommends the use of DRG stimulation in patients with chronic postoperative surgical pain. As data are emerging, decisions need to be made on a case-by-case basis. Level III, Grade C, Consensus Moderate.

Pelvic Pain

Pelvic pain, which may be somatic or visceral, is a nonspecific, all-inclusive term that represents a group of complex, debilitating disorders, often refractory to conventional medical management (96). Pelvic pain includes a variety of diagnoses, such as pudendal neuralgia, interstitial cystitis, endometriosis, vulvodynia, ilioinguinal neuralgia, genitofemoral neuralgia, or a combination of these maladies (96). Pelvic visceral pain, mediated by S2, S3, and S4, should be differentiated from groin pain (pelvic part of the abdominal wall), which is mediated by T12 and L1. In many cases, an injury or related surgical procedure will predate the onset of pain, which may have triggered a cascade of events leading to this neuropathic syndrome (97). Parallels have been drawn between pelvic somatic and visceral pain and neuropathic syndromes, including CRPS (98). The similarities would appear to make postsurgical pelvic pain appropriate for treatment with SCS. While traditional SCS has had a fair response with CRPS, pelvic pain patients have a very high rate of explant at 33%, with the most common reason cited as "loss of therapeutic effect" (39%) (12). Although no literature explains the exact cause of these failures, one can only speculate that difficulty in obtaining sufficient coverage over the necessary sacral fibers would play a role.

As previously stated, DRG stimulation can deliver focal coverage to precise regions of the body, one of several reasons why it is able to provide superior relief in postsurgical pelvic pain. This factor would appear to rectify the aforementioned shortcoming of SCS. Based on a sub-analysis of the ACCURATE study (23), the use of subthreshold DRG stimulation has been shown to have

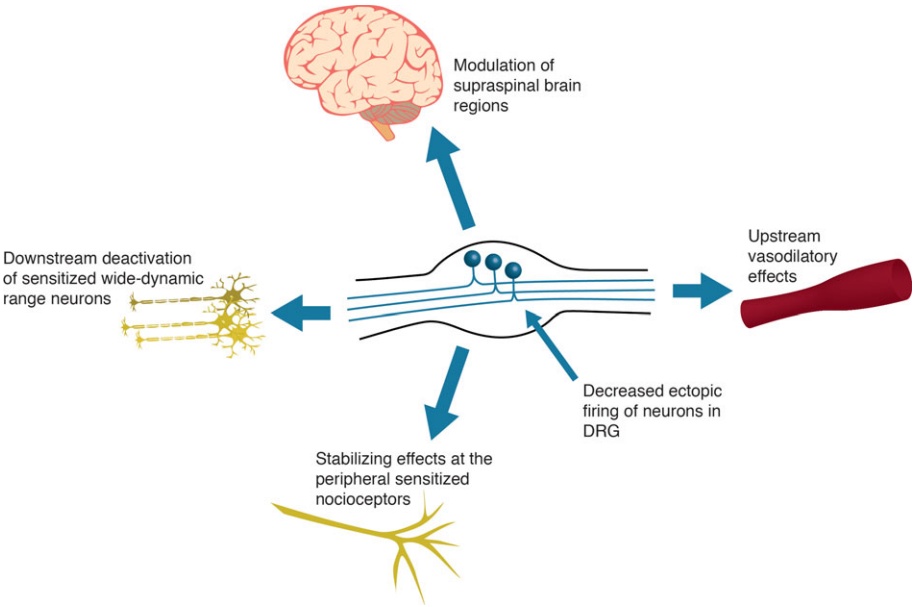

Figure 5. The physiology of the DRG on peripheral nerve injury states. [Color figure can be viewed at wileyonlinelibrary.com]

similar efficacy to paresthesia-mapped treatment; therefore, there does not seem to be a relationship between pain relief and mapping, but additional studies are needed.

Consensus point 7 At this time, the treatment of pelvic pain with DRG should occur using strict selection criteria, including the identification of the mechanism of injury (surgical or trauma-related) and related pathology, along with the designation of visceral or somatic. Currently, it is suggested that proceeding with DRG stimulation should be a team effort, combining specialists in gynecology, urology, and psychology. Patients with significant psychological issues should be excluded or treated prior to consideration of DRG stimulation. A history of sexual abuse or significant psychologic comorbidity should be considered a relative contraindication until proper counseling can be established and the therapist feels that an implant is indicated. Level III, Grade I, Consensus Moderate.

Groin Pain

Pain resulting from damage or disease of the ilioinguinal or genitofemoral nerves can be effectively treated with DRG stimulation. Note that testicular pain can manifest in the testicle itself (supplied by L1 and L2) or in the scrotum (supplied by S2 and S3). Schu and colleagues reported their experience with 29 patients, of whom 25 had a successful trial and went on to device implantation (99). Of the patients available for follow-up at seven months, the average pain relief achieved was 71%, with more than 80% achieving significant pain relief. These data were further supported by the ACCURATE study (23), which showed a significant response in those patients with groin pain diagnosed as CRPS II treated with DRG stimulation.

Consensus point 8 The NACC recommends DRG stimulation for the treatment of neuropathic groin pain. Level II-2, Grade B, Consensus Strong.

Phantom Limb and Stump Pain

There are few studies evaluating the use of DRG stimulation to treat phantom limb pain (PLP) and/or stump pain (Table 13). The only detailed published study is an uncontrolled case series that includes eight patients; six with lower extremity (LE) amputations and two with upper extremity (UE) amputations (22). Leads were implanted at levels corresponding to the area of the phantom sensation. Five of the eight patients (4/6 LE and 1/2 UE) obtained significant pain relief at a mean follow-up of 14.4 months, with VAS reductions ranging from 28–100%. Three had pain reduction of at least 50%. The lack of success in two cases was felt likely to be due to suboptimal lead placement. Small numbers of cases with positive results have been reported in conference proceedings (100,101). Recently, Hunter and colleagues published a mapping study using radiofrequency sensory stimulation to map the target for DRG in LE amputation patients (62). Future studies are required to determine

Table 10. Evidence for DRG in Treating CRPS.

Key statements	Supporting references	Levels of evidence	Recommendation strength	Consensus strength
DRG was effective in treating CRPS type I or type II of the lower extremity.	Deer et al. 2017 (23)	I	A	Strong
DRG stimulation of the upper extremity for CRPS type I or type II requires more study.	Deer et al. 2017 (23)	II-2	A	Strong
DRG achieved improved results for patients with CRPS compared to SCS.	Deer et al. 2017 (23)	I	A	Strong

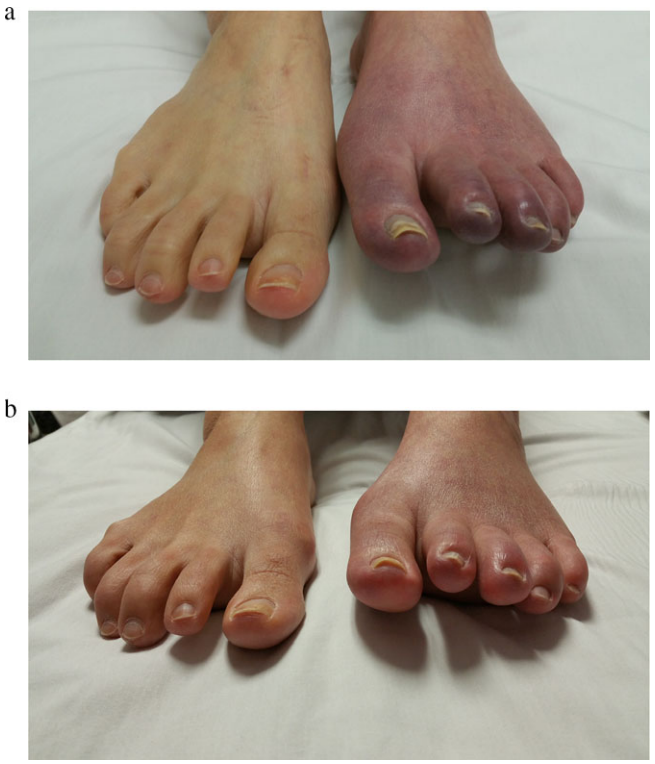

Figure 6. Patient with lower extremity complex regional pain syndrome (CRPS) a. before and b. after treatment with dorsal root ganglion (DRG) stimulation. [Color figure can be viewed at wileyonlinelibrary.com]

the efficacy and mechanism of DRG stimulation in the treatment of PLP.

Despite fewer studies evaluating DRG stimulation in this group, there is limited information regarding competing neuromodulatory options and none have any more compelling evidence. A recent PRISMA systematic review of SCS encompassing 12 primary studies concluded that, although it is clear that some patients respond, the evidence for SCS in PLP is mixed and further research is needed (101). Lack of other options has led to some patients undergoing more invasive treatments such as motor cortex stimulation (102), or even dorsal root entry zone (DREZ) lesioning (103), again with very little published evidence.

Consensus point 9 The NACC acknowledges that DRG stimulation in phantom limb pain may be considered in select patients. Further study is needed. Level III, Grade I, Consensus Moderate.

Consensus point 10 Mapping of the appropriate DRG with sensory stimulation may be helpful in proper lead placement in specific patients with phantom limb pain. Further study is needed. Level III, Grade I, Consensus Moderate.

Consensus point 11 The NACC recommends that the DRG(s) targeted should be those corresponding to the location of the phantom sensation. If there is significant pain in the stump itself, a further lead can be added to cover the relevant dermatome. Further study is needed. Level III, Grade I, Consensus Moderate.

Postherpetic Neuralgia

The use of DRG stimulation to treat postherpetic neuralgia is moderately supported in the literature (104–107) and has better evidence than SCS (Table 14). The DRG is damaged in this disorder and there has been discussion about targeting the DRG at the level of the injury vs. targeting above and below the primary level of infection. This would allow for treatment based on the convergence and divergence of the DRG at the levels near the pain lesion.

CONTRAINDICATIONS

DRG stimulator implantation has most of the same procedural contraindications as other spinal stimulator device implantation procedures. The risk for complication is impacted by comorbidities such as active coagulopathy, active infection, medical risk factors, such as uncontrolled diabetes mellitus and immune incompetence, patient inability to understand and operate the device, and spinal anatomic factors that limit safe lead placement (5). Current labeling in the United States is for the device to be placed most rostrally at or below the T10 spinal level, with the proviso that "The safety and efficacy of implantation of leads implanted above the T10 vertebral level have not been evaluated" (108,109). However, like most neuromodulation devices, off-label use is not uncommon and many American clinicians perform DRG lead placement above T10. Approval in Europe and Australia is unrestricted as to the level of implant. The majority of experts surveyed agree that DRG stimulation can be safely performed up to the C6 level. There is limited published safety data above the level of C6. Additional studies may give insight as to the safety of implantation at higher levels. Development of a paddle lead may further improve safety at higher levels.

Due to the unique placement techniques for the epidural needle and the placement of the DRG leads into the neural foramen, there are some unique risks and contraindications for DRG stimulation compared to SCS devices. First, the L5-S1 interspace is a commonly accessed level for DRG stimulation, as this is a common lead location for foot coverage, as compared to SCS, for which it is exceedingly rare. The L5-S1 level often has a thinner ligamentum flavum and less capacious epidural space than other lumber levels, and thus extra care must be taken to avoid dural puncture at this level. Second, most often a contralateral epidural

Table 11. Evidence for DRG in Treating Peripheral Neuropathies.

Key statements	Supporting references	Levels of evidence	Recommendation strength	Consensus strength
DRG stimulation may be effective for the pain of diabetic peripheral neuropathy.	Schu et al. 2015 (86) Eldabe et al. 2017 (87)	III	C	Strong
No recommendations can be made for other forms of peripheral neuropathy, but considering the orientation of the pain, patients should be implanted on a case-by-case basis.	Falowski et al. 2017 (88)	III	B	Moderate

Table 12. Evidence for Chronic Postsurgical Pain.

Key statements	Supporting references	Levels of evidence	Recommendation strength	Consensus strength
In a small prospective, noncontrolled study, DRG stimulation demonstrated relief of CPSP.	Espinet 2015 (91)	III	B	Moderate
Preliminary data from this prospective study suggests that stimulation of the DRG may be an effective intervention for CPSP.	Liem et al. 2014 (92)	III	B	Strong
After six months, VAS and BPI scores decreased significantly. The median satisfaction rating with the overall therapy was 8.0 out of 10.0.	Breel et al. 2016 (93)	III	B	Strong

access technique to L5-S1 is advised for DRG lead placement. Third, the DRG introducer and lead will be placed into the intervertebral foramen. Accordingly, the target foramen must not be critically stenotic. The implanting physician should personally review neuroimaging to determine if a patient's spinal canal, lateral recess, foramen, and epidural space anatomy are suitable for needle, introducer, and lead placement at each target level. If not skilled at radiologic interpretation, the implanting physician should consult with a radiology specialist for a report focusing on these specific issues. In patients where MRI is contraindicated, CT myelography is a valid alternative for assessing anatomy. Interventions such as neuromonitoring or discussion with the awake patient during placement can enhance safety. In comparison, many of the DRG implants to date have been below the level of the conus medullaris, thus eliminating the risk of spinal cord injury and making the risk of serious injury with DRG stimulation less common at L2 or lower.

In the recently published RCT comparing DRG stimulation to conventional SCS, there was no significant difference in serious AEs between the two groups and there were no stimulation-induced neurologic deficits for the duration of the 12-month follow-up (23). There are, however, several differences in the techniques, requiring some unique considerations for DRG lead placement compared to conventional dorsal epidural SCS lead placement.

In addition to the prior discussions of epidural and spinal anatomy, the state of the lateral recess and neuroforamen must be considered prior to DRG lead placement. Previous surgery at the target spinal level is a relative contraindication for percutaneous lead placement. In the future, there may be options for open paddle lead placement. Also, the lateral recess and foramen should be sufficiently capacious to allow for introducer and lead access. Severe lateral recess and/or foraminal stenosis are relative contraindications to percutaneous placement (110).

In addition to these technical considerations, proper patient selection, including a stable psychological profile, no untreated addiction issues, a probable pain origin of neuropathic cause, a well-controlled medical status, and an ability to understand the risk and benefit considerations of the device are critical elements for improving outcomes.

Consensus point 12 DRG stimulator leads are currently approved by the Food and Drug Administration (FDA) in the United States with the most rostral spinal level of T10. Off-label placement above T10 has been performed routinely and appears safe. The use of DRG stimulation is common from C5 downward in Europe and Australia, and safety profiles appear similar in the United States. Based on the current body of literature and experience, the NACC recommends that DRG leads should not be placed above the C5 level, and the epidural needle entry should be at C6 or lower. Level II, Grade C, Consensus Moderate.

Consensus point 13 Safe epidural needle placement for DRG stimulation requires satisfactory spinal and epidural anatomy. The NACC recommends that appropriate neuroimaging be personally reviewed by the implanting physician. Epidural needle placement should not be attempted at a level of moderate or severe central or lateral spinal stenosis. In cases where the implanting doctor is unsure of the anatomical limitations, a consultation with a radiologist or other physician experienced in the local anatomy surrounding the DRG is indicated. Level III, Grade 1, Consensus Strong.

Consensus point 14 DRG sheath and lead placement necessitates satisfactory lateral recess and foraminal anatomy for safe placement. The NACC recommends that appropriate neuroimaging be personally reviewed by the implanting physician and that percutaneous lead placement should not be attempted in the setting of severe lateral recess or foraminal stenosis. Level III, Grade I, Consensus Moderate.

Consensus point 15 Epidural needle placement should not be attempted at the level of previous spinal surgery, and percutaneous DRG sheath and lead placement should not be attempted at the level of previous spinal surgery. Level III, Grade I, Consensus Strong.

DORSAL ROOT GANGLION DEVICES AND PROCEDURE TECHNIQUES

Dorsal Root Ganglion Systems

Currently there is only one device approved for DRG implantation in the United States, Australia and the EU. This device is

Table 13. Evidence for Phantom Limb Pain.

Key statements	Supporting references	Levels of evidence	Recommendation strength	Consensus strength
DRG stimulation may be effective for phantom limb pain.	Eldabe et al. 2015 (22) Hunter et al. 2017 (64)	III	I	Moderate

Table 14. Evidence for Postherpetic Neuralgia.

Key statements	Supporting references	Levels of evidence	Recommendation strength	Consensus strength
DRG is efficacious for postherpetic neuralgia.	Vesper et al. 2016 (104)	II-2	I	Moderate
	Sullivan et al. 2015 (105)	II-2	B	
	Yang et al. 2013 (106)	II-2	C	
	Yanamoto et al. 2012 (107)	III	B	
DRG stimulation is safe for postherpetic neuralgia.	Vesper et al. 2016 (104)	II-2	I	Strong
	Sullivan et al. 2015 (105)	II-2	B	

indicated for use at the DRG only and is made with an MRI conditional platform and nonrechargeable, primary-celled internal pulse generator (Proclaim DRG; Abbott Neurological, St. Jude Medical, Minneapolis, MN, USA) (108). One wireless device, which had been placed temporarily using a transforaminal approach, is currently not approved for use at the DRG in the regions listed above (Stimwave Inc., Pompano Beach, FL, USA). DRG paddle lead development to allow for direct placement under open visualization is under development.

Dorsal Root Ganglion Level Selection & Pre-Procedure Planning

One of the major differences between DRG stimulation and traditional SCS is the ability to offer targeted stimulation to distinct areas of the body by modulating focal areas of the spinal cord rather than the more indiscriminate approach inherent to leads placed over the dorsal columns. Intuitively, one may choose to target the level(s) most closely corresponding to the dermatome(s) where the pain is located. However, in cases of severe deafferentation or central sensitization (e.g., postamputation pain), the pain may not conform to basic dermatomal patterns, meaning pain in what would appear to be the L5 dermatome may not respond to a lead placed over the L5 DRG (55–57,62). This presents a potential dilemma for DRG lead placement.

One proposed method for predicting which DRG level(s) to target involves using selective sensory stimulation of the suspected segments (62,63). This technique has been described by Hunter and Zuidema, whereby a radiofrequency cannula is placed using the conventional "transforaminal" approach used for epidural injections, targeting the posterior aspect of the foramen. The tip is advanced just beyond the mid-pedicular line such that the active tip is proximal to the DRG, in the dorsal aspect of the foramen. Several cannulae are placed sequentially such that multiple DRGs can be tested. Once the cannulae are all in position, the sensory testing function on the generator is utilized, delivering 50 Hz through the active tip to the adjacent DRG, and the energy is slowly increased until the patient reports feeling a sensation. The patient is then asked where the sensation was felt and if it covered the painful area(s); this is then repeated at each level where a cannula was placed. The patient is ultimately asked to rank which level(s) most closely corresponded to the area(s) of pain—those ranked highest are subsequently targeted for lead placement. This method has not been validated in a prospective randomized fashion for predicting outcomes, but additional studies are recommended to determine the value of this advanced mapping technique.

Table 15. Effective DRG-Lead Combinations for Various Pain Locations (64).

Pain location	Sample size	Most impactful DRG	Optimal lead combination(s)
Foot	106	S1	L5/S1 (include L4 if ankle pain is present)
Knee	23	L4	L3/4
Groin	25	T11	T12/L1/2 > T11/12/L1 = T11/12
Buttock	12	L2	T12/L1/L2 > T12/S1
Back	28	T12	T12/L1/2 > L5/S1
Pelvic	6	S2	L1/S2 (bilateral leads for bilateral pain)

Few large published DRG stimulation studies have comprehensively reported the levels used in all enrolled patients. Expert opinions on what is the optimal level to treat for any given condition and pain location vary, possibly because the convergence and divergence of pain pathways between adjacent levels means that different levels can achieve similar effects in some cases. Good examples of the differences in both published data and expert opinion are in foot pain and groin pain. In the ACCURATE study (23), foot pain was largely treated with L5 stimulation with excellent results. Only one patient received a permanent sacral lead. In contrast, a recent registry study (64, Table 15) advocated stimulation at S1 as well. A large study of groin pain cases (n = 29) (99) treated mainly the L1 or L2 ganglia, which correspond anatomically to the fibers comprising the relevant ilioinguinal (L1), iliohypogastric (L1) and genitofemoral (L2) nerves. In the ACCURATE study (23) only one of eight groin pain patients was implanted above T12, while in contrast, 25 patients with groin pain in the registry study were treated predominantly at T11 (64).

Consensus point 16 The NACC recognizes the number of leads implanted for unilateral and bilateral complaints may differ, based on pain coverage and anatomic considerations, with the maximum of four leads per implantable pulse generator (IPG). Level I, Grade A, Consensus Strong.

Consensus point 17 The NACC recommends a trialing methodology that attempts to treat the painful areas with coverage of bilateral complaints bilaterally. Unilateral coverage trialing strategies in patients with bilateral complaints are not recommended. Level II-1, Grade B, Consensus Strong.

At present it appears reasonable to conclude that in many situations there is more than one option that may be effective, but insufficient published data to give firm guidance on which level is best. Implanters should be aware of the various options that have been used with success, and that they may need to trial more than one in any given case. In Figure 7, we present the levels that the authors feel are effective for the treatment of pain in different locations.

Table 16 presents the available evidence for level selection and planning.

Preoperative Imaging Considerations

As the placement of the electrodes over the DRG involves access to the intervertebral foramen via the dorsal epidural space,

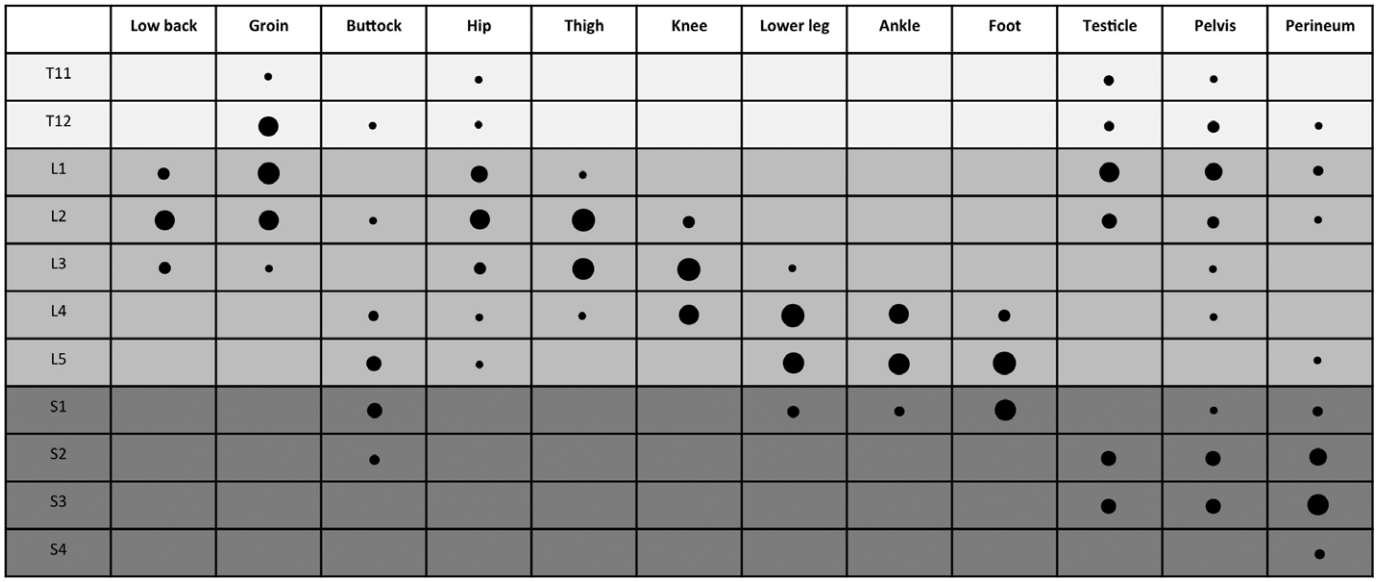

Figure 7. Suggested stimulation levels by pain location. Data compiled from a poll of the authors; area of circle represents the number of implanters recommending each level.

one of the prime concerns among implanters is the volume of the space available in the foramen to accommodate the electrodes without compromising the DRG, nerve root or other intraforaminal structures.

The sub-pedicular notch, which houses the DRG and its surrounding structures, normally occupies 30% of the available foraminal area (111). The prevalence of lumbar foraminal stenosis has been reported to be 8–11%, with one cadaveric study reporting 21% (112,113). This can be more of a concern at the vertical interpedicular zone (foraminal zone) or at the extra-foraminal zone (114,115), the two most common lumbar locations for the DRG.

Preoperative radiological evaluation hence becomes important to assess the central canal, lateral recess and the target neural foramen for any stenosis or other hindrance to lead placement. This becomes especially true in the context of previous spinal surgery, where scar tissue and recurrent pathology may be involved.

Preoperative Radiologic Screening

Plain radiographs help screen foraminae (65). While plain CT scans may provide information on bony encroachment in the foraminae, the shape may not be well depicted unless reconstructed parasagittal images are obtained.

MRI plays a more important role as it can be used to evaluate both central and lateral spinal canal pathology. Preoperative assessment of the parasagittal images would enable surgical level planning, providing visualization of the epidural fat and of the foramen while allowing superior resolution of any associated disc and vertebral body changes. MRI is also the imaging of choice in patients having undergone previous surgery and in need of assessment of the scar tissue formation and recurrent pathology. CT myelography with 3D reconstruction can provide adequate information in patients for whom MRI is contraindicated.

Table 16. Evidence for Level Selection and Planning.

Key statements	Supporting references	Levels of evidence	Recommendation strength	Consensus strength
The guidewire should be loaded into the sheath prior to inserting the sheath into the epidural space.	Clinical experience-based opinion	III	I	Low
Radiofrequency stimulation is a potential means for choosing the proper DRG(s) to target for stimulation.	Hunter et al. 2017 (62) Zuidema et al. 2014 (63)	II-2	C	Low
Certain DRG combinations seem to respond better for treating particular body parts, regions, or pain presentations.	Hunter et al. 2017 (64)	II-2	B	Moderate
Cervical DRG stimulation should not be attempted without having placed at least 20+ lumbar leads.	Clinical experience-based opinion	III	I	Low

Of special note is the fact that the generators used for DRG stimulation are continuously changing. At the time of this publication two generators are commercially available and a third generator is under clinical study. The implanter should check with the manufacturer regarding MRI compatibility of the devices and should consider preoperative MRI if indicated by clinical history.

Critical dimensions of the foramen and posterior intervertebral disc may bear a direct correlation with foraminal stenosis (114). Paucity of the perineural fat on T1-weighted sagittal images has been used to define the degree of foraminal narrowing (114,116). Assessment of nerve root morphology further improves interobserver variability and may pick up vertical foraminal stenosis (117).

With foraminal height being the same from L1 to S1 but the DRG diameter increasing (largest at L5-S1, 8.3 mm), the largest root/foramen area ratio approximates 50% at the L5/S1 foramen. With the natural pedicle width also increased maximally at L5, the L5 nerve root has normally less space in the rostro-caudal direction and occupies a greater distance in the foramen compared to other levels (118). In addition, the L5 DRG is anatomically placed more laterally in the foramen than at higher vertebral levels. L5 also has a higher incidence of degenerative disc disease and spondylosis. Furthermore, lower nerve roots have a more oblique course through the lateral canal, increasing their susceptibility to the effects of pedicular kinking and foraminal stenosis. Hence, preoperative radiological evaluation is even more important when L5 is the target DRG.

Lead Implantation

Patient Positioning

Proper patient positioning remains of utmost importance for successful placement of DRG leads. As is the case with placement of conventional SCS leads, measures to minimize lumbar lordosis should be utilized to facilitate needle entry into the epidural space. Arm boards, if used, should be properly positioned to not impede lateral imaging. Bolsters, frames, or pillows placed under the umbilicus can aid in reducing the lumbar lordosis. Using fluoroscopy, the physician may decide to mark the skin needle-entry point into the epidural space, and the location of the target DRG. As skin entry is traditionally approximated two levels below the target DRG, the physician will need to extend the sterile field more caudally then one would expect with a conventional SCS lead implantation technique.

Needle Selection

A straight 14-gauge delivery needle is typically used to access the epidural space for DRG lead placement. The manufacturer provides a 4.5-inch 14-gauge delivery needle in each lead kit. In patients with a larger body habitus, a larger 6.0-inch 14-gauge delivery needle can be utilized. If so desired, a curved delivery needle can also be utilized to access the epidural space, although this is typically avoided to allow for greater control of the trajectory of the delivery sheath. A technique to access the S1 DRG is described in this text in which the curved needle may help facilitate placement, but this is at the discretion of the implanting physician and is currently an adjuvant method.

Sheath Selection

After access into the intralaminar opening with the delivery needle, placement of the lead on the target DRG is accomplished via the delivery sheath (Fig. 8) (110,119). The delivery sheath is placed through the epidural needle to facilitate delivery of the lead to the inferior portion of the target DRG. Delivery sheaths are internally reinforced with thin stainless steel braiding to minimize kinking. Sheaths have a locking hub as well as a side-injection port. The side-injection port can be used to inject medications or saline, but is used most commonly to determine the orientation of the curve of the sheath, with the injection port and curve of the sheath pointing in the same direction. Sheaths are produced in a more acute "big curve" and less acute "small curve." Typically, it has been observed that access to the DRG is easier with the "big curve" sheath. The "small curve" sheath can be used in scenarios when a more contralateral approach is attempted. The delivery sheaths come in a standard 22 cm length as well as a 30 cm length when utilizing the longer 6.0-inch delivery needle.

Consensus point 18 The NACC recommends considering the potential risks and benefits when employing the guidewire/sheath introductory method compared to the lead/sheath introductory method. Preloading the sheath with the guidewire may allow for more maneuverability of the sheath system, but the increased rigidity may increase the likelihood of nerve irritation. Utilizing the sheath loaded with the lead system may increase procedural time. Level III, Grade I, Consensus Low.

Retrograde Access

After several failed antegrade passes using large and small curved needles and midline and off-midline needle access, you may choose to try a retrograde approach, while keeping antegrade access active. Figure 9 illustrates this option.

Guidewire Use

Each kit contains a single guidewire intended to assist with gaining epidural access via the loss of resistance technique. The approval of the guidewire for use and subsequent inclusion in the kit by the FDA is specifically for that purpose. However, the guidewire has been found to potentially serve in another important role by aiding the sheath's passage through the foramen.

There are a number of foraminal ligaments collectively arranged like a web that stand to obstruct smooth passage of the sheath under the pedicle and out the foramen. In certain instances, the sheath may not be able to penetrate this web, thus preventing proper lead placement. Applying more force will simply cause the sheath to bow and ultimately kink. Placing the guidewire within the sheath instead of the lead can substantially reduce the pliability of the sheath, thus giving the apparatus more rigidity. This rigidity translates to a greater lateral force vector, allowing the sheath to overcome most resistance from local ligaments within the foramen. The guidewire may be substituted in place of the lead either at the onset, prior to the initial insertion of the sheath through the needle, or after the sheath has been introduced into the epidural space, depending on the operator's preference.

The position of the DRG within the foramen is variable and cannot be directly visualized under fluoroscopy without the addition of contrast. The resistance that is encountered may, thus, be from the DRG or nerve root. So while the addition of the guidewire into the sheath may offer the benefit of providing more rigidity, this rigidity may have a potentially negative impact if used incorrectly.

The guidewire loaded into the sheath apparatus will typically overcome minor resistance as posed by the foraminal ligaments, thus gentle force should allow the tip of the sheath to pass under the pedicle and exit the foramen. In cases where the tip of the

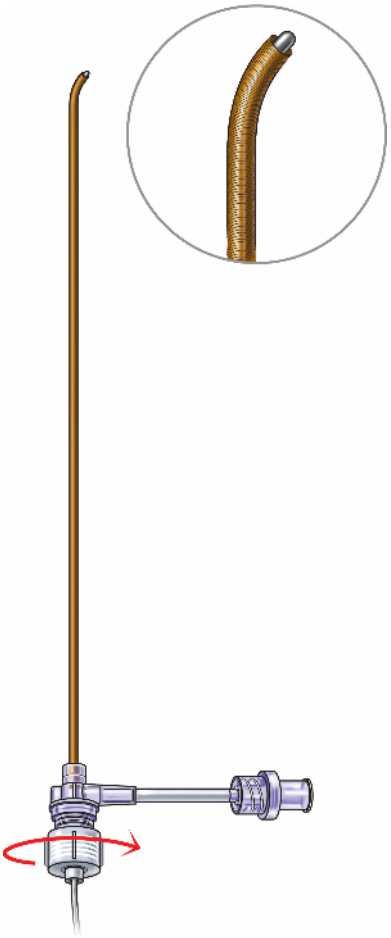

Figure 8. Delivery sheath with preloaded guidewire. The side-injection port and the curve are oriented in the same direction. [Color figure can be viewed at wileyonlinelibrary.com]

sheath containing the lead is pressing against the DRG, it will bow as a safety precaution to prevent subsequent nerve injury. However, if the guidewire is being used within the sheath, it may not bow and will continue to apply pressure and irritate the DRG. In cases of foraminal stenosis or anatomical variations that would prevent safe passage of the sheath, the guidewire may be used in an alternative fashion.

An alternative method of entry is to use the guidewire on the initial sheath placement. After the tip is advanced to the entry point of the superior foramen, the sheath remains locked and the system is advanced in one movement. Some of the expert panel members have recommended an alternative guidewire use in which the locking mechanism at the back of the sheath is loosened, freeing the guidewire to be moved independently of the sheath. In this modified method, the guidewire is gently advanced beyond the tip of the sheath, while keeping the sheath itself stationary. The tip of the guidewire is rounded and narrower than the sheath, which allows the guidewire to pass between areas of friction with greater ease. Using a gentle tapping motion, the guidewire may move itself through an opening that may have been too small for the sheath but big enough for the guidewire. After the guidewire has "popped" through the foramen, one can attempt to advance the sheath more than the guidewire similar to the Seldinger technique used for central line placement. If one is still unable to advance the sheath, one can simply remove the guidewire while keeping the tip of the sheath stationary and

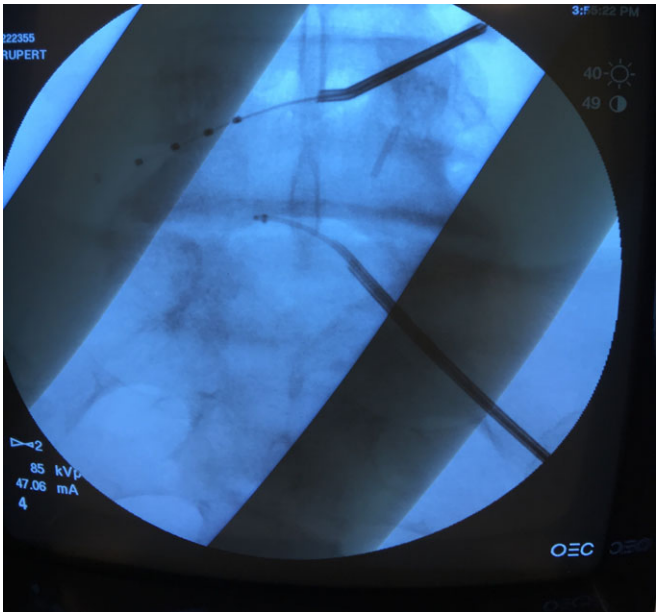

Figure 9. Extreme paramedian approach to DRG at L4/5 and paramedian approach to DRG at L5/S1. [Color figure can be viewed at wileyonlinelibrary.com]

replace it with the lead. The guidewire should have made a small channel just big enough for the lead to now be advanced beyond the tip of the sheath. It should be noted that this modified method is used by some advanced practitioners; additional study on overall safety is needed prior to the NACC panel recommending it for general use.

Regardless of the decision to use the lead or guidewire loaded into the sheath as the primary implant method, the foramen should be entered first at its superior aspect just below the pedicle. Navigating the intra-foraminal ligaments can be performed with the lead within the sheath system by applying gentle pressure and a "shimmy and shake" movement to gently glide it into place. This can be aided by a lateral x-ray view once the sheath and lead system is placed near the medial aspect of the foramen and then steering the direction of the curve to optimize foraminal entry. This may reduce the risk of DRG or nerve irritation.

Consensus point 19 The proper position of the needle within the midline of the interlaminar epidural space is a major factor in entering the foramen at the superior aspect with the sheath. If the needle is not in the recommended position, attention should be given to repositioning the needle prior to attempting lead or guidewire placement. Level III, Grade I, Consensus Strong.

Decreasing Lead Migration

Routine physical activity producing flexion, extension, lateral bending, or axial rotation of the thoracic lumbar spine affects the anatomic relationship of the nerve root and connective tissue. This is of practical importance as lead contacts deployed over the DRG in the foramen may migrate (120).

As the DRG electrode delivery system is advanced from the dorsal inter-laminar epidural space to the target neural foramen for final deployment of the electrodes, three main steps in this trajectory serve to indirectly anchor the electrodes and lessen chances of migration. The redundant strain-relief curves, of course, serve as final anchors. The epidural approach is a major factor in reducing migration, and is thought to be one of the

major drawbacks of a transforaminal approach, along with potential nerve injury and lack of supporting evidence.

STEP 1: As the delivery system is advanced into the dorsal epidural space it is directed towards the 7 o'clock (left) and 5 o'clock (right) border of the pedicle to approach the neural foramen. This serves two purposes: the system follows a parabolic or elliptical path along the inferior vertebral notch to the DRG and allows the contacts to stay superior in the foramen, thus minimizing risk of any displacement away from the target DRG.

Note that the roof of the neural foramen is formed by the inferior vertebral notch of the target pedicle. The inferior pole also helps delineate the vertical inter-pedicular zone, which houses the DRG in most foramen (115). The DRGs with the exiting nerve root in the foramen and surrounding fat are often located in the superior and anterior region of the foramen or sub-pedicular notch, normally occupying approximately 30% of the available foraminal area (111).

STEP 2: As the delivery system is advanced towards the entrance zone of the neural foramen, firm resistance from the foraminal ligaments may be encountered in its path. Gentle manipulation of the lead delivery system enables continued progression of the leads between foraminal structures to the exit zone of the canal for electrode deployment.

There are at least four to five transforaminal ligaments that span the bony boundaries of the foramen from superior to inferior, anterior to posterior and obliquely across its walls. Each of these ligaments measure from 2 to 5 mm (121,122). Another set of intra-foraminal ligaments reinforces the neural structures by connecting the periosteum and transforaminal ligaments to the nerve root sleeves and vessels within the foramen.

The DRG within the foraminal zone could be partially or completely embedded beneath either the transforaminal ligamentous web, the intra-foraminal ligaments or both. Because of this anatomical arrangement, paying attention to a ligamentous loss of resistance when advancing the delivery system may be a marker of electrode deployment between the fibrous ligaments. This serves to anchor the electrodes in the foramen, minimizing any migration.

STEP 3: Once the contacts are deployed at the optimal position over the DRG, usually defined by the second and third contact in the superior part of the vertical interpedicular zone and over the DRG in most thoracic-lumbar sites, the next step is to form the strain-relief curves in the epidural space. The sheath is retracted to the needle bevel, with the same alignment as the direction of the curve of the sheath. Once performed, the lead is then locked in the sheath and advanced cephalad with the big curve of the sheath and the bevel of the needle facing perpendicular concave to the surface of the skin, until an inflection is noted in the cephalad direction. The lead is then unlocked from the sheath and advanced, creating the superior loop, not above the inferior endplate of the immediately adjacent cephalad vertebral body.

STEP 4: The sheath is again retracted to the needle. The locked system is then turned to face the target DRG and the bevel of the needle and the big curve is turned inferiorly. The locked system is advanced slightly, creating the apex of the inferior loop. The stylet within the lead is retracted approximately 12–15 cm and the lead is advanced as the sheath is retracted to the needle, creating half of the inferior loop. The lead/sheath system is then locked, turned superior, and advanced, towards the target DRG, completing the inferior loop. The lead is unlocked and retracted back to the needle, maintaining the alignment of the big curve and the bevel of the needle.

STEP 5: The needle and the sheath now need to be removed. During this step the stress-loops are most commonly accidentally withdrawn, so care is required to maintain these important points of lead stabilization. The lead and needle can be removed by two strategies with a different sequence under AP fluoroscopic view: 1) removal of the sheath, leaving the needle in place with subsequent removal; or 2) removal of the needle onto the sheath, then removing the needle and sheath system over the lead.

Unique Considerations for Dorsal Root Ganglion Lead Placement

Routine Dorsal Root Ganglion Lead Placement T10-L5

The general technique described above is primarily for DRG stimulation from T10 to S2. The recommendations for lead placement are important and the physician should pay special attention to the needle entry within the midline of the interlaminar space, more cephalad within the space if possible, sheath/lead/stylet or sheath/guidewire placement in the foramen, and the placement of the lead with contacts two and three spanning the medial and lateral borders of the pedicle. The AP and lateral view are very important for confirmation of proper lead placement. Figures 10 and 11–14 illustrate proper DRG lead placement in the lumbar and thoracic spine, respectively.

Thoracic Dorsal Root Ganglion Lead Placement

The thoracic approach to DRG stimulation can be separated into slightly different techniques for the upper and lower thoracic spine. The lower thoracic spine is much like the upper lumbar spine and the technique is similar with the lead placed into the foramen with the medial contacts hugging the pedicle. In the upper thoracic spine, needle angles may be steeper, the spinal diameter may be smaller and the foramen has a somewhat different angle. In some cases the small curved sheath may be needed. Generally speaking, finesse is required more often when placement is attempted above T10, with a clear need to monitor for potential neurologic injury, either with direct patient feedback or neuromonitoring.

Figures 11–14 illustrate DRG lead placement in the thoracic spine.

Sacral DRG Lead Placement

The technique for DRG stimulation of the sacral root ganglia differs significantly from the technique described for the lumbar and thoracic area. DRG locations in the sacral area differ between levels and are either intra-canalar or intra-foraminal, but never extra-foraminal (43,44).

STEP 1: The sacral DRGs are accessed utilizing a percutaneous fluoroscopic technique. The sacral neuro-foramena are identified with a posterior–anterior fluoroscopic view, utilizing a very slight cephalic tilt when necessary, angled to best visualize the S1 foramen. After the patient is prepped and draped utilizing a standard surgical preparation and draping technique, the skin, and subcutaneous tissues are infiltrated with local anesthetic to the edge of the foramina to be accessed. With right S1 and S2 DRG lead placement utilizing a transforaminal approach, the 5 o'clock position on the bony perimeter of the right S1 and/or S2 foramen is identified fluoroscopically, and with left S1 and S2 DRG lead placement utilizing a transforaminal approach, the 7 o'clock position on the bony perimeter is identified fluoroscopically. During the procedure, the patient is either awake under moderate intravenous sedation, or under general anesthesia while employing neurological monitoring.

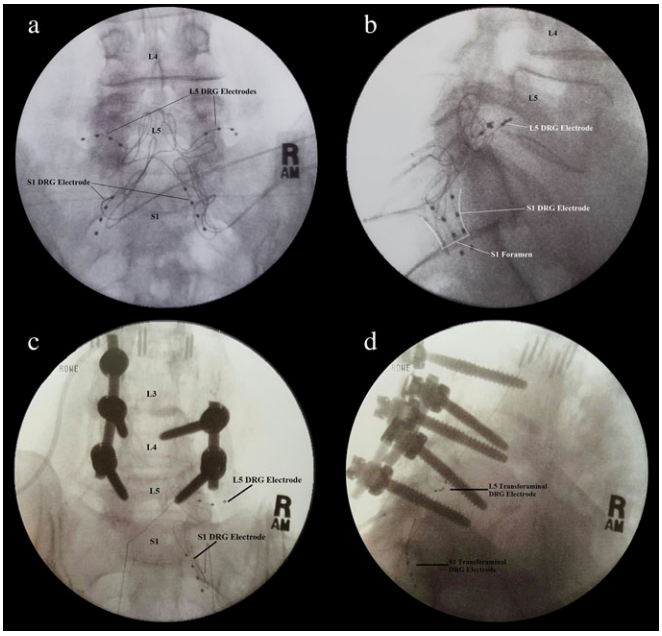

Figure 10. DRG lead placement in the lumbar spine. DRG bilateral lead placement in the lower lumbar spine. AP (a) and lateral (b) views of L5 and S1 leads. AP (c) and lateral (d) views of L5 and S1 leads. [Color figure can be viewed at wileyonlinelibrary.com]

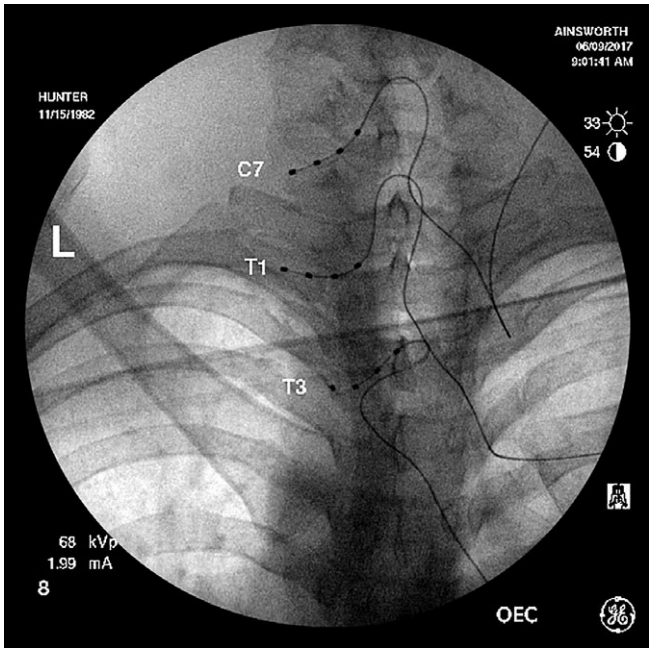

Figure 11. Cervical and high thoracic DRG placement with epidural strain-relief loops.

STEP 2: The introducer needle is placed at the S1 and/or S2 levels under posterior–anterior fluoroscopic view. The supplied 14-gauge introducer needle is then used to penetrate the skin with the bevel of the needle facing in a caudal direction to a depth allowing contact with the bony edge of the foramen to be accessed. With the bevel of the needle maintained in a caudal direction, the needle is stepped off the bony edge of the foramen and advanced approximately 1–1.5 cm into the foramen. Proper depth confirmation is then obtained utilizing a lateral fluoroscopic view to visualize the bevel of the needle position within the ventral foramen. It is important to note that the stress curves are created while observing the lateral fluoroscopic view with the sacral technique, unlike the cervical, thoracic, and lumbar positioning, which is performed using the AP view.

STEP 3: The big curve sheath/lead/stylet is introduced, advanced and locked in place with the bevel of the needle turned in the caudal direction. This configuration generally allows for easy placement within intra-foraminal space. The system is advanced until distal electrode contact occurs just outside of the anterior endplate of the sacral foramen or at the ventral edge of the sacrum in the lateral view. It is understood that 55% of the time the DRG lies within the neuroforamen and 45% of the time the DRG lies within the caudal spinal canal. In this situation one may need the fourth contact to lie within the caudal canal to stimulate the DRG selectively. With electrodes positioned at the ventral edge of the sacrum or ventral to the sacrum, one may still obtain stimulation that improves pain but this may represent S1 nerve root stimulation. All four or the three proximal electrodes may remain intra-foraminal. Optimal position that gives the best relief should be confirmed with the aid of neuromonitoring or with the use of testing during surgery to get the desired stimulation with appropriately low amplitude.

After confirmation of proper placement with lateral fluoroscopy, the hub of the sheath is unlocked from the lead to allow retraction of the sheath, leaving the lead behind at the depth and position confirmed under lateral fluoroscopy.

STEP 4: The sheath is slowly retracted into the tip of the needle under continuous fluoroscopy, and needle and sheath are rotated 180° so that now both the hub of the needle, as well as the side port of the introducer sheath, face in a cephalad direction. From this position and after the stylet of the electrode has been retracted approximately 10–15 cm, the sheath is again locked onto the lead and the system is advanced to create the apex of the superior loop. If resistance is met, the needle bevel/sheath system may be "danced" in the cephalo-medial direction to find passage for creation of the first loop. The sheath is then unlocked and slowly retracted back to the needle bevel, leaving the lead in proper position.

STEP 5: The sheath and needle are rotated back 180° to face in a caudal direction. From this position, the sheath is again locked on the lead and advanced into the foramen, creating the second loop apex. Once the lead/sheath assembly is advanced in the middle of the foramen, the sheath is unlocked and retracted back to the needle, leaving the lead properly positioned.

STEP 6: The needle and sheath are removed, as previously described, under lateral fluoroscopy.

Figure 14 illustrates DRG lead(s) placement in the sacral spine.

Cervical DRG Lead Placement: Access and General Technique.

The cervical lead placement method is very similar to the thoracic method, but with some fine differences that require special attention. The pre-procedure assessment is generally the same with special attention to the central canal diameter and the foramen. Similar suggestions arise regarding anatomic considerations, with less space available for device placement and vascular protection in the high cervical spine. The patient is placed in the prone position and widely prepped and draped. The arms of the patient are traditionally positioned next to the trunk, with the "hands in the front pocket" orientation. The entry point of the intralaminar space is identified, along with the target DRG and the skin entry site. The needle entry point is placed one-and-a-half to two levels below the intralaminar target. The needle angle

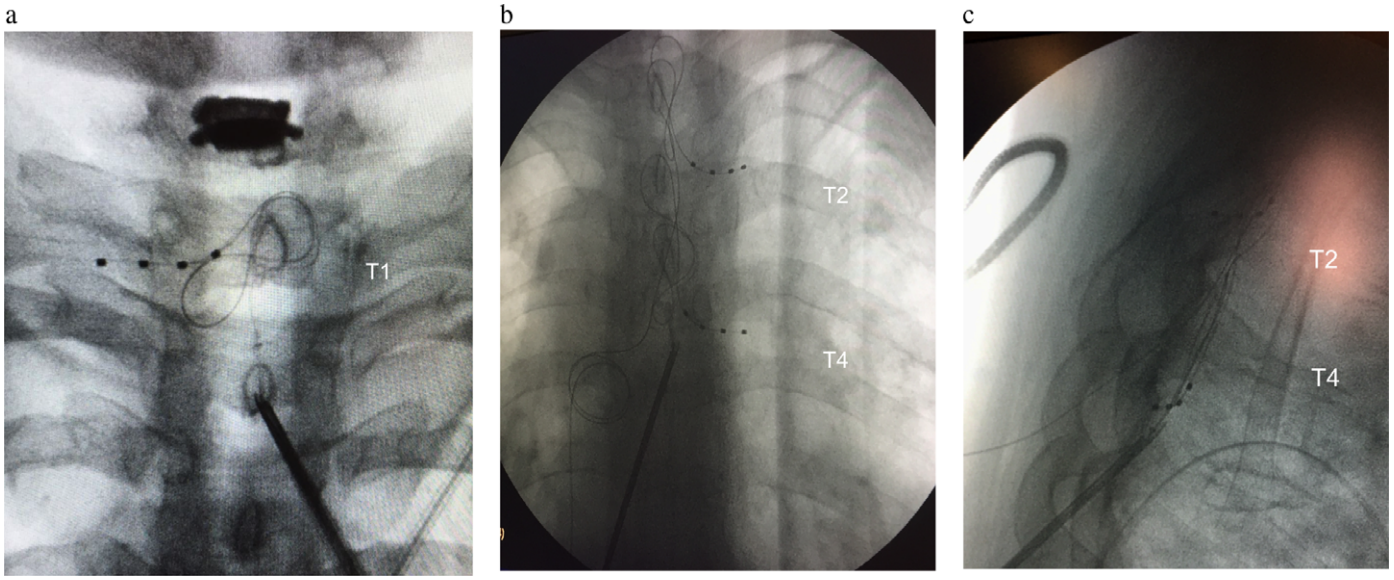

Figure 12. Cervical and high thoracic DRG placement with lateral and A/P views. [Color figure can be viewed at wileyonlinelibrary.com]

is often slightly steeper than that for targets lower in the spine. Once the needle is in the epidural space with the needle bevel below the spinous process, the depth is confirmed on lateral view. Once confirmed on both views, the bevel is pointed towards the foramen. The sheath/lead system is guided to the superior aspect of the foramen and passed through the intra-foraminal ligament, with gentle pressure as previously described. At this level the ligaments tend to be easy to traverse. After AP and lateral fluoroscopic confirmation, the lead can be tested for impedance, and its position confirmed by radiology, neuromonitoring or mapping. In most patients there is a great deal of sensory fiber convergence at this level so the targeting is fairly straightforward. The most common placements are at C6 or C7. In rare cases the DRG at the C5 level can be stimulated with caution. Depending on the intended location of the pocket and the potential need to tunnel the lead longer distances, a connector or longer lead may be used to accommodate the longer tunneling length. This additional lead length allows the implanter to adequately place S loops in the epidural space, use redundant lead length at the lead skin incision site and redundant lead length at the pocket site, if desired.

Figures 15 and 16 illustrate DRG lead placement in the cervical spine.

Trialing Philosophy

The methods of trialing are many and varied and no best practice for DRG stimulation trialing has been established. Table 17 shows the methods of trialing and the benefits and drawbacks of each choice.

Anchoring

Anchoring of the DRG leads is inherently different from anchoring traditional SCS leads. The lower profile structure of the DRG lead and the strain-relief curve inside the epidural space suggest a very different method is at play. In fact, some experts advocate not suturing or anchoring the leads at all. That said, for any percutaneously placed lead, anchoring balances the reduction of lead migration with the potential for fracture. Specifically, traditional anchoring is to the deep fascia. Most leads placed during the ACCURATE study were secured by this method (23). That said, many DRG implanters point to the stress-relief curves as the primary mechanism of securing the lead. Some advocate for additional direct lead anchoring, either by employing the provided plastic anchor or suturing directly to the lead. Again, critics of this technique suggest this may increase the fracture rate.

Regardless of the anchoring strategy employed, either the lumbodorsal fascia or the superficial fascia are used to secure the anchor or lead. Anchoring within these tissue planes typically involves the placement of a loosely tied suture, so as not to form a fulcrum or stress point for the lead motion, but merely to maintain it within a relative zone of possible motion.

No high-quality data exist comparing the possible methods of anchoring; therefore, our recommendation is based on the clinical experience of the expert consensus group. Many physicians with

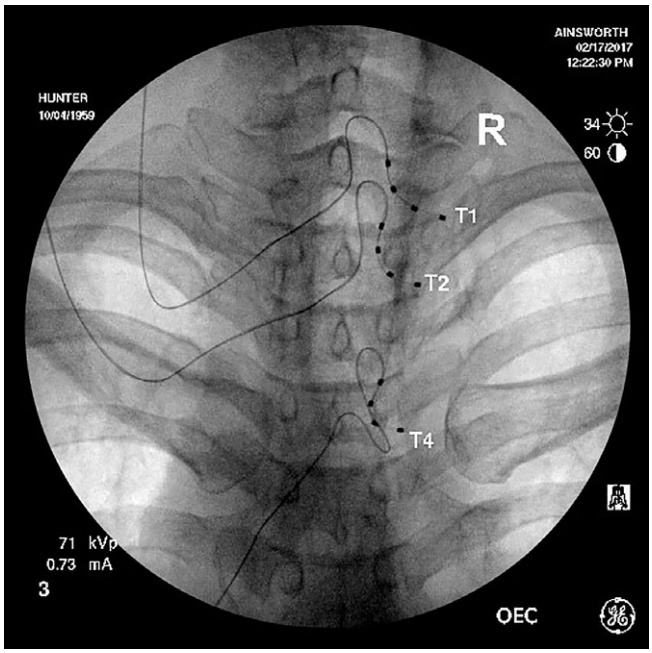

Figure 13. Lead placement at T1, T2 and T4 in a patient with post-mastectomy syndrome.

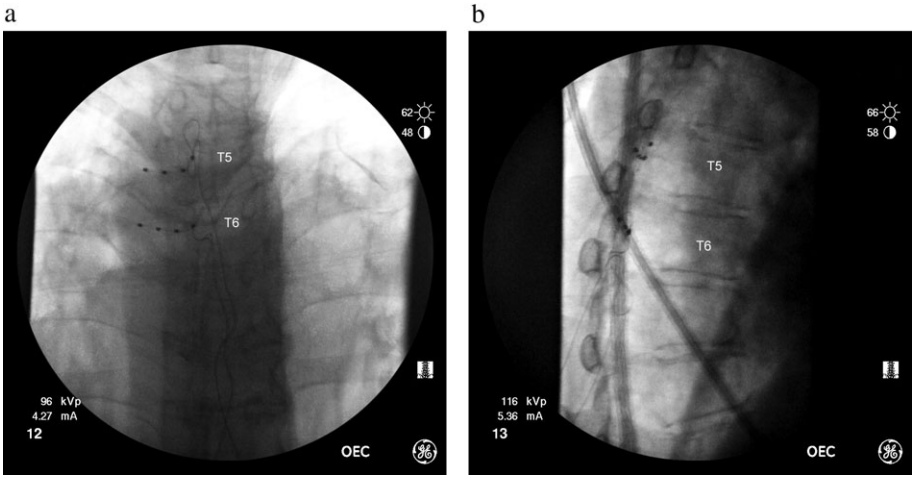

Figure 14. Thoracic DRG placement with A/P and lateral views.

extensive experience do not use any anchoring method, largely based on the low incidence of migration with the use of the S loop in the epidural space.

Consensus point 20 The anchoring method is at the discretion of the implanter. If anchoring is to be used, the NACC suggests securing the lead with a loosely tied anchoring suture, either employing the provided plastic anchor or directly to the lead. Level III, Grade I, Consensus Low.

Consensus point 21 Intra-epidural curve creation with an S-shaped strain-relief curve seems imperative to reduce migration. The NACC recommends creating well-developed inferior and superior curves. Additional configurations may also be useful, but additional studies are needed. Level III, Grade C, Consensus Strong.

Consensus point 22 In settings where the ability to create sufficient epidural strain-relief curves may be limited, such as in some sacral or cervical settings, additional extra-spinal anchoring is recommended. This may require undermining the tissue to allow for a 1–2 cm loop in the lead wound. Level III, Grade I, Consensus Moderate.

Tunneling

The process of tunneling the lead(s) or lead connectors is critical to allow communication of the electrode contacts with the target DRG and the power source. While the surgical concepts of tunneling are similar to those of conventional SCS placement, certain differences must be considered. First, the anatomical path of tunneling depends upon the patient's body habitus, bony margins, and natural landmarks, and should limit transfer across varying depths of adipose tissue. The path of each individual lead is a direct course between the needle-entry deep-tissue plane and the dissected implanted pulse generator (IPG) pocket. The plane of tunneling should be in the deeper subcutaneous adipose tissue.

Second, the chosen tissue plane affects tunneling. If the tunneling path is too superficial, the patient may complain of skin irritation, eventually leading to lead erosion. If the tunneling path is too deep, the lead can lie beneath the muscle fascia, causing postoperative pain or in rare instances visceral damage.

Third, tunneling can be done with either the manufacturer-provided tunneling device or with the epidural Tuohy needle if the incision sites are in close proximity. Because the incision and dissected plane around the needle is usually 2 to 3 cm long and the leads flexible with low tensile strength, a Tuohy needle adds the advantage of precise control over the lead, preventing the lead from falling into the path of the tunneling tool.

Fourth, the area of tunneling should be inspected postoperatively for expansion or swelling. If there are any signs of either, tissue pressure should be applied until the situation has stabilized.

When higher levels of DRG stimulation are planned or multiple leads placed for optimal pain coverage, then the distance between the lead entry tissue plane and the IPG pocket increases with multiple leads tunneled into the pocket. As each lead placement oftentimes requires a new incision and a distinct needle placement within the epidural space, the leads are commonly tunneled to a central lead incision in the paramedian plane contralateral to the DRG locations, and tunneled to the battery site. For bilateral placements of the leads, the same strategy is followed. The lead may or may not be coiled into an additional loop in this secondary pocket. No high-level evidence exists on tunneling and best practices have yet to be determined.

Consensus point 23 The NACC recommends careful preoperative planning for tunneling from the lead placement incisions to the implantable pulse generator, with central lead consolidation when many leads are implanted. Level III, Grade B, Consensus Strong.

Implantable Pulse Generator Pockets and Placement

DRG IPG permanent placement is similar to traditional SCS IPG placement. Although the location varies, the DRG IPG is typically implanted in the posterior lateral flank below the Scarpa's fascia. The IPG is often implanted on the same side as the lead entry, with the lead entry itself on the contralateral side to the target DRG. When possible, this approach is recommended to minimize any undue traction placed on the leads if they cross over the spine. Placing additional strain-relief loops of the lead in the dissected IPG pocket minimizes any traction or mechanical stress on the leads upon undue spine motion. Remaining electrode loops should be placed deep to the IPG to minimize risk of lead damage if the battery pocket needs to be accessed in the future.

As with any neuromodulation permanent implantation procedure, careful hemostasis and avoiding unnecessary tissue damage will minimize resulting seroma formation and subsequent healing complications, such as infection and dehiscence. Meticulous closure in layers will further increase the chance of a successful implant.

The size of the pocket should be of sufficient volume to accommodate the IPG without significant dead space. The pocket incision can be positioned in the midportion of the battery silhouette

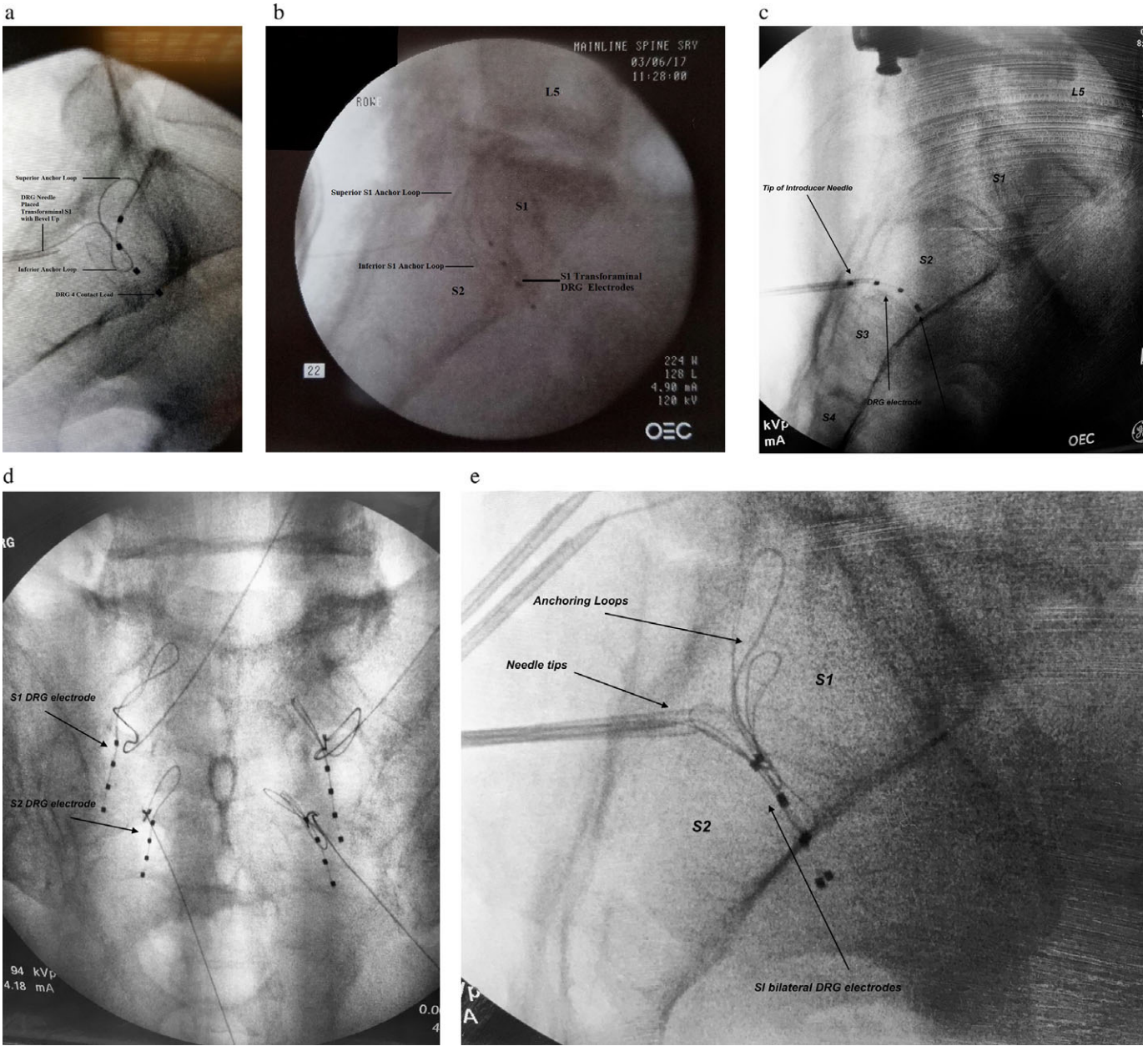

Figure 15. DRG lead placement in the sacral spine. a. S1 transforaminal placement of the needle during dorsal root ganglion (DRG) lead placement. b. Lateral view of final DRG lead placement at S1 with superior and inferior anchoring loops. c. The lateral fluoroscopic image illustrates placement of a S2 DRG-stimulating electrode. The introducer needle has entered the S2 neuroforamen with the needle hub looking caudad. The electrode has been advanced into the neuroforamen, occupying its entire length, while the DRG introducer sheath is located at the very anterior aspect of the neuroforamen. d. This AP fluoroscopic image illustrates placement of bilateral S1 and S2 DRG electrodes. The neuroforamina are clearly visible, as well as multiple sacral anchoring loops for each DRG electrode. e. Lateral fluoroscopic image illustrating two anchored bilateral sacral (S1) DRG electrodes. The electrodes have been placed too far ventral and with both distal contacts outside the anterior S1 endplate. The sheaths have already been retracted and the needles are still in place. Sacral epidural anchoring loops can be identified for both the sacral electrodes. This DRG electrode configuration represents a common suboptimal placement. The electrodes need to be further retracted dorsally with all contacts in the neuroforamen or sacral canal. [Color figure can be viewed at wileyonlinelibrary.com]

or at the top. Being at the midportion allows the battery to be placed in like a button. For obese patients or patients in whom the battery pocket is not snug, an abdominal binder can be used for the first two weeks postimplantation during healing.

If loosening during healing is a concern, sutures can be placed to anchor the fascia. Although the size of the pocket must accommodate the battery, the edges of the wound should come together without undue tension on the tissue. Remaining electrode loops should be placed deep to the IPG to minimize risk of lead damage if the battery pocket needs to be accessed in the future.

Consensus point 24 The NACC recommends the dissection and creation of the IPG pocket in the posterior lateral flank or buttock ipsilateral to the needle skin entrance for DRG lead placement. Level III, Grade B, Consensus Moderate.

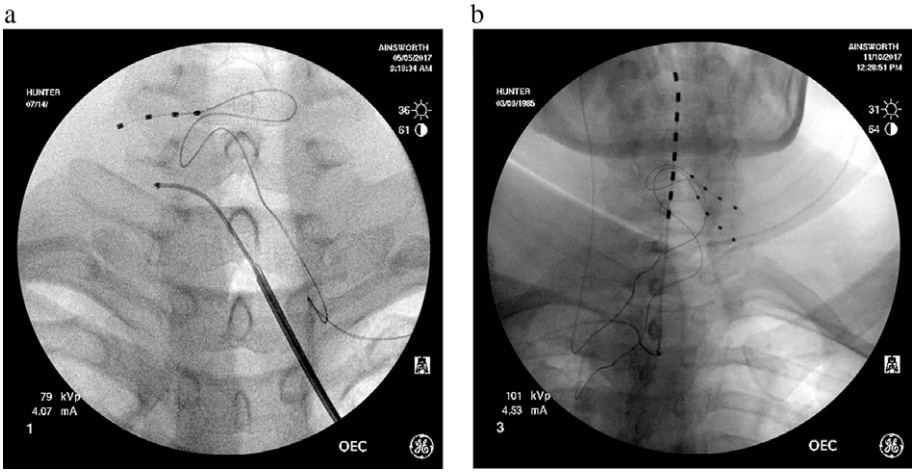

Figure 16. DRG lead placement in the cervical spine. a. Left C7 lead in place with sheath positioned over the C8 dorsal root ganglion (DRG). The guidewire is contained within the sheath. Patient was diagnosed with left upper extremity complex regional pain syndrome (CRPS) following trauma. b. Dorsal column lead as well as right C7 and C8 leads. Patient was diagnosed with CRPS of the right upper extremity as well as cervical radiculopathy.

DORSAL COLUMN SPINAL CORD STIMULATION OR DRG SPINAL STIMULATION?

There is one large prospective RCT comparing SCS to DRG stimulation – the ACCURATE study (23), which investigated CRPS (type I and type II) in the lower extremities and demonstrated that 81.2% of DRG patients achieved ≥50% pain relief compared to 55.7% in the SCS arm ($p < 0.001$) (Table 18). Accumulating evidence from uncontrolled case series suggests that DRG stimulation is effective for focal neuropathic pain of other etiologies, especially when pain is restricted to a small number of dermatomes that can be treated with one or two DRG leads, such as groin pain (63,99). However, RCT evidence of DRG stimulation for these indications is lacking.

For treating widespread pain, SCS provides broader coverage than DRG stimulation. In failed back surgery syndrome (FBSS), there is Level 1 evidence that SCS is better than both conventional medical management (CMM) and reoperation (10,123,125–127). For DRG stimulation for FBSS, there is only weak, preliminary evidence. Most of the evidence relates to back pain rather than radicular pain. For example, Huygen et al. (19) showed that L2-L3 DRG stimulation can provide back pain relief in a series of 12 patients. Weiner et al. used the Stimwave® device (Pompano Beach, FL, USA) at a single level in 11 patients and showed ≥50% pain relief in seven cases at six weeks follow-up (124). Another case series included patients with FBSS and radicular symptoms and showed that for leg pain, DRG stimulation can provide good pain relief, but generally more electrodes are required (25). Furthermore, in this series, DRG stimulation was less effective for FBSS than the other conditions treated: only eight of 16 patients with FBSS (50%) had successful trials compared to 69% of 35 patients being treated for other indications. Evidence is Level II-3 at best (recommendation B) for DRG stimulation in FBSS and there have been no head-to-head studies comparing DRG stimulation to SCS. DRG stimulation may, therefore, be considered following a failure of SCS for this indication.

Placing DRG electrodes in the setting of FBSS may require placement through scar tissue and previous surgical sites, which may obliterate the epidural space. The risk of dural puncture and inability to place a lead is therefore higher than with normal anatomy (consensus view), while SCS does not have this disadvantage as the electrodes may be placed through normal anatomy in the thoracic spine with either percutaneous or paddle leads. Scar tissue may also lead to an increase in impedance (128). These factors may contribute to the apparent lower efficacy of DRG stimulation in FBSS. However, it should be noted that some have advocated for open DRG placement in this situation with the assistance of a spinal surgeon. Most clinical descriptions of DRG stimulation for axial back stimulation have involved placement of the leads at a level much higher than the level of pain. In recent presentations of data, the leads have been placed in a variety of the first three lumbar foramen to treat pain that appears to be mainly discogenic in nature and not consistent with failed back surgery. At the present time, the consensus is not to use DRG stimulation as a primary treatment method for FBSS.

Table 17. Trialing Methods.

Trialing Method	Advantages	Disadvantages
On-table testing with same-day planned implant	Only need to place the lead(s) on one occasion	There is no time period to assess patient response
Staged trialing with permanent trial lead	The lead is only placed once	The lead is externalized and this may increase infection risks The trial is more invasive.
Percutaneous skin trial	Less invasive, and gives time for patient and physician assessment of effect	The lead(s) must be placed on two occasions, increasing risk of suboptimal lead placement
Open surgical trial lead placement	In a difficult foramen, this trial technique allows for direct visualization and may reduce risk	Current leads are not designed for this method of placement and it would be impossible to make the appropriate S loops

Table 18. Evidence for DRG Stimulation vs. SCS.

Key statements	Supporting references	Levels of evidence	Recommendation strength	Consensus strength
DRG stimulation is preferable to standard SCS for pain caused by CRPS in the lower limb.	Deer et al. 2017 (23)	I	A	Strong
For FBSS, SCS stimulation has proven efficacy.	Kumar et al. 2008 (10) North et al. 1994 (123)	I	A	Strong
Evidence for DRG stimulation in FBSS is weak.	Huygen et al. 2017 (19) Weiner et al. 2016 (124) Liem et al. 2015 (25)	II-3/III	C	Moderate

In certain situations, percutaneous DRG may not be feasible regardless of the diagnosis, such as in a CRPS patient who has also had previous spinal fusion. This would normally exclude placement of DRG electrodes via the percutaneous approach and may lead to a patient not being considered for the therapy. Currently this same patient may then be trialed for SCS, but there are the options of either open placement with the DRG percutaneous electrodes or, potentially, the use of a DRG paddle if and when available.

In the setting of open placement of DRG electrodes, whether or not through a previous surgical site, general anesthesia may be necessary. In the asleep or sedated patient, the use of neuromonitoring has been demonstrated as a method of confirming proper placement of the lead intraoperatively (129). General anesthesia may also be used in cases where a patient cannot tolerate local anesthesia for placement of routine DRG percutaneous electrodes, and neuromonitoring may serve as a useful adjunct. In these instances, a staged implantation may be preferred.

Consensus point 25 DRG stimulation is superior to SCS for unilateral focal pain caused by CRPS and causalgia in the groin and lower extremity. Level I, Grade A, Consensus Strong.

Consensus point 26 For other indications there is presently no firm basis on which a recommendation can be made for DRG stimulation over SCS.

PROGRAMMING

DRG programming is dictated by the anatomy of the DRG, the spatial relationship of the lead to the DRG, the design of the device, and the physiology of the T-junction. Best practices for programming are

Table 19. Programmed Stimulation Parameters From the ACCURATE Study (23).

	One months	Three months	Six months	Nine months	Twelve months
Number of Subjects	61	59	59	55	55
Number of Active Leads	124	118	117	107	110
Frequency/Rate Range (Hz)					
N	123	118	117	107	110
Mean	22.5	20.8	20.0	19.0	19.0
SD	6.4	7.1	6.8	5.5	5.1
Median	20	20	20	20	20
Minimum	10	10	10	8	10
Maximum	40	48	48	40	36
Pulse Width (μs)					
N	124	118	117	107	110
Mean	312.4	308.9	315.4	295.6	289.8
SD	148.6	145.9	166.0	140.7	133.8
Median	300	300	300	300	255
Minimum	100	100	60	90	90
Maximum	1000	1000	1000	1000	1000
Amplitude (μA)					
N	122	118	116	107	107
Mean	892.3	915.4	836.4	764.6	827.4
SD	703.9	822	721.9	630.9	657.1
Median	687.5	675	650	575	650
Minimum	150	75	100	100	75
Maximum	4400	6000	4600	3950	4000
Impedance (Ω)					
N	116	116	114	107	110
Mean	1321.2	1431.7	1504.7	1583.9	1458.9
SD	527.9	571.4	700.4	792.S	714.5
Median	1225.5	1329.5	1324.5	1355.0	1256.5
Minimum	645	589	586	572	547
Maximum	5000	4795	5000	5000	4962

Reproduced with permission from Ref. (23).

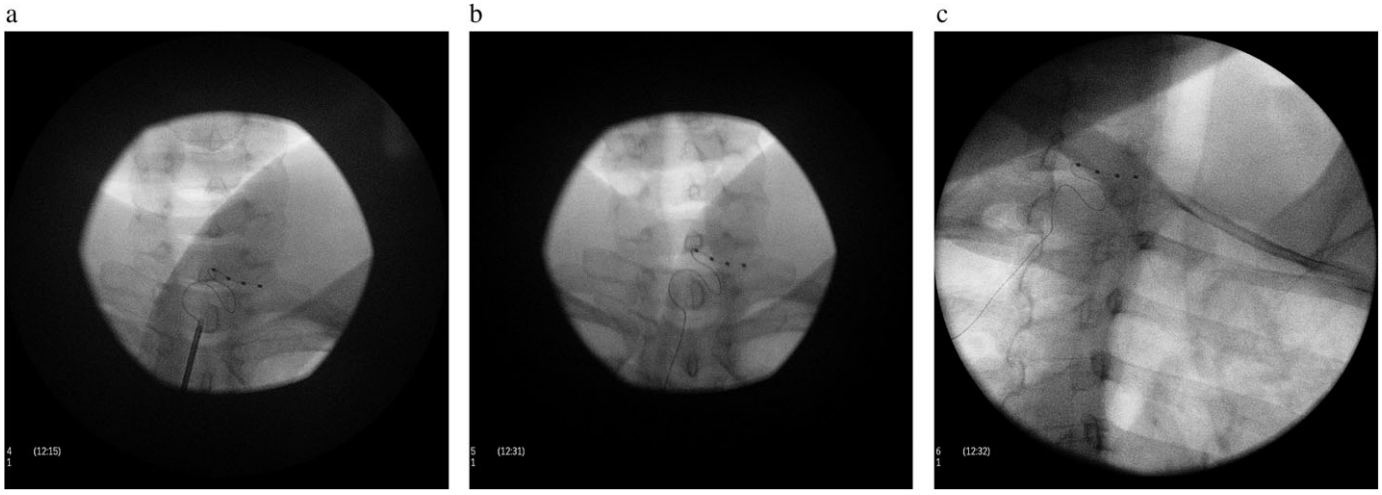

Figure 17. DRG lead placement in the cervical spine. a. AP view right C8 electrode with a flat entry of the epidural needle to aid easy placement. b. AP view showing the C8 dorsal root ganglion (DRG) lead in place with an S loop. c. Inferior oblique view showing the electrode in place.

general principles since individual patients may require different patterns, amplitudes, and spatial arrays of stimulation.

Clinical Parameters

Following successful implantation of the lead into the superior dorsal aspect of the foramen, the programming is performed by handheld mobile devices. The DRG is a discrete structure and the cathode placement on the anatomical location can determine the dispersion of current in the depth and dispersion of electricity in the nerve targets. In the ACCURATE study (23), the median programmed frequency was 20 Hz, with a median pulse width (MPW) of 300 μs at end points (Table 19). The MPW was reduced to 255 μs at one year, consistent with a trend towards a reduced need for paresthesia seen in other studies (130). The median amplitude had a range of 575 μA to 687.5 μA. These stimulation amplitudes are far lower than those used for conventional or high frequency SCS. Impedance levels should be lower than 3000 Ω, and ranged from 1225.5 to 1355.0 Ω in the ACCURATE study (23). Stimulating above 1 millivolt is normally not tolerated by the DRG and indicates poor placement in most settings.

Technique

In the standard programming algorithm for DRG stimulation, low amplitude cathodal stimulation directed at the ganglionic body is optimized using bipolar and extended bipolar arrays (Fig. 17) that have the cathode at the 6 o'clock position under the pedicle, utilizing the above parameters. When multiple electrodes are equidistant from the optimal DRG location, bipolar cathodic stimulation should be initiated at each location (see descending array options in Fig. 17), and the electrode that initiates paresthesia in the area of pain at the lowest amplitude should be chosen. The location of the DRG may be more lateral in relation to the foramen in the lower lumbar spine, and be more medial in the foramen as leads are placed in the upper lumbar spine. This may impact programming.

If any motor contractions occur, the lead is likely in the ventral aspect of the foramen, thus stimulating the ventral root, and should be repositioned. The lowest amplitude at which the patient reports any change in sensation in the painful area should be used. Utilizing this paresthesia threshold to determine optimal stimulation amplitude will avoid overstimulating the DRG. In most current clinical settings, this threshold number is reduced by 40%, to a subthreshold level that does not produce paresthesia. A subset analysis of ACCURATE data showed equal or superior efficacy in this group compared to those obtaining stimulation-induced paresthesia (23).

Unique Characteristics of Dorsal Root Ganglion Programming

There are a few unique approaches to programming the DRG relative to dorsal column stimulation. First, while the DRG is an intradural structure, it is surrounded by a minimal volume of CSF, thus lowering the amount of energy required to stimulate the DRG compared to the dorsal columns. Therefore, sub-milliamp amplitudes are often sufficient to provide the therapeutic benefit. Second, the use of low pulse widths (200–300 μs) is preferred because narrower pulse widths tend to maximize the width of the therapeutic window. Third, complex programming arrays are not necessary, as simple bipolar arrays can achieve optimal activation of the DRG. Finally, while patient movement can produce significant changes in stimulation intensity when using SCS, this does not occur with DRG stimulation and does not need to be considered when programming.

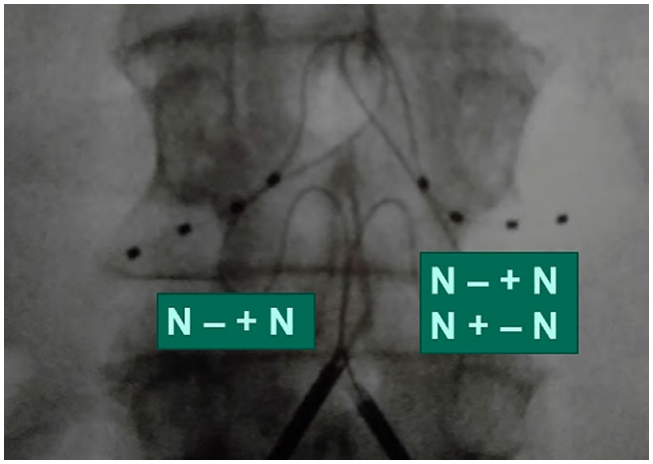

Figure 18. Position of DRG stimulator arrays. [Color figure can be viewed at wileyonlinelibrary.com]

Table 20. Local Anesthetics Used During DRG Lead Placement.

Drug	Onset	Maximum dose (with epinephrine)
Lidocaine	Fast	4.5 mg/kg (7 mg/kg)
Bupivacaine	Slow	2.5 mg/kg (3 mg/kg)
Ropivacaine	Medium	2–3 mg/kg

Anesthetic Management During Dorsal Root Ganglion Procedures

With the evolution of the DRG stimulation technique following commercialization, physician guidance and training have also evolved. The NACC recommendation updates on neurologic risk reduction, published early in 2017, stated that it is critical to be able to detect neural injury (7). Although balancing risks and benefits of a clinical scenario is up to the discretion of the surgeon, clearly safety and efficacy are the primary motivators. Anesthetic techniques among implanters widely vary, from completely awake placement with no sedation and performed under local anesthetic, to monitored anesthesia care with sedation, to general anesthesia. Typically, once the electrode is placed under fluoroscopy, the placement in the dorsal foramen is confirmed with a sensory perception threshold with awake testing via feedback from the patient, or alternatively the absence of a motor contraction after a greater than 2 mA pulse. Impedance testing can also be helpful in determining proper position with respect to the nerve. The use of neuromonitoring has also been demonstrated as a targeting strategy for confirmation of lead placement in sleeping patients (129).

Surgical interventions require a suitable operative field and an experience that is safe and tolerable for the patient. Balancing these surgical necessities requires an appreciation of risks and benefits. Along the sedation spectrum, patients can be prepared with local anesthetic only, with the other extreme being general anesthesia and the need to support the airway and homeostasis. Please see Table 20 regarding local anesthetics commonly employed, including maximal doses.

Table 21. Anesthetic Effect on Electrophysiologic Monitoring.

Agent	SSEPS	MEPS
Volatile anesthetics	Increase latency and decrease amplitude	Depress
Nitrous oxide	Depressant effects	
Propofol	Increases latency and decreases amplitude	Depresses
Opioids	Minimal changes	
Dexmedetomidine	Minimal changes	
Etomidate	Increases amplitude	
Ketamine	Increases amplitude	
Benzodiazepines		Depress

Placement of the electrode in the awake patient with only local anesthesia, allowing for clear confirmation of appropriate lead placement, is possible in selected patients. However, because placement of the lead within the foramen and adjacent to the target DRG can be associated with transient pain, and as it is already hypersensitized, and as navigating the intra-foraminal ligaments requires finesse, it is important to be able to offer appropriate analgesia as needed. Therefore, some implanters have used light or moderate sedation with medications including midazolam, fentanyl, propofol, and/or dexmetomidine. Titration is critical, as time to peak effect varies, requiring careful monitoring. Unequivocally, the patient needs to remain responsive to painful stimuli and communicate with the surgeon, as the patient is used as the monitor of neurological function.

On the other end of the spectrum, asleep placement is another option. This includes a patient under general anesthesia or under deep sedation where the patient is not responsive to painful stimuli while the airway is maintained. This approach has been used safely in many centers since the inception of DRG stimulation. Some have advocated electrophysiological neuromonitoring in either of these scenarios as a means of detecting nerve injury, but there is presently no published data to support this and such neuromonitoring is not widespread. When using neuromonitoring, it

Table 22. Evidence for Neuromonitoring During DRG Implantation.

Key statements	Supporting references	Levels of evidence	Recommendation strength	Consensus strength
DRG placement has been performed either awake with local anesthesia, or under sedation, with varying degrees of depth, to general anesthesia requiring airway management. The risk of neurological injury is accepted as very low and, therefore, it is difficult at present to comment on safety. Some have advocated for the use of neuromonitoring when performed under general anesthesia.	Falowski et al. 2017 (133) Falowski et al. 2016 (134)	II-2	B	Strong
Fluoroscopic imaging, in both an anterior–posterior and lateral projection, is generally utilized as a first step in confirmation of the lead placement, but in certain placements good quality images may not be able to be obtained.	Shils et al. 2012 (132)	II-3	B	Strong
Confirmation of lead placement is effective with the use of neuromonitoring to confirm placement in an asleep patient.	Falowski et al. 2017 (133) Falowski et al. 2016 (134) Shils et al. 2012 (132) Mammis et al. 2012 (135) Falowski et al. 2011 (131)	II-1	B	Strong

Table 23. Risk Mitigation of Possible Complications From DRG Therapy.

Complication	Mechanism of complication	Mitigation technique
Nerve injury	Needle puncture	Appropriate angle, landmarks and pre-procedure imaging
Nerve injury	Lead or sheath trauma	Gentle technique, pre- procedure imaging, patient conversation or neuromonitoring
Dural puncture or CSF leak	Needle puncture	Shallow angle, appropriate pathway to space. Loss of resistance with lateral view
Lead migration	Lack of proper strain relief, not piercing the ligaments	S-loop strain relief, assure sheath is through ligaments
Infection	Surgically acquired	Follow NACC guidance (8)
Bleeding	Perioperatively	Follow NACC guidance (9)
Lead fracture	Fracture at the ligament or at the anchor	Modify needle angle, modify tunneling angle, modify anchoring method
Lead retention	At time of removal, revision or indwelling	Remove the lead under fluoroscopy if resistance occurs; if retained consult neurosurgery. Usually no need to surgically remove the lead unless causing impingement
Pocket pain	Shallow implant, recharging, body contour	Implant as deep as possible, use non-rechargeable devices if possible, assess contour preoperatively

Table 24. Future Developments in DRG Systems.

Advancement	Benefit	Status
Full MRI compatibility	Lessen the need for explant and allow additional testing	Approved conditionally now with some devices with 50 cm leads. Currently, 90 cm leads are not MRI conditional. MRI parameters need to be changed to accommodate device conditional labeling
DRG paddle leads	Allow access to difficult spinal segments	In development; clinical studies soon
Hybrid systems	Allow for conventional SCS and DRG systems to be connected to the same generator	In development
Additional waveforms, frequencies or pulse trains	Permit additional salvage of therapy and reduction of explants	Preliminary work underway

is important to be aware of the influence that anesthetic agents have on recordings, including somatosensory evoked potential (SSEPS) and motor evoked potentials (MEPS) (Table 21). It is important to maintain a stable depth of anesthesia to ensure dependable recordings. Increasing minimum alveolar concentration (MAC) or administering intravenous agents by bolus may depress these readings.

In the case of deep sedation, monitoring respiration, heart rate and blood pressure, as well as managing the patient's airway are critical. Anesthetic agents commonly employed include propofol and volatile anesthetics, with potential securing of the airway with endotracheal intubation, as patients are commonly in the prone position. As noted in Table 21, total intravenous anesthesia (TIVA) is commonly performed, with avoidance of neuromuscular blockade.

Neuromonitoring

Neuromonitoring has been demonstrated as a means of optimizing lead location with SCS systems (131–133). There are published protocols recommend using SSEPs and EMG (electromyography) (134). Potential benefits include improved accuracy of lead placement and an increased degree of comfort for the patient compared to intraoperative trialing using awake patient feedback. One study examined the placement of a DRG electrode in an asleep patient undergoing general anesthesia using neuromonitoring for safety, while guiding and confirming placement (129). In this case series, as with SCS placement, neuromonitoring with SSEPs served as a marker of generated paresthesia, and EMG indicated the presence of motor contractions. Proper lead placement in the dorsal foramen was confirmed by generating appropriate SSEP responses in the absence of EMG responses.

DRG stimulation remains a relatively new technique with insufficient evidence from clinical studies to determine whether overall success rate or procedure safety is influenced by variations in anesthetic technique or the use of adjuncts such as neuromonitoring. At present the full range of anesthetic options is used and there is currently no basis to recommend one over another (Table 22). Very large studies will be required to evaluate these questions. For example, the NACC (7) estimates that the risk of neurologic injury in SCS is at most 2.35%; an intervention which halved this risk would require a 4000-patient study to demonstrate benefit at the 95% confidence level with 80% power. The incidence of neurologic injury, particularly with lumbar DRG stimulation, is likely to be lower still, and the only practical way of evaluating the relative benefits and risks of different anesthetic and monitoring strategies within a reasonable timeframe is likely to be with large-scale registry studies.

COMPLICATIONS AND RISK MITIGATION

When invading the spine with a device, complications are to be expected. The NACC has an objective to reduce the risk and

incidence of these events. Table 23 identifies these complications and suggests mitigation of events.

REVISING A SYSTEM

Lead fracture or movement of the system may require revision. The criteria set in the risk evaluation section remain relevant. Prior to revision the implanter should consider spinal anatomy, medical comorbidities, and other features. In order to complete a successful revision, the implanted lead is identified by fluoroscopy, the lead is removed under both direct vision and x-ray guidance and a replacement lead is placed in the standard manner. In the event the lead is difficult to remove, the implanter should consider alternative spinal levels for lead placement. The use of an open neurosurgical approach to remove the lead is usually not warranted or recommended unless the lead is thought to be causing a complication or compression of the neural structures.

FUTURE DIRECTIONS

The use of DRG therapy represents a major advance in the use of neurostimulation to treat focal neuropathic pain in a very energy-efficient manner. The NACC recommends additional advancements be sought to further enhance the patient experience (Table 24).

CONCLUSIONS

DRG stimulation is a method of neuromodulation that provides potential relief to patients suffering from focal neuropathic pain syndromes. The procedure has a high degree of efficacy and safety based on the published evidence. It is the goal of the NACC to continue to improve on the neuromodulation outcomes. In addition, the NACC recommends that DRG therapy be used in an ethical and thoughtful manner to continue to improve pain relief, reduce complications and help additional patients worldwide.

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Dr. Deer served as primary author, project organizer and editor. All authors wrote sections of the manuscript or provided critical reviews and substantive editing. Drs. Levy and Mekhail served as senior manuscript editors. Opinions expressed herein are not necessarily shared by all authors.

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REFERENCES

1. Gaskin DJ, Richard P. The economic costs of pain in the United States. *J Pain* 2012;13:715–724.
2. Van Buyten JP, Wille F, Smet I et al. Therapy-related explants after spinal cord stimulation: results of an international retrospective chart review study. *Neuromodulation* 2017;20:642–649.
3. Deer TR, Mekhail N, Provenzano D et al. The appropriate use of neurostimulation of the spinal cord and peripheral nervous system for the treatment of chronic pain and ischemic diseases: the Neuromodulation Appropriateness Consensus Committee. *Neuromodulation* 2014;17:515–550.
4. Deer TR, Krames E, Mekhail N et al. The appropriate use of neurostimulation: new and evolving neurostimulation therapies and applicable treatment for chronic pain and selected disease states. *Neuromodulation* 2014;17: 599–615.
5. Deer TR, Mekhail N, Provenzano D et al. The appropriate use of neurostimulation: avoidance and treatment of complications of neurostimulation therapies for the treatment of chronic pain. Neuromodulation Appropriateness Consensus Committee. *Neuromodulation* 2014;17:571–597. discussion 597–578.
6. Deer TR, Mekhail N, Petersen E et al. The appropriate use of neurostimulation: stimulation of the intracranial and extracranial space and head for chronic pain. *Neuromodulation* 2014;17:551–570.
7. Deer TR, Lamer TJ, Pope JE et al. The Neurostimulation Appropriateness Consensus Committee (NACC) safety guidelines for the reduction of severe neurological injury. *Neuromodulation* 2017;20:15–30.
8. Deer TR, Provenzano DA, Hanes M et al. The Neurostimulation Appropriateness Consensus Committee (NACC) recommendations for infection prevention and management. *Neuromodulation* 2017;20:31–50.
9. Deer TR, Narouze S, Provenzano DA et al. The Neurostimulation Appropriateness Consensus Committee (NACC): recommendations on bleeding and coagulation management in neurostimulation devices. *Neuromodulation* 2017;20: 51–62.
10. Kumar K, Taylor RS, Jacques L et al. The effects of spinal cord stimulation in neuropathic pain are sustained: a 24-month follow-up of the prospective randomized controlled multicenter trial of the effectiveness of spinal cord stimulation. *Neurosurgery* 2008;63:762–770. discussion 770.
11. Sanders RA, Moeschler SM, Gazelka HM et al. Patient outcomes and spinal cord stimulation: a retrospective case series evaluating patient satisfaction, pain scores, and opioid requirements. *Pain Pract* 2016;16:899–904.
12. Hayek SM, Veizi E, Hanes M. Treatment-limiting complications of percutaneous spinal cord stimulator implants: a review of eight years of experience from an academic center database. *Neuromodulation* 2015;18:603–608.
13. Han JL, Murphy KR, Hussaini SMQ et al. Explantation rates and healthcare resource utilization in spinal cord stimulation. *Neuromodulation* 2017;20:331–339.
14. Pope JE, Deer TR, Falowski S et al. Multicenter retrospective study of neurostimulation with exit of therapy by explant. *Neuromodulation* 2017;20: 543–552.
15. New data confirms Abbott's dorsal root ganglion stimulation offers greater treatment success over traditional spinal cord stimulation. http://abbott.mediaroom.com/2017-01-17-New-Data-Confirms-Abbotts-Dorsal-Root-Ganglion-Stimulation-Offers-Greater-Treatment-Success-over-Traditional-Spinal-Cord-Stimulation. Accessed 17 Dec. 2017.
16. Bevan S, Yeats J. Protons activate a cation conductance in a sub-population of rat dorsal root ganglion neurones. *J Physiol* 1991;433:145–161.
17. Deer TR, Grigsby E, Weiner RL, Wilcosky B, Kramer JM. A prospective study of dorsal root ganglion stimulation for the relief of chronic pain. *Neuromodulation* 2013;16:67–71.
18. Liem L, Russo M, Huygen FJ et al. A multicenter, prospective trial to assess the safety and performance of the spinal modulation dorsal root ganglion neurostimulator system in the treatment of chronic pain. *Neuromodulation* 2013;16: 471–482. discussion 482.
19. Huygen F, Liem L, Cusack W, Kramer J. Stimulation of the L2-L3 dorsal root ganglia induces effective pain relief in the low back. *Pain Pract* 2018;18: 205–213. https://doi.org/10.1111/papr.12591.
20. Van Buyten JP, Smet I, Liem L, Russo M, Huygen F. Stimulation of dorsal root ganglia for the management of complex regional pain syndrome: a prospective case series. *Pain Pract* 2015;15:208–216.

21. Bayman EO, Brennan TJ. Incidence and severity of chronic pain at 3 and 6 months after thoracotomy: meta-analysis. *J Pain* 2014;15:887–897.
22. Eldabe S, Burger K, Moser H et al. Dorsal root ganglion (DRG) stimulation in the treatment of phantom limb pain (PLP). *Neuromodulation* 2015;18:610–617.
23. Deer TR, Levy RM, Kramer J et al. Dorsal root ganglion stimulation yielded higher treatment success rate for complex regional pain syndrome and causalgia at 3 and 12 months: a randomized comparative trial. *Pain* 2017;158:669–681.
24. Pope JE, Deer T, Kramer J. A systematic review: current and future dorsal root ganglion therapeutics to treat chronic pain. *Pain Med* 2013;14:1477–1496.
25. Liem L, Russo M, Huygen FJ et al. One-year outcomes of spinal cord stimulation of the dorsal root ganglion in the treatment of chronic neuropathic pain. *Neuromodulation* 2015;18:41–48.
26. Bennett G, Burchiel K, Buchser E et al. Clinical guidelines for intraspinal infusion: report of an expert panel. PolyAnalgesic Consensus Conference 2000. *J Pain Symptom Manage* 2000;20:S37–S43.
27. Hassenbusch SJ, Portenoy RK, Cousins M et al. Polyanalgesic Consensus Conference 2003: an update on the management of pain by intraspinal drug delivery--report of an expert panel. *J Pain Symptom Manage* 2004;27:540–563.
28. Deer T, Krames ES, Hassenbusch SJ et al. Polyanalgesic Consensus Conference 2007: recommendations for the management of pain by intrathecal (intraspinal) drug delivery: report of an interdisciplinary expert panel. *Neuromodulation* 2007;10:300–328.
29. Deer TR, Prager J, Levy R et al. Polyanalgesic Consensus Conference 2012: recommendations for the management of pain by intrathecal (intraspinal) drug delivery. report of an interdisciplinary expert panel. *Neuromodulation* 2012;15: 436–464. discussion 464–436.
30. Deer TR, Prager J, Levy R et al. Polyanalgesic Consensus Conference--2012: recommendations on trialing for intrathecal (intraspinal) drug delivery: report of an interdisciplinary expert panel. *Neuromodulation* 2012;15:420–435. discussion 435.
31. Deer TR, Prager J, Levy R et al. Polyanalgesic Consensus Conference--2012: consensus on diagnosis, detection, and treatment of catheter-tip granulomas (inflammatory masses). *Neuromodulation* 2012;15:483–495. discussion 496.
32. Deer TR, Levy R, Prager J et al. Polyanalgesic Consensus Conference--2012: recommendations to reduce morbidity and mortality in intrathecal drug delivery in the treatment of chronic pain. *Neuromodulation* 2012;15:467–482. discussion 482.
33. Lucas NP, Macaskill P, Irwing L, Bogduk N. The development of a quality appraisal tool for studies of diagnostic reliability (QAREL). *J Clin Epidemiol* 2010; 63:854–861.
34. Furlan AD, Malmivaara A, Chou R et al. Updated method guideline for systematic reviews in the Cochrane Back and Neck Group. *Spine* 2015, 2015;40: 1660–1673.
35. Manchikanti L, Hirsch JA, Cohen SP et al. Assessment of methodologic quality of randomized trials of interventional techniques: development of interventional pain management specific instrument. *Pain Physician* 2014;17: E263–E290.
36. Harris RP, Helfand M, Woolf SH et al. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med* 2001;20:21–35.
37. Olszewska B, Wozniak W, Gardner E, O'Rahilly R. Types of neural cells in the spinal ganglia of human embryos and early fetuses. *Z Mikrosk Anat Forsch* 1979;93: 1182–1199.
38. Mai JK, Paxinos G, editors. *The Human Nervous System (Third Edition)*. London: Academic Press (Elsevier), 2012;p. 14–30.
39. Sheng SR, Wang XY, Xu HZ et al. Anatomy of large animal spines and its comparison to the human spine: a systematic review. *Eur Spine J* 2010;19:46–56.
40. Kandel ER, Schwartz JH, Jessell TM, Siegelbaum SA, editors. *Principles of Neural Science*. 4th ed. Cambridge: McGrawHill, 2000; p. 24.
41. Gemes G, Koopmeiners A, Rigaud M et al. Failure of action potential propagation in sensory neurons: mechanisms and loss of afferent filtering in c-type units after painful nerve injury. *J Physiol* 2012;591:1111–1131.
42. Yabuki S, Kikuchi S. Positions of dorsal root ganglia in the cervical spine. An anatomic and clinical study. *Spine* 1996;21:1513–1517.
43. Ebraheim NA, Lu J. Morphometric evaluation of the sacral dorsal root ganglia. A cadaveric study. *Surg Radiol Anat* 1998;20:105–108.
44. Vialle E, Vialle LR, Contreras W, Chárbel J. Anatomical study on the relationship between the dorsal root ganglion and the intervertebral disc in the lumbar spine. *Rev Bras Ortop* 2015;50:450–454.
45. Sundt D, Gamper N, Jaffe DB. Spike propagation through the dorsal root ganglia in an unmyelinated sensory neuron: a modeling study. *J Neurophysiol* 2015; 114:3140–3153.
46. Hendry SHC, Hsiao SS, Brown HC. Fundamentals of sensory systems. In: Squire LR, Bloom FE, McConnell SK et al., editors. *Fundamental Neuroscience*. San Diego, CA: Academic, 1999; p. 657–670.
47. Zhou L, Chiu SY. Computer model for action potential propagation through branch point in myelinated nerves. *J Neurophysiol* 2001;85:197–210.
48. Zhang JM, Donnelly DF, LaMotte RH. Patch clamp recording from the intact dorsal root ganglion. *J Neurosci Methods* 1998;79:97–103.
49. Luscher C, Streit J, Quadroni R, Luscher HR. Action potential propagation through embryonic dorsal root ganglion cells in culture. I. Influence of the cell morphology on propagation properties. *J Neurophysiol* 1994;72:622–633.
50. Wang W, Gu J, Li YQ, Tao YX. Are voltage-gated sodium channels on the dorsal root ganglion involved in the development of neuropathic pain? *Mol Pain* 2011; 7:16.
51. Ueda H. Molecular mechanisms of neuropathic pain-phenotypic switch and initiation mechanisms. *Pharmacol Ther* 2006;109:57–77.
52. Xie WR, Deng H, Li H, Bowen TL, Strong JA, Zhang JM. Robust increase of cutaneous sensitivity, cytokine production and sympathetic sprouting in rats with localized inflammatory irritation of the spinal ganglia. *Neuroscience* 2006;142: 809–822.
53. Li JY, Xie W, Strong JA, Guo QL, Zhang JM. Mechanical hypersensitivity, sympathetic sprouting, and glial activation are attenuated by local injection of corticosteroid near the lumbar ganglion in a rat model of neuropathic pain. *Reg Anest Pain Med* 2011;36:56–62.
54. Sapunar D, Vukojevic K, Kostic S, Puljak L. Attenuation of pain-related behavior evoked by injury through blockade of neuropeptide Y Y2 receptor. *Pain* 2011; 152:1173–1181.
55. Castro-Lopes JM, Coimbra A, Grant G, Arvidsson J. Ultrastructural changes of the central scalloped (C_1) primary afferent endings of synaptic glomeruli in the substantia gelatinosa Rolandi of the rat after peripheral neurotomy. *J Neurocytol* 1990;19:329–337.
56. Woolf CJ, Shortland P, Coggeshall RE. Peripheral nerve injury triggers central sprouting of myelinated afferents. *Nature* 1992;355:75–78.
57. Cook AJ, Woolf CJ, Wall PD, McMahon SB. Dynamic receptive field plasticity in rat spinal cord dorsal horn following C-primary afferent input. *Nature* 1987;325:151–153.
58. Devor M, Wall PD. Plasticity in the spinal cord sensory map following peripheral nerve injury in rats. *J Neurosci* 1981;1:679–684.
59. Merzenich MM, Kaas JH. Reorganization of mammalian somatosensory cortex following peripheral nerve injury. *Trends Neurosci* 1982;5:434–436.
60. Doubell TP, Mannion RJ, Woolf CJ. The dorsal horn: state-dependent sensory processing, plasticity and the generation of pain. In: Fields HL, Basbaum AI, Heinricher MM, editors. *Textbook of Pain*. London: Churchill Livingstone, 1999; p. 165–181.
61. Vaso A, Adaban HM, Gijika A et al. Peripheral nervous system origin of phantom limb pain. *Pain* 2014;155:1384–1391.
62. Hunter CW, Yang A, Davis T. Selective radiofrequency stimulation of the dorsal root ganglion (DRG) as a method for predicting targets for neuromodulation in patients with post amputation pain: a case series. *Neuromodulation* 2017;20: 708–718.
63. Zuidema X, Breel J, Wille F. Paresthesia mapping: a practical workup for successful implantation of the dorsal root ganglion stimulator in refractory groin pain. *Neuromodulation* 2014;17:665–669. discussion 669.
64. Hunter C, Sayed D, Lubenow T et al. *A physician initiated, multicenter retrospective registry on dorsal root ganglion (DRG) stimulation - an analysis on the impact of lead location compared to the presentation of pain.* Presented at: International Neuromodulation Society - 13th World Congress; Edinburgh, Scotland, United Kingdom, 2017.
65. Hasegawa T, An HS, Haughton VM. Imaging anatomy of the lateral lumbar spinal canal. *Sem Ultrasound, CT MR* 1993;14:404–413.
66. Hasegawa T, Mikawa Y, Watanabe R, An HS. Morphometric analysis of the lumbosacral nerve roots and dorsal root ganglia by magnetic resonance imaging. *Spine* 1996;21:1005–1009.
67. Krames ES. The dorsal root ganglion in chronic pain and as a target for neuromodulation: a review. *Neuromodulation* 2015;18:24–32.
68. Devor M. Unexplained peculiarities of the dorsal root ganglion. *Pain* 1999;6:S27–S35.
69. Sapunar D, Ljubkovicm M, Lirk P, McCallum JB, Hogan QH. Distinct membraine effects of spinal nerve ligation on injured and adjacent dorsal root ganglion neurons in rats. *Anesthesiology* 2005;103:360–363.
70. Sukhotinzky I, Ben-Dor E, Raber P, Devor M. Key role of the dorsal root ganglion in neuropathic tactile hypersensibility. *Eur J Pain* 2004;8:135–143.
71. Chessell IP, Hatcher JP, Bountra C et al. Disruption of the P2X7 purinoceptor gene abolishes chronic inflammatory and neuropathic pain. *Pain* 2005;114: 386–396.
72. Wagner R, Myers RR. Endoneurial injection of TNF-alpha produces neuropathic pain behaviors. *Neuroreport* 1996;7:2897–2901.
73. Krames E. The role of the dorsal root ganglion in the development of neuropathic pain. *Pain Med* 2014;15:1669–1685.
74. Hanani M. Satellite glial cells in sensory ganglia: from form to function. *Brain Res Rev* 2005;48:457–476.
75. Colburn RW, Rickman AJ, DeLeo JA. The effect of site and type of nerve injury on spinal glial activation and neuropathic pain behavior. *Exp Neurol* 1999;157: 289–304.
76. DeLeo JA, Tanga FY, Tawfik VL. Neuroimmune activation and neuroinflammation in chronic pain and opioid tolerance/hyperalgesia. *Neuroscientist* 2004;10: 40–52.
77. Herdege T, Fiallos-Estrade CE, Schmid W, Braco R, Zimmerman M. The transcription factors c-JUN, JUN-D, and CREB, but no FOS and KROX-24, are differentially regulated in axotomized neurons following transection of rat sciatic nerve. *Brain Res Mol Brain Res* 1992;14:155–165.
78. Kostyuk PG, Veselovsky NS, Tsyandryenko AY. Ionic currents in the somataic membrane of rat dorsal root ganglion neurons. I. Sodium currents. *Neuroscience* 1981;6:2423–2430.
79. Kim SH, Chung JM. An experimental model for peripheral neuropathy produced by segmental spinal nerve ligation in the rat. *Pain* 1992;50:355–363.
80. Lirk P, Poroli M, Rigaud M et al. Modulators of calcium influx regulate membrane excitability in rat dorsal root ganglion neurons. *Anesth Analg* 2008;107:673–685.
81. Hogan QH. Role of decreased sensory neuron membrane calcium currents in the genesis of neuropathic pain. *Croat Med J* 2007;48:9–21.
82. Evans AR, Nichol GD, Vasko MR. Differential regulation of evoked peptide release by voltage-sensitive calcium channels in rat sensory neurons. *Brain Res* 1996;712:265–273.

83. Croom JE, Foreman R, Chandler MJ, Barron KW. Cutaneous vasodilation during dorsal column stimulation is mediated by dorsal roots and CGRP. *Am J Physiol* 1997;272:H950–H957.
84. Lee DC. *Modulation of bipolar neuron activity by extracellular electric field.* Presented at: Neuroscience; Washington, D.C., 2011
85. Koopmeiners AS, Meuller S, Kramer J, Hogan Q. Effect of electrical field stimulation on dorsal root ganglion neuronal function. *Neuromodulation* 2013;16: 304–311.
86. Schu S, Mutagi H, Kapur S et al. Sustained pain relief in painful diabetic neuropathy (PDN) achieved through targeted spinal cord stimulation (SCS): a retrospective case series. *Neuromodulation* 2015;18:e91.
87. Eldabe S, Espinet A, Kang P et al. Dorsal root ganglia stimulation for painful diabetic peripheral neuropathy: a preliminary report. *Neuromodulation* 2017;20:e51.
88. Falowski S, Pope J, Cusack W. *Early US experience with stimulation of the dorsal root ganglia for the treatment of peripheral neuropathy in the lower extremities: a multicenter retrospective case series.* Abstract from: International Neuromodulation Society - 13th World Congress; 2017; Edinburgh, Scotland, UK.
89. Slangen R, Schaper NC, Faber CG et al. Spinal cord stimulation and pain relief in painful diabetic peripheral neuropathy: a prospective two-center randomized controlled trial. *Diabetes Care* 2014;37:3016–3024.
90. de Vos CC, Meier K, Zaalberg PB et al. Spinal cord stimulation in patients with painful diabetic neuropathy: a multicentre randomized clinical trial. *Pain* 2014; 155:2426–2431.
91. Espinet AJ. Stimulation of dorsal root ganglion (DRG) for chronic post-surgical pain (CPSP): a retrospective single centre case series from Australia using targeted spinal cord stimulation (SCS). *Neuromodulation* 2015;18:e93.
92. Liem L, Nijhuis H, Huygen FJPM et al. Treatment of chronic post-surgical pain (CPSP) using spinal cord stimulation (SCS) of the dorsal root ganglion (DRG) neurostimulation: results from two prospective studies. *Pain Pract* 2014;14:3–4.
93. Breel J, Zuidema X, Schapendonk J, Lo B, Wille FF. Treatment of chronic post-surgical pain with dorsal root ganglion (DRG) stimulation (10701). *Neuromodulation* 2016;19:e15.
94. Wang L, Guyatt GH, Kennedy SA et al. Predictors of persistent pain after breast cancer surgery: a systematic review and meta-analysis of observational studies. *CMAJ* 2016;188:E352–E361.
95. Weigel R, Capelle HH, Schmelz M, Krauss JK. Thoracic ganglionectomy in segmental neuropathic pain. *Eur J Pain* 2012;16:1398–1402.
96. Hunter C, Dave N, Diwan S, Deer T. Neuromodulation of pelvic visceral pain: review of the literature and case series of potential novel targets for treatment. *Pain Pract* 2013;13:3–17.
97. Ploteau S, Labat JJ, Riant T, Levesque A, Robert R, Nizard J. New concepts on functional chronic pelvic and perineal pain: pathophysiology and multidisciplinary management. *Discovery Med* 2015;19:185–192.
98. Janicki TI. Chronic pelvic pain as a form of complex regional pain syndrome. *Clin Obst Gynecol* 2003;46:797–803.
99. Schu S, Gulve A, Eldabe S et al. Spinal cord stimulation of the dorsal root ganglion for groin pain-a retrospective review. *Pain Pract* 2015;15:293–299.
100. Mills D, Helm E, eds. *A case report of phantom limb pain relief with selective dorsal root ganglion stimulation over spinal cord stimulation following a simultaneous implantation trial.* Presented at: 41st Annual Regional Anesthesiology and Acute Pain Medicine Meeting of the American Society of Regional Anesthesia and Pain Medicine; San Diego, CA, 2016.
101. Aiyer R, Barkin RL, Bhatia A, Gungor S. A systematic review on the treatment of phantom limb pain with spinal cord stimulation. *Pain Manag* 2017;7:59–69.
102. Lazorthes Y, Sol JC, Fowo S, Roux FE, Verdie JC. Motor cortex stimulation for neuropathic pain. *Acta Neurochirurgica* 2007;97:37–44.
103. Chivukula S, Tempel ZJ, Chen CJ, Shin SS, Gande AV, Moossy JJ. Spinal and nucleus caudalis dorsal root entry zone lesioning for chronic pain: efficacy and outcomes. *World Neurosurg* 2015;84:494–504.
104. Vesper J, Schu S, Slotty P et al. Cervical and high-thoracic dorsal root ganglion stimulation (DRG) in chronic pain (10317). *Neuromodulation* 2016;19:388.
105. Sullivan R, Teddy P. Stimulation of dorsal root ganglion (DRG) for chronic intractable pain: a retrospective single centre case series from Australia using targeted spinal cord stimulation (SCS). *Neuromodulation* 2015;18:e95.
106. Yang YB, Fan F, Yang KQ et al. Interventional therapy for neuropathic pain. *Chinese J Contemp Neurology Neurosurg* 2013;13:831–837.
107. Yanamoto F, Murakawa K. The effects of temporary spinal cord stimulation (or spinal nerve root stimulation) on the management of early post-herpetic neuralgia from one to six months of its onset. *Neuromodulation* 2012;15: 151–154. discussion 154.
108. St. Jude Medical [now Abbott]. *Proclaim™ DRG Implantable Pulse Generator. Clinician's Manual*. Plano, TX: St. Jude Medical, 2017.
109. St. Jude Medical [now Abbott]. *Axium™ Neurostimulator System Physician Implant Manual*. Plano, TX: St. Jude Medical, 2016.
110. Vancamp T, Levy RM, Pena I, Pajuelo A. Relevant anatomy, morphology, and implantation techniques of the dorsal root ganglia at the lumbar levels. *Neuromodulation* 2017;20:690–702.
111. Hasue M, Kunogi J, Konno S, Kikuchi S. Classification by position of dorsal root ganglia in the lumbosacral region. *Spine* 1989;14:1261–1264.
112. Porter RW, Hibbert C, Evans C. The natural history of root entrapment syndrome. *Spine* 1984;9:418–421.
113. Kunogi J, Hasue M. Diagnosis and operative treatment of intraforaminal and extraforaminal nerve root compression. *Spine* 1991;16:1312–1320.
114. Jenis LG, An HS. Spine update. Lumbar foraminal stenosis. *Spine* 2000;25: 389–394.
115. Lee CK, Rauschning W, Glenn W. Lateral lumbar spinal canal stenosis: classification, pathologic anatomy and surgical decompression. *Spine* 1988;13:313–320.
116. Lee S, Lee JW, Yeon JS et al. A practical MRI grading system for lumbar foraminal stenosis. *Am J Roentgenol* 2010;194:1095–1098.
117. Yamada K, Aota Y, Higashi T et al. Lumbar foraminal stenosis causes leg pain at rest. *Eur Spine J* 2014;23:504–507.
118. Hasegawa T, An HS, Haughton VM, Nowicki BH. Lumbar foraminal stenosis: critical heights of the intervertebral discs and foramina: a cryomicrotome study in cadavera. *J Bone Joint Surg Am* 1995;77:32–38.
119. Kreis P, Fishman S, editors. *Spinal Cord Stimulation Implantation*. Oxford: Oxford University Press, 2009.
120. Nowicki BH, Haughton VM, Schmidt TA et al. Occult lumbar lateral spinal stenosis in neural foramina subjected to physiologic loading. *Am J Neuroradiol* 1996; 17:1605–1614.
121. Akdemir G. Thoracic and lumbar intraforaminal ligaments. *J Neurosurg Spine* 2010;13:351–355. Level: IIIB.
122. Zhao Q, Zhong E, Shi B, Li Y, Sun C, Ding Z. The morphology and clinical significance of the intraforaminal ligaments at the L5-S1 levels. *Spine J* 2016;16: 1001–1006. Level: IIIB.
123. North RB, Kidd DH, Lee MS, Piantodosi S. A prospective, randomized study of spinal cord stimulation versus reoperation for failed back surgery syndrome: initial results. *Stereotact Funct Neurosurg* 1994;62:267–272.
124. Weiner RLYA, Montes Garcia A, Tyler Perryman L, Speck B. Treatment of FBSS low back pain with a novel percutaneous DRG wireless stimulator: pilot and feasibility study. *Pain Med* 2016;17:1911–1916.
125. Kapural L, Yu C, Doust MW et al. Novel 10-kHz high-frequency therapy (HF10 therapy) is superior to traditional low-frequency spinal cord stimulation for the treatment of chronic back and leg pain: the SENZA-RCT randomized controlled trial. *Anesthesiology* 2015;123:851–860.
126. Kumar K, Taylor RS, Jacques L et al. Spinal cord stimulation versus conventional medical management for neuropathic pain: a multicentre randomised controlled trial in patients with failed back surgery syndrome. *Pain* 2007;132: 179–188.
127. North RB, Kidd DH, Farrokhi F, Piantadosi SA. Spinal cord stimulation versus repeated lumbosacral spine surgery for chronic pain: a randomized, controlled trial. *Neurosurgery* 2005;56:98–106.
128. Grill WM, Mortimer JT. Electrical properties of implant encapsulation tissue. *Ann Biomed Eng* 1994;22:23–33.
129. Falowski SM, Dianna A. A prospective analysis of neuromonitoring for confirmation of lead placement in dorsal root ganglion stimulation. *Oper Neurosurg* 2017;14:654–660.
130. Verrills P, Mitchell B, Vivian D et al. *Subthreshold Stimulation of the Dorsal Root Ganglia: Retrospective Study.* Presented at: North American Neuromodulation Society; Las Vegas, NV, USA, 2017.
131. Falowski SM, Celii A, Sestokas AK, Schwartz DM, Matsumoto C, Sharan A. Awake vs. asleep placement of spinal cord stimulators: a cohort analysis of complications associated with placement. *Neuromodulation* 2011;14:130–134. discussion 134–135.
132. Shils JL, Arle JE. Intraoperative neurophysiologic methods for spinal cord stimulator placement under general anesthesia. *Neuromodulation* 2012;15: 560–571.
133. Falowski S, Sharan A, McInerney J, Jacobs D, Venkatesan L. *Agnesi F. NAPS - Non-Awake versus awake placement of spinal cord stimulators: a prospective, multicenter study comparing safety and efficacy.* Presented at: North American Neurmodulation Society; Las Vegas, NV, USA, 2017
134. Falowski S, Dianna A. Neuromonitoring protocol for spinal cord stimulator cases with case descriptions. *Int J Acad Med* 2016;2:132–144.
135. Mammis A, Mogilner AY. The use of intraoperative electrophysiology for the placement of spinal cord stimulator paddle leads under general anesthesia. *Neurosurgery* 2012;70:230–236.

APPENDIX A

HOW EVIDENCE WAS EVALUATED FOR DRG CONSENSUS

	QAREL	Cochrane	RCT	OBS
Level 1 (Strong)	10–12	10–13	39 and greater	39 and greater
Level 2 (Moderate)	8–9	8–9	29–38	29–38
Level 3 (Fair)	6–7	6–7	16–28	16–28
Level 4 (Limited)	< 4	< 4	< 16	< 16

CRITERIA FOR SYSTEMATIC LITERATURE REVIEW GRADING

Qualitative modified approach to grading of evidence.

Level I	Strong	Evidence obtained from two or more relevant high quality randomized controlled trials for effectiveness. or Evidence obtained from four or more relevant high quality observational studies or large case series for assessment of preventive measures, adverse consequences, effectiveness of other measures.
Level II	Moderate	Evidence obtained from at least one relevant high quality randomized controlled trial or multiple relevant moderate or low quality randomized controlled trials. or Evidence obtained from at least two high quality relevant observational studies or large case series for assessment of preventive measures, adverse consequences, and effectiveness of other measures.
Level III	Fair	Evidence obtained from at least one relevant high quality nonrandomized trial or observational study with multiple moderate or low quality observational studies. or At least one high quality relevant observational study or large case series for assessment of preventive measures, adverse consequences, effectiveness of other measures.
Level IV	Limited	Evidence obtained from multiple moderate or low quality relevant observational studies. or Evidence obtained from moderate quality observational studies or large case series for assessment of preventive measures, adverse consequences, and effectiveness of other measures.
Level V	Consensus based	Opinion or consensus of a large group of clinicians and/or scientists for effectiveness as well as to assess preventive measures, adverse consequences, effectiveness of other measures.

Modified from Ref. (35).

Guide for strength of recommendations.

	Rating for Strength of Recommendation
Strong	There is high confidence that the recommendation reflects best practice. This is based on: 1) strong evidence for a true net effect (e.g., benefits exceed harms); 2) consistent results, with no or minor exceptions; 3) minor or no concerns about study quality; and/or 4) the extent the panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation.
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on: 1) good evidence for a true net effect (e.g., benefits exceed harms); 2) consistent results, with minor and/or few exceptions; 3) minor and/or few concerns about study quality; and/or 4) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation.
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on: 1) limited evidence for a true net effect (e.g., benefits exceed harms); 2) consistent results, but with important exceptions; 3) concerns about study quality; and/or 4) the extent of panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation.

Source: National Guideline Clearinghouse Extent Adherence to Trustworthy Standards (NEATS) instrument.

COCHRANE AND QAREL SCORE SHEETS

1. Sources of risk of bias and Cochrane Review rating system.

Bias domain	Source of bias	Possible answers
Selection	(1) Was the method of randomization adequate?	Yes/No/Unsure
Selection	(2) Was the treatment allocation concealed?	Yes/No/Unsure
Performance	(3) Was the patient blinded to the intervention?	Yes/No/Unsure
Performance	(4) Was the care provider blinded to the intervention?	Yes/No/Unsure
Detection	(5) Was the outcome assessor blinded to the intervention?	Yes/No/Unsure
Attrition	(6) Was the drop-out rate described and acceptable?	Yes/No/Unsure
Attrition	(7) Were all randomized participants analyzed in the group to which they were allocated?	Yes/No/Unsure
Reporting	(8) Are reports of the study free of suggestion of selective outcome reporting?	Yes/No/Unsure
Selection	(9) Were the groups similar at baseline regarding the most important prognostic indicators?	Yes/No/Unsure
Performance	(10) Were cointerventions avoided or similar?	Yes/No/Unsure
Performance	(11) Was the compliance acceptable in all groups?	Yes/No/Unsure
Detection	(12) Was the timing of the outcome assessment similar in all groups?	Yes/No/Unsure
Other	(13) Are other sources of potential bias unlikely?	Yes/No/Unsure

Modified from Ref (34).

2. Quality Appraisal of Diagnostic Reliability (QAREL) checklist.

Item	Yes	No	Unclear	N/A
1. Was the test evaluated in a spectrum of subjects' representative of patients who would normally receive the test in clinic practice?				
2. Was the test performed by examiners representative of those who would normally perform the test in practice?				
3. Were raters blinded to the reference standard for the target disorder being evaluated?				
4. Were raters blinded to the findings of other raters during the study?				
5. Were raters blinded to their own prior outcomes of the test under evaluation?				
6. Were raters blinded to clinic information that may have influenced the test outcome?				
7. Were raters blinded to additional cues, not intended to form part of the diagnostic test procedure?				
8. Was the order in which raters examined subjects varied?				
9. Were appropriate statistical measures of agreement used?				
10. Was the application and interpretation of the test appropriate?				
11. Was the time interval between measurements suitable in relation to the stability of the variable being measured?				
12. If there were dropouts from the study, was this less than 20% of the sample.				
TOTAL				

Reproduced from Ref. (33).

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Safety Analysis of Dorsal Root Ganglion Stimulation in the Treatment of Chronic Pain

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Background: Stimulation of the dorsal root ganglion (DRG) in the treatment of chronic, intractable pain has shown excellent clinical results in multiple published studies, including a large prospective, randomized, controlled trial. Both safety and efficacy have been demonstrated utilizing this therapeutic approach for many chronic complaints. Continued assessment of neuromodulation therapies, such as DRG stimulation, are not only an important aspect of vigilant care, but are also necessary for the evaluation for safety.

Materials and Methods: Safety and complaint records for DRG and spinal cord stimulation (SCS) stimulation were obtained from the manufacturer, analyzed and compiled to further assess ongoing device safety. Complaint event data were stratified according to complain type as well as overall rates. Data from similar time periods were compared between epidural neurostimulation devices by the same manufacturer as well as rates reported in the literature.

Results: Overall, DRG stimulation device event rates were lower or comparable to similar epidurally placed neurostimulation devices. Rates of events varied from 0 to 1.0% for DRG stimulation (n >500+ implants) which was similar to the event rate for SCS by the same manufacturer (n >2000+ implants). In comparison, complaints and adverse events ranged from 0 to 14% for SCS in the literature.

Discussions: The current results from a large consecutive cohort obtained from manufacturer records indicates that DRG stimulation demonstrates an excellent safety profile. Reported event rates are similar to previously reported adverse event and complaint rates in the literature for this therapy. Similarly, safety events rates were lower or similar to previously reported rates for SCS, further demonstrating the comparative safety of this neuromodulation technique for chronic pain treatment.

Keywords: chronic pain, epidural, implant, Neurostimulation, safety

Conflict of Interest: Dr. Deer is a consultant for Abbott, Axonics, Nalu, Saluda, Vertos, Vertiflex, Flowonix, and SpineThera, and has funded research from Abbott, Saluda, Vertiflex, and Vertos and Mainstay. He has minority equity in Axonics, Bioness, Ethos, Flowonix, Saluda, Nalu, Cornerloc, Spinethera, Vertos, and Vertiflex. Dr. Pope is a consultant for Abbott, Saluda, VertiFlex, Vertos, SpineThera, Jazz Pharmaceuticals, Flowonix, and SPR Therapeutics, has funded research with Abbott, Flowonix, VertiFlex, Saluda, and has minority equity in AGR, SPR Therapeutics, Celeri Health. Dr. Kramer is a consultant for Abbott, Autonomic Technologies, Nalu Medical, Circuit Therapeutics, CereVu and ENSO. Dr. Levy––Abbott (consultant, Medical Advisory Board), Mainstay Medical (consultant, Medical Advisory Board), Nalu (consultant, Medical Advisory Board), Nuvectra (consultant, Medical Advisory Board), Saluda (consultant, Medical Advisory Board). Dr. Falowski is a consultant for Abbott, Medtronic, Nevro, Vertiflex, Saluda, and SPR therapeutics; funded research from Abbott, Medtronic, Nuvectra, Biotronik; has minority equity in SpineThera, SPR therapeutics, Saluda, AGR, and Suture Concepts. Dr. Kapural is consultant for Nevro, Abbott, Best Doctors and has funded research from Biotronik, SPR Therapeutics, Medtronic, Boston Scientific, Neuros, Gimer, Sollis Medical. Dr. Hunter is a consultant for Abbott, Saluda, Nuvectra, Flowonix and serves on the Medical Advisory Board for Vertiflex.

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For more information on author guidelines, an explanation of our peer review process, and conflict of interest informed consent policies, please go to http://www.wiley.com/WileyCDA/Section/id-301854.html

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INTRODUCTION

The dorsal root ganglion is a sensory neural structure located within the intervertebral foramen that contains the primary sensory neuron (PSN) somata (1–3). Several reviews have outlined the importance that the PSN plays in the development and maintenance of chronic pain (1,4,5). Many of the pathophysiologic changes in neuronal function of PSNs observed in models of chronic pain are specifically located in the neuronal cell body, and these can include increased membrane excitability as well as the generation of ectopic action potentials (1,6–8). The PSNs also contain a t-junction where the distal and primary axons combine with a stem axon that connects the soma. This junction in the pseudounipolar neurons acts as a junctional failure point for centrally projecting neural traffic. It also serves as a modulatory area for controlling sensory information originating from both the periphery and cell body to more central neural pathways (9,10). Given these functional considerations and the anatomic accessibility of the dorsal root ganglion (DRG) in the spine, neurostimulation techniques have been developed to therapeutically target this spinal structure (3,11–13).

Clinically, it has been shown in multiple, published studies that DRG stimulation produces significant analgesia in patients suffering from chronic pain (11,14–17). This includes results from a large, prospective, multi-center, randomized controlled trial (ACCURATE study) in which DRG stimulation was shown to be safe and effective (11). The ACCURATE study also demonstrated that DRG stimulation is superior to spinal cord stimulation (SCS) in the treatment of CRPS types I and II (causalgia). Subsequent studies have not only shown utility of this neuromodulation target in other pain conditions outside CRPS, but also have continued to document the clinically efficacy and safety of this therapeutic approach in "real-world" settings (12,14,16,18–21). After regulatory approvals (both CE Mark and FDA) commercialization of the only product approved for DRG stimulation in the treatment of chronic pain has allowed increased patient access to this important neuromodulation therapy.

One important aspect of medical device use is ongoing safety assessments and vigilance efforts by both physicians and manufacturers. There are multiple ways to adequately assess postmarket safety including running specific postmarket safety studies in large patient populations (often a requirement of device regulatory approval), systematic reviews of peer-reviewed published data, analysis of public safety databases as well as review of manufacturer internal complaint and safety records. Each of these approaches have their strengths and weaknesses (22), but given the regulatory requirements for device vigilance reporting, internal company records are generally the most accurate reporting methods for very large cohorts. Quite often, however, these records and results are not made public. Many of these approaches have been used to assess ongoing safety of neuromodulation devices (12,22–25) and are synthesized in clinical consensus recommendations, such as those published by the Neuromodulation Appropriate Use Consensus Committee (NACC) (26–28).

To assess the ongoing performance and safety of DRG stimulation, we have compiled and analyzed device specific manufacturer safety and complaint records. For comparative purposes, the records analyzed included both DRG and SCS systems from the same manufacturer.

METHODS

A postmarket surveillance analysis was conducted to generate performance and safety data for both DRG and SCS stimulation. Data, generously provided by Abbott Neuromodulation (Chicago, IL, USA), were systematically collected from an internal complaint reporting and handling database and utilized in the current analysis. The product experiences reported and recorded in this type of database are used to collect any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a distributed product. The time frame selected was April 2016 to March 2018 based on DRG stimulation FDA approval. Comparative safety data were also acquired through a review of the DRG and SCS published literature (data sources: Medline and EMBASE).

The comparison between the two therapies was limited only to products implanted within this time frame to provide a direct comparison of product performance utilizing the same associated implant durations. Data were validated through the manufacturer's quality assurance system for complaint handling, and both a unique patient identifier as well as specific data fields for device identification and the specific complaint descriptor/category were compiled. The sources of potentially reportable events included, but were not limited to, the following: Customer complaints (primary source), contact with manufacturer employees or contract personnel, field service records, device malfunctions, advertising and promotion materials, professional meetings, congresses, seminars, clinical studies using manufacturer marketed products and clinical research, product actions, legal actions, regulatory affairs, manufacturer employees of different divisions, other companies with manufacturer/distributor relationships with manufacturer, regulatory agencies, and other telecommunications (internet), website postings, web logs (blogs) and published literature. Each of the patient implant records were characterized into groups based on the implantable pulse generator (IPG) and leads that were implanted together. Only implanted systems where both an IPG and a lead were implanted were included for this evaluation. Implant records were excluded from the investigation in rare cases where there were multiple IPGs and leads implanted involving both DRG and SCS devices in the same patient. Records from any associated accessories (eg, lead anchors, lead extensions, etc.) were not included in this analysis.

Based on the implant data records, the "Implant Therapy" was determined based on the IPG model utilized. Products were further grouped into "Implant Family" based on the IPG model (SMI-Axium [DRG] Proclaim DRG or Proclaim SCS) and the implanted lead models (DRG lead, SCS percutaneous lead, SCS surgical/paddle lead). Information (patient ID, model, serial/lot number, implant date) from the patient implant data was used to identify the related complaint records. Once matched, the complaint record details were then associated with the patient implant event and the associated "Implant Therapy" and "Implant Family," after which the patient implant record was marked to indicate whether there was a complaint and/or explant associated with the implant event. Comparative rates of complaint and explant were calculated using either the "Implant Therapy," "Implant Family," individual product model, or specific complaint record variable by summing the number of associated complaints and explant records and normalizing by the number of overall implant records for the "Implant Therapy," "Implant Family," or individual product model.

Data were compiled and stratified according to general event categories as has been previously published (11,25,29). Event categories ranged from biological/physical descriptor to device events (device malfunction or related events). A literature review was also conducted to retrieve safety reporting from the published literature. Multiple databases (Medline and EMBASE) were searched with

Table 1. Rates of Reported Events From Both DRG and SCS Systems.

Event description	SCS incidence rate	DRG incidence rate
Allergic reaction	0.09%	0.18%
Cardiovascular changes	0.04%	0
CSF leaks	0.30%	0.54%
Device related pain	0.30%	0.54%
Diminished or loss of motor or musculoskeletal symptom control	0.09%	0
Gastroesophageal or gastrointestinal changes	0	0.18%
Headache	0.04%	0
Hematoma	0.17%	0
Infection	1.12%	1.08%
Neurological deficit/dysfunction (NDD)	0.13%	0
Persistent pain at the implant site	0.56%	0.18%
Pocket heating	0.04%	0
Post Op pain	0	0
Pulmonary changes	0.04%	0
Reduced surgical would healing	0.17%	0.18%
Seizure	0.04%	0
Skin erosion	0.04%	0.36%
Total incidence rate	3.09%	3.24%

N = >500 systems for DRG and *n* = >2000 systems for SCS.

relevant search terms ("Dorsal root ganglion stimulation," "DRG stimulation," "spinal cord stimulation," "safety," etc.) in order to produce comparative data from peer-reviewed publications.

RESULTS

Manufacturer records yielded data from over 500 DRG stimulator and 2000 spinal cord stimulator implants. Primary results and outcomes from the manufacturer records are presented in Table 1. Overall, DRG stimulation reported safety event rates were 3.2%. This compares to an event rate during the same time frame of 3.1% in SCS. Infection was the most frequent event noted, with an overall rate of approximately 1% for both DRG and SCS systems. This was one-third of overall event incidence. All other biologically classified event rates were less than 1%. Comparatively, both the DRG and SCS systems demonstrated equivalent event rates from the manufacturer records with slight variations in individual categories. Table 2 lists the comparative incident rates of the highest occurring events (infection, pain at implant site and CSF leaks) in the current data set and literature for both DRG and SCS. In all cases, the incident rates reported in the literature are either higher or the same as reported from the manufacturer records in the current analysis.

Table 3. Comparison Between Reported Adverse Event Rates (by Subject) in the ACCURATE Clinical Trial and the Current Manufacturer Safety Surveillance Data.

Event description	Accurate DRG	Incidence rate
Allergic reaction	2.7%	0.18%
Cardiovascular changes	1.4%	0%
CSF leaks	2.7%	0.54%
Device related pain	1.4%	0.54%
Diminished or loss of motor or musculoskeletal symptom control	3.9%	0%
Gastroesophageal or gastrointestinal changes	1.3%	0.18%
Headache	1.4%	0%
Hematoma	0%	0%
Infection	1.3%	1.08%
Neurological deficit/dysfunction (NDD)	0%	0%
Persistent pain at the implant site	1.4%	0.18%
Pocket heating	0%	0%
Post Op pain	1.4%	0%
Pulmonary changes	1.3%	0%
Reduced surgical would healing	0%	0.18%
Seizure	0%	0%

Note the event rate calculations and specific categorical definitions differ between the ACCURATE study and the current analysis.

Event rates were also comparable or better than the published literature for both SCS and DRG systems. Table 3 shows the manufacturer event rates compared to the event rates reported in the ACCURATE study. The manufacturer postmarket events rates were either comparable or less than the rates reported in the ACCURATE clinical trial demonstrating continued or improved safety of the DRG stimulation system. Results from a literature review demonstrated that the current event rates compared favorably to published SCS clinical event rates.

DISCUSSION

The findings from this safety analysis, including >500 DRG system implants from a 2-year time period following commercial approval, demonstrate that clinical adverse events and device complaint rates were comparably or less frequent than those reported for, 1) similar epidural SCS neurostimulation systems in the literature, 2) similar SCS systems from the same manufacturer in the same time frame as DRG stimulation, 3) a similar DRG system as

Table 2. Most Common Events Reported From DRG and SCS Systems.

Event description	Nerve root incidence rate*	Published SCS incidence rates	SCS incidence rate	DRG incidence rate
CSF leaks	12%	0.3%-7%	0.30%	0.54%
Infection	12%	2.5%-14%	1.12%	1.08%
Persistent pain at the implant site	N/A	0.9%-12%	0.56%	0.18%

Comparison between events reported in current analysis and published rates from SCS and nerve root stimulation.
*Reference (31).

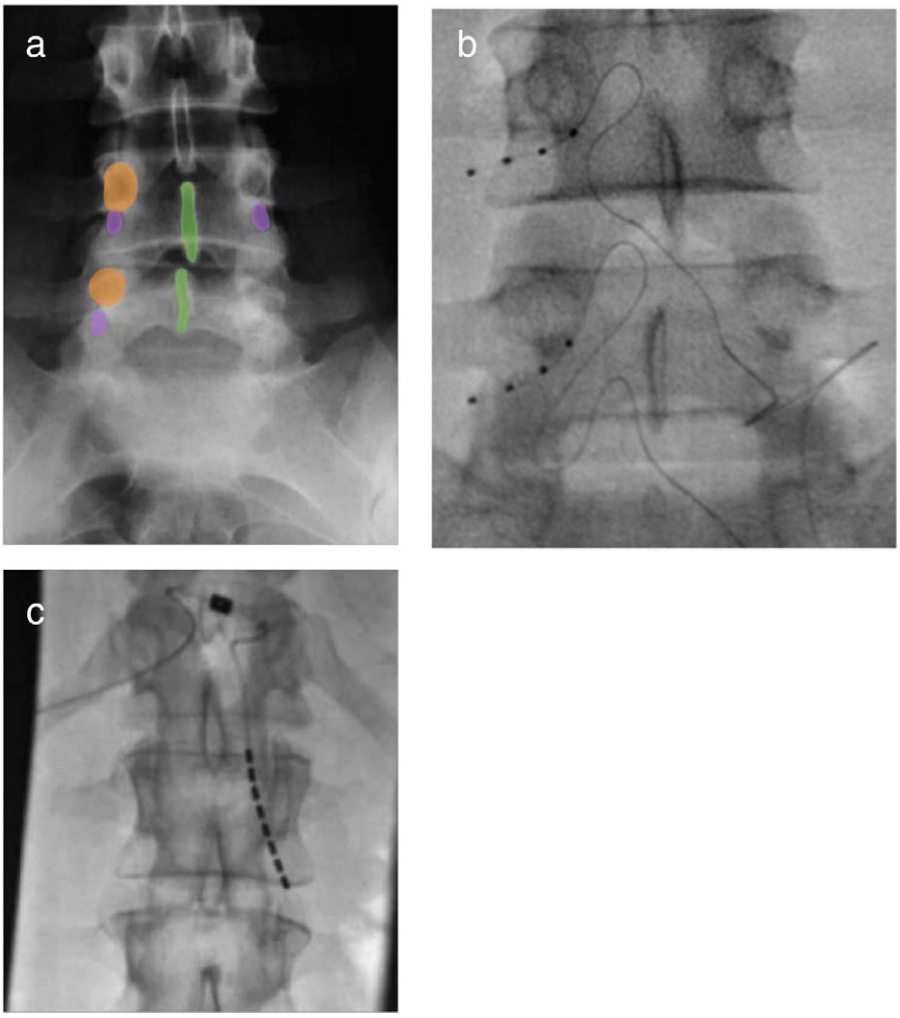

Figure 1. Fluoroscopic images of spine anatomy relating location of the dorsal root ganglia as well as implanted DRG leads in the foramen and SCS lead in the lateral epidural space. Panel A depicts relevant spinal anatomy and location of the DRG within the dorsal aspect of the neural foramen just under the spinal pedicle. Panel B shows a lead specifically designed for DRG stimulation in the dorsal intervertebral foramen adjacent to the DRG. Note the flexibility and outer diameter of the lead. Panel C shows a lead deigned for spinal cord stimulation in the lateral epidural space partly extending into the ventral spinal foramen. Note the difference in lead approaches and locations in the lateral recess. [Color figure can be viewed at wileyonlinelibrary.com]

reported in the results from a large, prospective, multi-center, randomized controlled trial (ACCURATE), and, 4) a similar DRG stimulation system as reported in the literature. These findings represent the most complete postmarket safety analysis completed for DRG stimulation and consider all reported events from a manufacturer quality system for commercially implanted systems within a 2-year time frame. This approach helped to avoid biases of event reporting in public databases and also allows for a larger sample size of device reporting than all published clinical studies combined.

The overall incidence rate of 3.2% for DRG stimulation was comparable to the event rate for fully-implantable SCS systems (3.1%) from the same manufacturer and so represents a true comparison of rates given that the same requirements for reporting and methods for data collection were taken as a part of the required device vigilance monitoring. These rates are similar to those observed during the ACCURATE clinical trial conducted for FDA approval as well as those reported in the literature (11,12,15,17,18,30). The latter of these two data collection methods (clinical studies) yield fairly large ranges of events, mostly due to the heterogeneity in data collection methods, reporting decisions and the fact that data was obtained from different geographies as well as different clinical sites. This approach, however, provides event rates from different sources, and in so doing yields data from larger patient samples than available through single clinical studies.

To that extent, the results from the current analysis are also in agreement with event rates published from the ACCURATE study (11). Safety event rates published from large clinical studies are another good source for comparative data. Generally, the events reported from high-quality clinical trials involve smaller and more homogeneous patient populations than larger postmarket patient cohorts. The data is also collected within a highly controlled environment, generally with very experienced physicians participating as investigators. It is very encouraging to see that, in the current analysis, data collected from a "real-world" setting, such as clinical practice across multiple locations and physicians, matches or exceeds the safety rates from controlled clinical studies. Not only do the postmarket results substantiate those findings from the approval study, but also demonstrate increased external validity of the initial safety results within a more varied patient group in variable practice environments. Refined placement techniques and safety considerations, including neuromonitoring and awake

placement of leads, will help continue to maintain safety and efficacy in the hands of practicing physicians.

The DRG stimulation system examined in the current analysis was specifically designed, tested and validated for the clinical use and safety of epidural access and placement in the lateral epidural space around the DRG. While other approaches have been utilized for lateral epidural lead placement as well, the published results from the use of these systems have been typically substandard (Fig. 1) (31–33). Generally, the systems utilized have either been standard SCS systems or systems not generally designed or intended to be anatomically placed for any appreciable amount of time near the DRG (31,32,34). As a result, lead designs and delivery approaches are inadequate for long-term, effective use in stimulating the DRG. The use of these approaches results in relative lack of long-term efficacy of stimulation as well as higher safety event incidence (31,32). For example, Weigel and colleagues published a case series attempting to repurpose standard SCS hardware for DRG stimulation (32). Ultimately, this group found that stimulating the DRG with this system did not result in long-term clinical benefit and also resulted in overstimulation producing uncomfortable paresthesias. Similarly, a recent report by Levine and colleagues reported higher clinical event rates when placing leads in the lateral recess, or "gutter" of the epidural space. Presumably the size and flexibility of the leads as well as other aspects of the system resulted in the clinical performance noted.

It is not surprising to see that leads and systems not specifically designed to be anatomically located, and stably positioned, in the lateral epidural space do not perform as well as systems that do take these design considerations into account. Similar findings have been observed when SCS leads have been repurposed to be positioned in other anatomies (27). As it would be expected, the design engineering of specialized leads can result in better overall performance and clinical outcomes, especially when the intended neural target is relatively small. It is also not surprising to find that these results manifest themselves over longer time periods as well. Clinically, the results from nerve root stimulation were very different than those published for dorsal root ganglion stimulation (11,31,32). Specifically, Levine and colleagues demonstrated no difference between nerve root stimulation and SCS when treating neuropathic pain (31). The response rates of patients treated with nerve root stimulation was less than 50%, as opposed to the responder rate of greater than 90% observed in the ACCURATE trial (11). While anatomically connected, critical cytoarchitectonic structures such as the cell bodies and T-junction of the PSNs that are housed in the ganglia are distinct from the nerve roots. As it has been shown that these structures play a large role in the putative mechanisms underlying DRG stimulation (1,9,35) and so it is not surprising that clinical results would show differences between nerve root and DRG stimulation.

The analysis presented are not without limitations. The data collected represent safety findings soon after FDA approval. Most of the data were collected from sites with experienced implanters, so it is unclear how results may or may not differ from sites with less experienced implanters. Currently, there are comprehensive training programs required by the manufacturer in order for physicians to begin utilizing the therapy. This also might be a partial explanation for the safety results obtained. Data were obtained from manufacturer records and so may face bias issues, similar to other forms of data collection (results from published clinical studies, public databases, etc.). We feel that this method of data collection offers benefits such as comprehensive collection of events that avoids underreporting often encountered from public databases as well as large sample sizes for analysis.

CONCLUSION

Following review and analysis of manufacturer safety records, DRG stimulation continues to demonstrate an excellent safety profile with low adverse event rates. The current analysis has reinforced the initial findings that DRG stimulation demonstrates an excellent safety profile that is equal or better to, 1) the ACCURATE pivotal trial results, 2) SCS devices, 3) results from published literature on both DRG and SCS therapies.

These event rates are also consistent or lower with rates previously deemed acceptable by neuromodulation consensus committees and regulatory agencies. Ongoing device vigilance and safety reporting by physicians will continue to be a valued assessment of the safety and performance attributed to DRG stimulation therapy as well as other neuromodulation approaches.

Authorship Statements

Drs. Deer and Kramer conducted the data analysis and assembly for presentation in the document. Dr. Kramer prepared the manuscript draft with important intellectual input from Drs. Deer, Levy, Falowski, Pope, Kapural, and Hunter. All authors provided editorial input. Abbott provided safety and device diligence data from internal databases for analysis and inclusion in the manuscript.

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REFERENCES

1. Krames ES. The dorsal root ganglion in chronic pain and as a target for neuromodulation: a review. *Neuromodulation* 2015;18:24–32, discussion 32.
2. Vancamp T, Levy RM, Peña I, Pajuelo A. Relevant anatomy, morphology, and implantation techniques of the dorsal root ganglia at the lumbar levels. *Neuromodulation* 2017;20:690–702.
3. Liem L, van Dongen E, Huygen FJ, Staats P, Kramer J. The dorsal root ganglion as a therapeutic target for chronic pain. *Reg Anesth Pain Med* 2016;41:511–519.
4. Hogan QH. Role of decreased sensory neuron membrane calcium currents in the genesis of neuropathic pain. *Croat Med J* 2007;48:9–21.
5. Pope JE, Deer TR, Kramer J. A systematic review: current and future directions of dorsal root ganglion therapeutics to treat chronic pain. *Pain Med* 2013;14:1477–1496.
6. Koplovitch P, Devor M. Dilute lidocaine suppresses ectopic neuropathic discharge in dorsal root ganglia without blocking axonal propagation: A new approach to selective pain control. *Pain* 2018;159:1244–1256.
7. Devor M. Ectopic discharge in Abeta afferents as a source of neuropathic pain. *Exp Brain Res* 2009;196:115–128.
8. Devor M. Unexplained peculiarities of the dorsal root ganglion. *Pain* 1999;Suppl 6: S27–S35.
9. Kent AR, Min X, Hogan QH, Kramer JM. Mechanisms of dorsal root ganglion stimulation in pain suppression: a computational modeling analysis. *Neuromodulation* 2018;21:234–246.
10. Gemes G, Koopmeiners A, Rigaud M et al. Failure of action potential propagation in sensory neurons: mechanisms and loss of afferent filtering in C-type units after painful nerve injury. *J Physiol* 2013;591:1111–1131.
11. Deer TR, Levy RM, Kramer J et al. Dorsal root ganglion stimulation yielded higher treatment success rate for complex regional pain syndrome and causalgia at 3 and 12 months: a randomized comparative trial. *Pain* 2017;158:669–681.
12. Harrison C, Epton S, Bojanic S, Green AL, FitzGerald JJ. The efficacy and safety of dorsal root ganglion stimulation as a treatment for neuropathic pain: a literature review. *Neuromodulation* 2018;21:225–233.

13. Vuka I, Vučić K, Repić T, Ferhatović Hamzić L, Sapunar D, Puljak L. Electrical stimulation of dorsal root ganglion in the context of pain: a systematic review of in vitro and in vivo animal model studies. *Neuromodulation* 2018;21:213–224.
14. Liem L, Russo M, Huygen FJPM et al. One-year outcomes of spinal cord stimulation of the dorsal root ganglion in the treatment of chronic neuropathic pain. *Neuromodulation* 2015;18:41–48, discussion 48-49.
15. Liem L, Russo M, Huygen FJPM et al. A multicenter, prospective trial to assess the safety and performance of the spinal modulation dorsal root ganglion neurostimulator system in the treatment of chronic pain. *Neuromodulation* 2013;16: 471–482, discussion 482.
16. Deer TR, Grigsby E, Weiner RL, Wilcosky B, Kramer JM. A prospective study of dorsal root ganglion stimulation for the relief of chronic pain. *Neuromodulation* 2013;16:67–71, discussion 71-72.
17. Morgalla MH, Fortunato M, Lepski G, Chander BS. Dorsal root ganglion stimulation (DRGS) for the treatment of chronic neuropathic pain: a single-center study with long-term prospective results in 62 cases. *Pain Physician* 2018;21:E377–E387.
18. Huygen F, Liem L, Nijhuis H, Cusack W, Kramer J. Evaluating dorsal root ganglion stimulation in a prospective Dutch cohort. *Neuromodulation* 2018;22:80–86.
19. Eldabe S, Espinet A, Wahlstedt A et al. Retrospective case series on the treatment of painful diabetic peripheral neuropathy with dorsal root ganglion stimulation. *Neuromodulation* 2018;21:787–792.
20. Huygen F, Liem L, Cusack W, Kramer J. Stimulation of the L2-L3 dorsal root ganglia induces effective pain relief in the low Back. *Pain Pract* 2018;18:205–213.
21. Eldabe S, Burger K, Moser H et al. Dorsal root ganglion (DRG) stimulation in the treatment of phantom limb pain (PLP). *Neuromodulation* 2015;18:610–616, discussion 616-617.
22. Levy R, Henderson J, Slavin K et al. Incidence and avoidance of neurologic complications with paddle type spinal cord stimulation leads. *Neuromodulation* 2011; 14:412–422, discussion 422.
23. Deer T, Skaribas I, McJunkin T et al. Results from the partnership for advancement in neuromodulation registry: a 24-month follow-up. *Neuromodulation* 2016; 19:179–187.
24. Kumsa D, Steinke GK, Molnar GF et al. Public regulatory databases as a source of insight for neuromodulation devices stimulation parameters. *Neuromodulation* 2018;21:117–125.
25. Bendersky D, Yampolsky C. Is spinal cord stimulation safe? A review of its complications. *World Neurosurg* 2014;82:1359–1368.
26. Deer TR, Lamer TJ, Pope JE et al. The Neurostimulation Appropriateness Consensus Committee (NACC) safety guidelines for the reduction of severe neurological injury. *Neuromodulation* 2017;20:15–30.
27. Deer TR, Mekhail N, Provenzano D et al. The appropriate use of neurostimulation of the spinal cord and peripheral nervous system for the treatment of chronic pain and ischemic diseases: the Neuromodulation Appropriateness Consensus Committee. *Neuromodulation* 2014;17:515–550, discussion 550.
28. Deer TR, Mekhail N, Provenzano D et al. The appropriate use of neurostimulation: avoidance and treatment of complications of neurostimulation therapies for the treatment of chronic pain. *Neuromodulation* 2014;17:571–597, discussion 597-598.
29. Cameron T. Safety and efficacy of spinal cord stimulation for the treatment of chronic pain: a 20-year literature review. *J Neurosurg* 2004;100:254–267.
30. Schu S, Gulve A, ElDabe S et al. Spinal cord stimulation of the dorsal root ganglion for groin pain-a retrospective review. *Pain Pract* 2015;15:293–299.
31. Levine AB, Steven DA, Parrent AG, MacDougall K. Successful long-term nerve root stimulation for chronic neuropathic pain: a real world, Single Center Canadian Experience. *Pain Physician* 2017;20:95–106.
32. Weigel R, Capelle HH, Krauss JK. Failure of long-term nerve root stimulation to improve neuropathic pain. *J Neurosurg* 2008;108:921–925.
33. Levine AB, Parrent AG, MacDougall KW. Cervical spinal cord and dorsal nerve root stimulation for neuropathic upper limb pain. *Can J Neurol Sci* 2017;44:83–89.
34. Levine AB, Parrent AG, MacDougall KW. Stimulation of the spinal cord and dorsal nerve roots for chronic groin, pelvic, and abdominal pain. *Pain Physician* 2016;19: 405–412.
35. Koopmeiners AS, Mueller S, Kramer J, Hogan QH. Effect of electrical field stimulation on dorsal root ganglion neuronal function. *Neuromodulation* 2013;16: 304–311, discussion 310-311.

Washington State Health Care Authority

Spinal cord stimulation

Assessing signals for update

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Spinal Cord Stimulation: Assessing Signals for Update

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Previous coverage decision

A Health Technology Assessment titled: Spinal Cord Stimulation, was originally released on July 23, 2010 by the Washington State Health Technology Clinical Committee. Additionally, two update signal assessments were published on December 29, 2014 and August 29, 2016. The Committee's Coverage Decision for the original report is summarized below, followed by the main conclusions from the 2014 and 2016 Signal Update reviews.

Health Technology Background

The Spinal Cord Stimulation topic was selected and published in December 2009 to undergo an evidence review process. Spinal Cord Stimulation (SCS) is an alternative treatment proposed for patients with chronic neuropathic pain who have not responded to conventional therapies such as medication, physical and/or psychological therapy, and in some case, re-operation. Current best evidence is available primarily from four trials on 375 patients; which are rated at a Level 1 or 2 (good quality), which is a better level of evidence than some interventions. However, total patient sample size is small, comparators were weak or inappropriate, reported outcomes are mostly subjective and not consistently reported, industry funding and management may have an impact, and no trial included a sham stimulation/procedure arm. The overall body of evidence was inconsistent, with several trials showing benefits on some outcomes at generally shorter follow up periods and others showing no difference. SCS is an implanted, long term treatment, but no evidence exists on either long term efficacy or safety.

The committee agreed that SCS is less safe than alternatives, is an invasive procedure, and has many adverse events. While conventional medical management is not invasive, so would generally have a lower risk profile, re-operation is also a comparator and had less complications. SCS device related complications can be serious and include dural punctures, amplitude by bodily movements; paresthesia in other body parts, pain, disturbed urination, lead fracture, loss of effect, infection. Indications for SCS (FDA): Chronic intractable pain in the trunk and/or limbs including unilateral or bilateral pain associated with FBSS and intractable low back and leg pain, and for some devices: CRPS, radicular pain syndrome or radiculopathies resulting in pain, post-laminectomy pain, unsuccessful disc surgery, degenerative disc disease or herniated disc pain refractory to conservative or surgical interventions, peripheral causalgia, epidural fibrosis, arachnoiditis or lumbar adhesive arachnoiditis, and multiple back surgeries. Potential patients should undergo a period of trial stimulation prior to permanent SCS implantation. Contraindications for SCS (FDA): Failed trial stimulation due to ineffective pain relief; poor surgical risks; pregnancy; active general infections or multiple illnesses; inability to operate the SCS system; and cardiac pacemakers (with specific exceptions and precautions) or cardioverter defibrillators.

In June 2010, the HTA posted a draft and then followed with a final report from a contracted research organization that reviewed publicly submitted information; searched, summarized, and evaluated trials, articles, and other evidence about the topic. The comprehensive, public and peer reviewed Spinal Cord Stimulation report is 164 pages, and identified a relatively large amount of literature.

An independent group of eleven clinicians who practice medicine locally meet in public to decide whether state agencies should pay for the health technology based on whether the evidence report and other

presented information shows it is safe, effective and has value. The committee met on August 20, reviewed the report, including peer and public feedback, and heard public and agency comments. Meeting minutes detailing the discussion are available through the HTA program or online at http://www.hta.hca.wa.gov under the committee section.

Committee Conclusions

Having made findings as to the most significant and relevant evidence regarding health outcomes, key factors and identified evidence related to those factors, primarily based on the evidence based technology assessment report, the committee concludes:

(1) Evidence availability and technology features

The committee concludes that the best available evidence on Spinal Cord Stimulation has been collected and summarized.

- Spinal Cord Stimulation (SCS) is an alternative treatment proposed for patients with chronic neuropathic pain who have not responded to conventional therapies such as medication, physical and/or psychological therapy, and in some case, re-operation.
- Current best evidence is available primarily from four trials on 375 patients; which are rated at a Level 1 or 2 (good quality), which is a better level of evidence than some interventions. However, total patient sample size is small, comparators were weak or inappropriate, reported outcomes are mostly subjective and not consistently reported, industry funding and management may have an impact, and no trial included a sham stimulation/procedure arm. The overall body of evidence was inconsistent, with several trials showing benefits on some outcomes at generally shorter follow up periods and others showing no difference.
- SCS is an implanted, long term treatment, but no evidence exists on either long term efficacy or safety.

(2) Is it safe?

The committee concludes that the comprehensive evidence indicates that Spinal Cord Stimulation is less safe than alternative treatments. Key factors to the committee's conclusion included:

- The committee agreed that SCS is less safe than alternatives, is an invasive procedure, and has many adverse events. While conventional medical management is not invasive, so would generally have a lower risk profile, re-operation is also a comparator and had less complications. SCS device related complications can be serious and include dural punctures, amplitude by bodily movements; paresthesia in other body parts, pain, disturbed urination, lead fracture, loss of effect, infection.
- The committee agreed that safety was a significant factor: the number of trial reported complications ranged from 8 to 100%. Device related complication requiring revision ranged from 25% to 38% of patients in short term and 42% to 60% in up to 5 years (not including 54% of patients undergoing pulse generator replacements due to battery life).

- The committee agreed that there were currently no reported mortality rates, but that the FDA data was not available and the small sample size is likely underpowered to detect.
- The committee agreed that the removal rate could be considered an efficacy or safety issue, but the rates ranging from 4% to 17% were concerning, especially considering that trial stimulation is done first on all patients.

(3) Is it effective?

The majority of the committee concludes that the comprehensive evidence about Spinal Cord Stimulation effectiveness is unproven.

- The committee agreed that the studies had serious limitations in design, low patient sample sizes, and weak or inadequate comparators. Additionally, placebo effects of a new intervention for patients with chronic pain who have already failed multiple therapies is a serious concern and no study involved sham stimulation or procedures and outcome measures were generally subjective.
- The committee found that evidence overall on important patient outcomes was limited. For all outcomes, there is no evidence of longer term improvement, particularly important when there are significant risks (including 1/3 revision and high removal rate) and the device is intended for permanent implant.
- Given the serious limitations of the studies, the committee agreed that, at best, weak evidence exists that SCS may provide temporary improvement of pain in some patients, but there is no evidence of mid or long term pain improvement.
- While pain is a critical patient outcome, evidence about other important patient outcomes was either not available or not consistent with the pain findings.
    - For instance, for reduction in pain medication in short term: Kumar and Turner found no difference, while North found SCS patients did have reduction.
    - For functional improvements, 1 trial found short term functional improvement, but 2 others did not; and there was no reliable evidence of functional improvement at mid (or long) term.
- For all other outcomes, including improvement in quality of life, there is no reliable evidence of effect.

(4) Evidence about the technology's special populations, patient characteristics and adjunct treatment

The committee agreed that no compelling evidence exists to differentiate sub groups or special populations.

- The committee agreed with the evidence based report that there is inadequate evidence to identify characteristics that either enhance or reduce the efficacy of SCS such as age, sex, workers' compensation or other disability payments, duration of pain, pain intensity, time since first lumbar surgery, number of prior operations for pain, pain location, laterality of pain, allodynia or hypoesthesia at baseline, McGill Pain Questionnaire or the Minnesota Multiphasic Personality Inventory (MMPI)

(5) Is the technology cost-effective?

- The committee concludes that SCS is unproven to be cost effective.
- The committee agreed that the cost of SCS is substantial, averaging $27,000 per patient.
- The committee agreed that overall value cannot be ascertained without evidence of net benefit of effectiveness and reduced harm. Reliable cost-effectiveness analysis cannot be performed.

Committee Decision

Based on the deliberations of key health outcomes, the committee decided that it had the most complete information: a comprehensive and current evidence report, public comments, and agency and state utilization information. The committee concluded that the current evidence on Spinal Cord Stimulation demonstrates that there isn't sufficient evidence to cover the use of Spinal Cord Stimulation for chronic neuropathic pain. The committee considered all the evidence and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable. Based on these findings, the committee voted 8 to 1 to not cover Spinal Cord Stimulation.

The committee reviewed the Clinical guidelines and Medicare decision. The Medicare decision was did not cite evidence and was decided prior to any of the studies reviewed by the committee. The guidelines recommendations conflict and not all have reviewed the latest trials included in this report.

Conclusions of the 2014 Signals for Update Assessment - SCS

***Key Question* 1**: What is the evidence of efficacy and effectiveness of spinal cord stimulation?

Efficacy: All conclusions are still valid and this portion of the CER does not need updating.
Effectiveness: All conclusions are still valid and this portion of the CER does not need updating.

Key Question 2: What is the evidence of the safety of spinal cord stimulation?

All conclusions are still valid and this portion of the CER does not need updating.

Key Question 3: What is the evidence that spinal cord stimulation has differential efficacy or safety issues in sub populations?

All conclusions are still valid and this portion of the CER does not need updating.

Key Question 4: What is the evidence of cost implications and cost-effectiveness of spinal cord stimulators?

This section of the report could be updated with the results of the cost-effectiveness analysis of the cohort of Washington State workers' compensation patients with FBSS (Hollingworth 2011)3.

However, the addition of this analysis (which suggests that SCS is not cost-effective in this patient population compared with pain clinic or usual care) would not affect the coverage decision (SCS is not covered).

Conclusions of the 2016 Signals for Update Assessment – SCS

Key Question 1: What is the evidence of efficacy and effectiveness of spinal cord stimulation?

With respect to efficacy, two studies compared SCS to conventional treatment in patients with diabetic neuropathy. Both found a short term pain improvement in favor SCS. There were no assessments of function or quality of life. Both studies report complications, some serious, to include serious infection and dural puncture leading to death. Three studies looked at new applications of SCS, high frequency SCS and burst stimulation. All were short term (1 or 2 weeks) crossover studies in patients who were already receiving traditional SCS. While burst stimulation shows some promise in these early cross-over studies, longer follow-up studies that compare burst stimulation in parallel arms to both non-stimulation therapy and placebo are needed in patients naïve to stimulation. Unfortunately, there are no current studies registered in ClinTrials.gov making these assessments, Appendix C. The five new RCTs evaluated in this signal report do not invalidate the previous evidence (criteria A-1 or A3), nor provide major changes in the evidence (criteria B-1 – B4).

Key Question 2**:** What is the evidence of the safety of spinal cord stimulation?

With respect to safety of spinal cord stimulation, data from two studies continue to underscore that SCS is not without complications and do not invalidate the previous evidence (criteria A-2)

Key Question 3: What is the evidence that spinal cord stimulation has differential efficacy or safety issues in sub populations?

There is no new evidence with respect to differential efficacy or safety of SCS in subpopulations.

Key Question 4: What is the evidence of cost implications and cost-effectiveness of spinal cord stimulators?

A new cost-utility study does not invalidate the previous evidence (criteria A-1 or A-3), nor provide major changes in the evidence (criteria B-1).

1. Purpose of Report

A prior update report was completed in October 2010 and signal update assessments in January 2014 and August 2016. The purpose of this additional literature update is to determine whether or not there is sufficient evidence published after the previous signal assessments to conduct a further review of this technology. The key questions from the original report are listed below:

Key Question 1: What is the evidence of efficacy and effectiveness of spinal cord stimulation?

Key Question 1: What is the evidence of the safety of spinal cord stimulation?

Key Question 3: What is the evidence that spinal cord stimulation has differential efficacy or safety issues in sub populations?

Key Question 4: What is the evidence of cost implications and cost-effectiveness of spinal cord stimulators?

2. Methods

2.1 Literature Searches

We conducted a limited literature search for articles published between May 1, 2016 and June 29, 2018 that addressed key questions 1 through 4. This search included three main databases: PubMed/Medline and Cochrane Library. We used key words to detect articles that used the terms “spinal cord stimulation”, “spinal cord stimulator”, or “spinal cord stimulation”. Appendix A includes the search methodology for this topic. Additionally, we reviewed ClinicalTrials.gov for relevant ongoing studies (Appendix B).

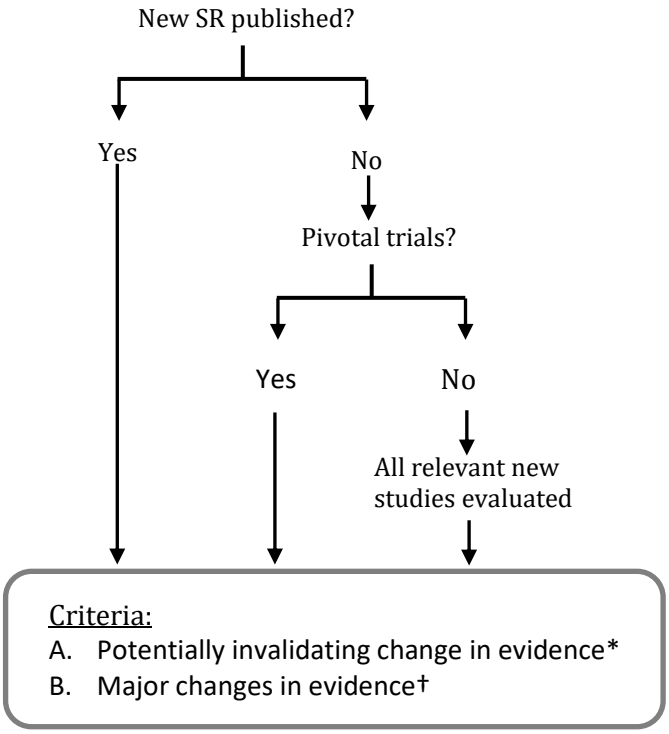
2.2 Study Selection

We sought systematic reviews (SR) of randomized controlled trials (RCTs) of efficacy and safety with meta-analysis that included articles that met inclusion and exclusion criteria similar to the original report and previous signal updates. In addition we sought SRs reflecting updates or new advances for the technology. Consistent with the previous report and updates, case-series specifically designed to evaluate safety with at least 5 years of follow-up were considered.

2.3 Compilation of Findings and Conclusions

For this assessment we abstracted the data from the included studies and constructed a demographics/results table (see Appendix C). We also constructed a summary table that included the key questions, the original conclusions, conclusions from prior updates, new sources of evidence, new findings, and conclusions based on available signals, Table 1 below. To assess whether the conclusions are still relevant, we used an algorithm based on a modification of the Ottawa method, Figure 1.

Figure 1. Algorithm of the modified Ottawa Method of Identifying Signals for SR Update3. Results



*A-1. Opposing findings: Pivotal trial or SR including at least one new trial that characterized the treatment in terms opposite to those used earlier

A-2. Substantial harm: Pivotal trial or SR whose results called into question the use of the treatment based on evidence of harm or that did not proscribe use entirely but did potentially affect clinical decision making

A-3. Superior new treatment: Pivotal trial or SR whose results identified another treatment as significantly superior to the one evaluated in the original review, based on efficacy or harm.

†B-1. Important changes in effectiveness short of "opposing findings"

B-2. Clinically important expansion of treatment

B-3. Clinically important caveat

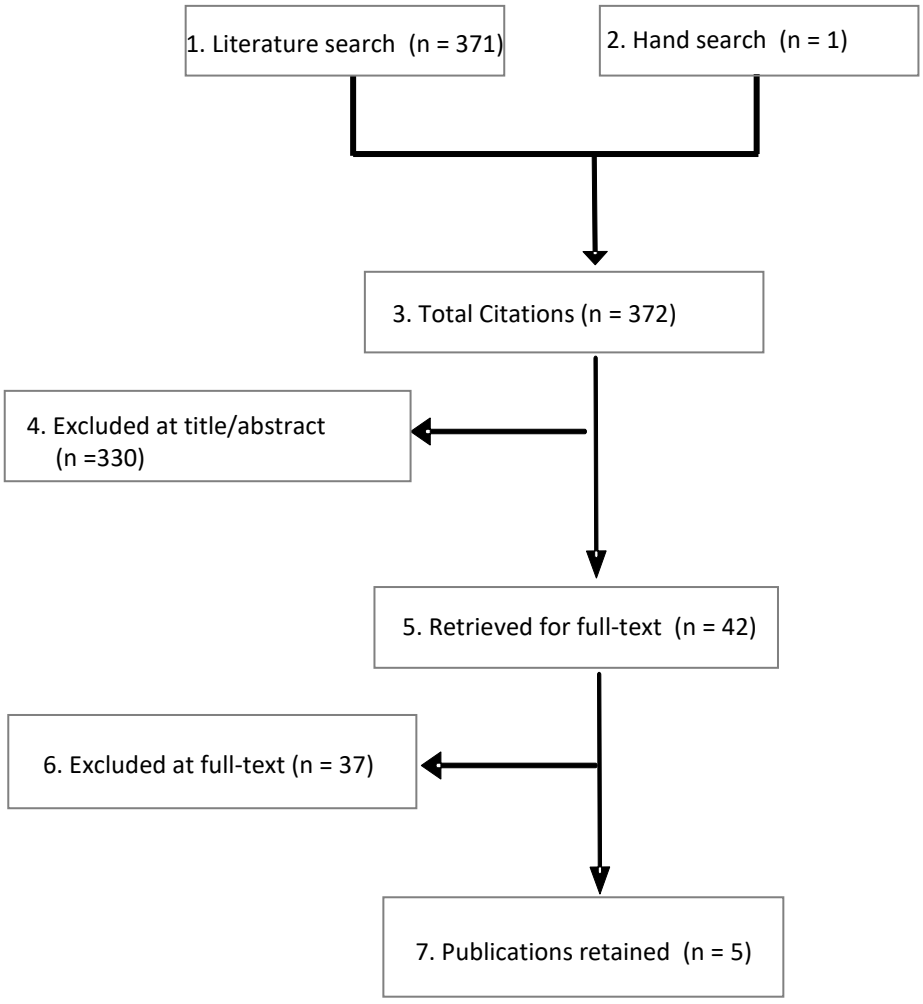
B-4. Opposing findings from discordant meta-analysis or nonpivotal trial

3.1 Search

From 372 citations identified (via literature search plus hand searching), 330 were excluded at title/abstract review. Of the remaining 42 reviewed at full-text, five studies that addressed key questions 1–4 in part or in full were retained (Figure 2), including three RCTs, one case series specifically evaluating safety, and one cost-utility analysis. No new systematic reviews with quantitative synthesis of relevant RCTs were identified in keeping with the focus on new evidence of efficacy. Comparative observational

studies evaluating effectiveness were not sought. Consistent with the prior report and updates, studies that compared different frequencies or modes of spinal cord stimulation with each other only were excluded. Additionally, studies of dorsal root ganglion stimulation were excluded as this technology is different from spinal cord stimulation due to its action on peripheral nerves. Dorsal root ganglion stimulation was FDA approved via the PMA process in 2016. A full list of excluded studies and the reasons for exclusions can be found in Appendix D.

Figure 2. Flow chart showing results of literature search



3.2 Identifying Signals for Re-review

Table 1 shows the original key questions, the conclusions of the original report, the new sources of evidence, the new findings, and the recommendations of Aggregate Analytics, Inc. (AAI) regarding the need for update. Appendix B includes updated information on currently ongoing trials assessing spinal cord stimulators.

Table 1. Summary Table of Key Questions 1-6

Conclusions from HTA Executive Summary	Conclusions from 2014 and 2016 Signal Update	New Sources of Evidence (2018)	New Findings	Conclusion from AAI
Key Question 1: What is the evidence of efficacy and effectiveness of spinal cord stimulation?				
1. a) Efficacy (Short-term, <5 years): • **Pain, perceived effect of treatment/patient satisfaction:** There is moderate evidence from three small randomized controlled trials that SCS is superior to conventional therapies (conservative medical management [CMM], physical therapy or re-operation) in patients with chronic neuropathic pain during the first 2–3 years with respect to patient reported outcomes of pain, and perceived effect of treatment/patient satisfaction. In the only RCT that measured outcomes for a longer period of time, the benefit of SCS decreased over time and was not significantly different than controls for leg pain after 3 years of treatment (see mid-term below). • **Function, quality of life:** The effect on quality of life outcomes is less clear with one RCT reporting substantial benefit of SCS compared with CMM at 6 months follow-up, while another study found	2014: This section of the report is still valid and does not need updating (no new data identified). 2016: 5 new RCTs (de Vos 2014, Slangen 2014, Schu 2013, De Ridder 2013, Perruchoud 2013) do not invalidate the previous evidence (criteria A-1 or A3), nor provide major changes in the evidence (criteria B-1 – B4).	3 RCTs Al-Kaisy (2018)[1] Durate (2016)[2] Kriek (2017)[4]	All RCTs reported **short-term efficacy**. There were no data available to assess mid-term or long-term efficacy. **SCS vs. Conventional Medical Practice (CMP)** One small parallel-design RCT (Durate) compared CMP supplemented with SCS versus CMP alone in patients with diabetic neuropathy. Follow-up was 6 months. • **Pain and quality of life (QoL):** SCS resulted in a statistically significant improvement in pain intensity and health-related QoL compared with CMP alone. The mean difference between groups in VAS (0-10) pain of 3.7 may be clinically meaningful. **SCS vs. sham** Two small cross-over trials (with various levels of industry involvement) compared different frequencies of SCS with each other and with sham (Al-Kaisy, Kriek); one trial also included burst SCS (Kriek). Both trials had very short follow-up of 2 or 3 weeks. • **Pain:** Across RCTs, results were conflicting which may be due to	This section of the report is still valid and does not need updating (criteria A-1 or A-3; B-1–4).

Conclusions from HTA Executive Summary	Conclusions from 2014 and 2016 Signal Update	New Sources of Evidence (2018)	New Findings	Conclusion from AAI
quality of life outcomes to be similar between SCS + physical therapy and physical therapy alone at 2 years follow-up. Similarly, function as measured by the Oswestry Disability Index score was better in the SCS group at 6 months versus CMM in one study but the ability to perform daily activities after 3 years was not different in a second study. The strength of this evidence is low. **b) Efficacy (Mid-term, 5-10 years):** • **Pain, quality of life, perceived effect of treatment:** There is low evidence from one small randomized controlled trial that SCS is no different from conventional therapy (physical therapy) in patients with chronic neuropathic pain 5-10 years following implant with respect to pain, quality of life, and patient-reported global perceived effect. **c) Efficacy (Long-term, ≥10 years):** • There are no data available to assess long-term efficacy. **2. a) Effectiveness (Short-term, <5 years):** • **Composite of pain, function, and opioid use:** One prospective cohort study on workers' compensation patients reported similar success on a composite score that includes pain, function and opioid use between SCS and either Pain Clinic or			differences in methodology and pathology. Compared with sham, one trial in patients with FBSS found that SCS performed at a frequency of 5882 Hz, but not at 3030 or 1200 Hz, resulted in statistically significant back pain relief; in the second trial SCS at all tested frequencies (40, 500, and 1200 Hz) and burst SCS were significantly better in patients with CRPS. Mean differences between groups were not reported; informal estimates suggest differences of 1.6 to 2.5 on VAS (0-10), which may not be clinically meaningful. • **Global perceived effect (GPE):** For self-assessed "improvement" on the GPE scale in one trial, SCS at 40 and 500 Hz were significantly better than sham, but no difference was seen between sham and 1200 Hz or burst SCS. For GPE satisfaction, all active SCS settings including burst were significantly better than sham stimulation.	

Conclusions from HTA Executive Summary	Conclusions from 2014 and 2016 Signal Update	New Sources of Evidence (2018)	New Findings	Conclusion from AAI
Usual Care treatment groups. There was a modest improvement in leg pain in the SCS group compared with the control groups at 6 months follow-up but this did not persist at the 12 month or 24 month evaluation. **b) Effectiveness (Mid- and long-term, ≥5 years):** There are no data available to assess mid- or long-term effectiveness.				
Key Question 2: What is the evidence of the safety of spinal cord stimulation?				
1. Revision • There is high evidence from three randomized controlled trials, one prospective comparative cohort study and six case series that revision of SCS components is not uncommon. Overall short-term revision rates ranged from 12–38% of patients. Mid-term revision rates were 42% in one RCT and 60% in one case series. Reasons for revision include electrode repositioning or replacement, generator revision or replacement, revision of the connecting cable, and total removal and replacement of the system due to infection. There are no long-term data available. **2. Other SCS-related side effects**	2014: This section of the report is still valid and does not need updating (3 case series: Falowski 2011, Kumar 2011, Wolter 2012) 2016: Two new studies (de Vos 2014, Slangen 2014) do not invalidate the previous evidence (criteria A-2)	2 RCTs Al-Kaisy (2018)[1] Kriek (2017)[4] 1 case series Nissen (2018)[5]	Two small cross-over trials (with various levels of industry involvement) compared different frequencies/settings of SCS with each other and with sham; one trial also included burst SCS (Kriek). Both trials had very short follow-up of 2 or 3 weeks. Comparative data was limited. Additionally, one case series was identified that reported mid-term (median 5 year) complication rates. **Revision.** *Short-term* revision rates were 4% (due to pain at IPG site) and 10% (due to electrode dislocation) of patients across the two trials. In the latter trial, an additional eight instances of electrode reconfiguration was reported (unclear if the 8 refers to patients or events). The other trial also notes that 12.5% of patients had radiographically confirmed "minor" lead migration but do not mention whether or not these patients required revision. *Mid-term* revision rates were 37% overall in the case series; the revision rate due specifically to	This section of the report is still valid and does not need updating (criteria A-2).

Conclusions from HTA Executive Summary	Conclusions from 2014 and 2016 Signal Update	New Sources of Evidence (2018)	New Findings	Conclusion from AAI
• Side effects reported varied widely among studies and included infection, change in amplitude by bodily movements, paresthesia in other body parts, pain/irritation from the pulse generator, transient neurological defects, severe wound-related pain at the stimulator implantation site, cerebrospinal fluid leak, and subcutaneous hematoma. The rate of side effects could not be determined from the papers reviewed; however, one RCT reported that all patients experienced at least one side effect. **3. Mortality** • There is high evidence that the rate of mortality due to SCS is low. Among the four comparative studies, 2 deaths were reported in patients receiving SCS (2/139); one as a result of a cardiac event six months following SCS implantation, and the cause of one was not reported. No deaths were recorded in the control groups during the same time period (0/179). Two additional deaths were identified in three case series with five year follow-up; one from a cerebrovascular accident in a patient implanted for cardiac ischemic pain, one as a result of suicide. No death was attributed to SCS; however one patient nearly died as a result of complications that arose following trial stimulation.			complications was 14% (included deep infection, hardware malfunction, hematoma, IPG discomfort, and electrode migration). **Other SCS-related side effects** varied across the trials and only one trial provided comparative data for some outcomes (Kriek 2017). Over the *short-term*, itching and/or rash was more common with SCS vs. sham (6.9% vs. 0%); the same number of patients in both groups experienced headache (3.4%). Other adverse events (not reported by group) included axial paresthesia (3.4%) in one trial, and skin heating during recharging (4.2%) and intercostal pain (4.2%) in the other. No serious adverse events were reported to include infection or neurological sequelae. At *mid-term* follow-up in one case series, the overall infection rate was 3.1% and there were no neurological injuries requiring surgical intervention. **Mortality** was not reported by either trial or the case series.	

Conclusions from HTA Executive Summary	Conclusions from 2014 and 2016 Signal Update	New Sources of Evidence (2018)	New Findings	Conclusion from AAI
Key Question 3: What is the evidence that spinal cord stimulation has differential efficacy or safety issues in sub populations?				
1. Age • There is conflicting evidence whether patient age at baseline is associated with outcome. Two studies found that age did not correlate with either pain relief or success (combination of pain relief and patient satisfaction), while one study found that younger age was correlated with pain relief of at least 50%. One of these studies also reported no correlation between age and SF-36 or GPE scores. **2. Sex** • There are mixed results regarding whether patient sex is associated with outcome following SCS. Three studies found that sex was not associated with pain relief, one showed no correlation between sex and SF-36 or GPE scores. In contrast, one study found that females had a significantly higher rate of success (pain relief and patient satisfaction), improved function and activity, and decreased medication usage at five years compared with males. **3. Workers' compensation or other disability payments** • One prospective study suggests that whether patients receive workers' compensation/other disability payments or no compensation has no effect on pain	2014: This section of the report is still valid and does not need updating (no new data identified). 2016: No new data.	No new evidence	No new evidence	No new data.

Conclusions from HTA Executive Summary	Conclusions from 2014 and 2016 Signal Update	New Sources of Evidence (2018)	New Findings	Conclusion from AAI
relief among patients receiving SCS. Another prospective study found that among patients on workers' compensation, successful outcomes of pain relief, improved function and reduced opioid use was similar between SCS and two control treatment groups. The percentages of success were low in all groups. **4. Duration of pain** • There is moderate evidence from three cohort studies that duration of pain prior to SCS implantation is not associated with pain relief or success within the first year after implantation. **5. Pain intensity** • There is low evidence from one cohort study to suggest that pain intensity at baseline is not associated with success. **6. Time since first lumbar surgery** • There is low evidence from one cohort study to suggest that time since first lumbar surgery is not predictive of success.				
Key Question 4: What is the evidence of cost implications and cost-effectiveness of spinal cord stimulation?				
Cost Effectiveness • There is moderate evidence from three complete economic evaluations that in the short-term, SCS is associated with improved outcomes and increased costs	2014: This section of the report could be updated with the results of the cost-effectiveness analysis of the cohort of Washington State	Slagen 2017[6]	Slagen et al conducted a cost-utility analysis alongside a multicenter RCT comparing SCS versus best medical treatment in patients with painful diabetic peripheral neuropathy. The time horizon was 12 months in the base case analysis. From societal and payer perspectives,	This section of the report is still valid and does not need updating (criteria A-1 or A3; B-1).

Conclusions from HTA Executive Summary	Conclusions from 2014 and 2016 Signal Update	New Sources of Evidence (2018)	New Findings	Conclusion from AAI
compared with CMM and/or re-operation for the treatment of neuropathic pain. In the long-term, SCS appears to be dominant over the control treatments; however, only one study included in this assessment was conducted in a U.S. setting. More specifically, we found that there is some evidence that SCS is cost-effective at moderate (<$20,000) incremental cost effectiveness ratio (ICER) levels compared with CMM or re-operation, and that SCS cost-effectiveness increases and may be dominant over time compared with control treatments (i.e., CMM or re-operation) assuming device longevity of 4 years and at least a 30% pain threshold criteria. However, the assumption of continued efficacy past 3 years is questionable from the only RCT reporting pain 5-10 years after implantation. Furthermore, only one study was conducted in a US setting.	workers' compensation patients with FBSS. However, the addition of this analysis (which suggests that SCS is not cost-effective in this patient population compared with pain clinic or usual care) would not affect the coverage decision (SCS is not covered) (Hollingworth 2011, Kemler 2010). 2016: One new cost-utility (Zucco 2015) study does not invalidate the previous evidence (criteria A-1 or A3), nor provide major changes in the evidence (criteria B-1).		ICERs were €94,159.56/QALY and €34,518.85/QALY, respectively. From the societal perspective, at a willingness-to-pay threshold of €80,000, SCS would be cost-effective in only 46% of cases. The authors conclude that SCS is not cost-effective in the short-term in this patient population, primarily due to the high initial investment costs of SCS. Sensitivity analyses testing the impact of baseline differences in costs and extending the depreciation period of the SCS material to 4 years, indicated that SCS is likely to become cost effective over the longer-term.	

AAI = Aggregate Analytics, Inc.; CRPS = complex regional pain syndrome; FBSS = failed back surgery syndrome; HTA = health technology assessment; ICER = incremental cost-effectiveness ratio; RCTs = randomized controlled trials; SCS = spinal cord stimulation.

4. Conclusions

Table 1 shows the original key questions, the conclusions of the original report, the new sources of evidence, the new findings, and the conclusions of AAI with respect to the criteria that identify a trigger for an update (Figure 1).

4.1 Key Question 1: With respect to efficacy, one new small RCT compared SCS versus conventional medical practice in patients with diabetic neuropathy and reported short-term (6 months) improvements in pain and quality of life in favor of SCS. Two new small crossover trials with very short follow-up (2 or 3 weeks) compared different frequencies of SCS versus sham; one trial also included burst SCS. Results were inconsistent. In the trial evaluating patients with failed back surgery syndrome (FBSS), SCS performed at a frequency of 5882 Hz, but not at 3030 or 1200 Hz, resulted in statistically significant pain relief compared with sham. The second trial included patients with complex regional pain syndrome and found that SCS performed at all tested frequencies (40, 500, and 1200 Hz) and burst SCS provided statistically better pain relief. It is difficult to draw conclusions across these two trials given the variability in methodology and pathology. Across all three trials, although authors report statistically significant improvement in pain it is unclear whether these differences are clinically meaningful. There were no data available to assess mid-term or long-term efficacy. The three new RCTs do not provide major changes in the evidence. This section of the report is still valid and does not need updating (criteria A-1 or A3; B-1–4).

4.2 Key Question 2: With respect to safety of SCS, short-term data from two new small crossover trials (comparing burst SCS and SCS at various frequencies with sham stimulation) and mid-term data from one new case-series in patients with FBSS show similar frequencies of complications as those previously reported and continue to underscore that SCS is not without complications. This section of the report is still valid and does not need updating (criteria A-2).

4.3 Key Question 3*:* There is no new evidence with respect to differential efficacy or safety of SCS in subpopulations.

4.4 Key Question 4*:* With respect to cost-effectiveness, one new cost-utility analysis of SCS versus best medical treatment in patients with diabetic peripheral neuropathy concluded that SCS is not cost-effective in the short-term, primarily due to the high initial investment costs of SCS. This section of the report is still valid and does not need updating (criteria A-1 or A3; B-1).

REFERENCES

1. Al-Kaisy A, Palmisani S, Pang D, et al. Prospective, Randomized, Sham-Control, Double Blind, Crossover Trial of Subthreshold Spinal Cord Stimulation at Various Kilohertz Frequencies in Subjects Suffering From Failed Back Surgery Syndrome (SCS Frequency Study). Neuromodulation : journal of the International Neuromodulation Society 2018.

2. Duarte RV, Andronis L, Lenders MW, de Vos CC. Quality of life increases in patients with painful diabetic neuropathy following treatment with spinal cord stimulation. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 2016;25:1771-7.

3. Hollingworth W, Turner JA, Welton NJ, Comstock BA, Deyo RA. Costs and cost-effectiveness of spinal cord stimulation (SCS) for failed back surgery syndrome: an observational study in a workers' compensation population. Spine 2011;36:2076-83.

4. Kriek N, Groeneweg JG, Stronks DL, de Ridder D, Huygen FJ. Preferred frequencies and waveforms for spinal cord stimulation in patients with complex regional pain syndrome: A multicentre, double-blind, randomized and placebo-controlled crossover trial. European journal of pain (London, England) 2017;21:507-19.

5. Nissen M, Ikaheimo TM, Huttunen J, Leinonen V, von Und Zu Fraunberg M. Long-Term Outcome of Spinal Cord Stimulation in Failed Back Surgery Syndrome: 20 Years of Experience With 224 Consecutive Patients. Neurosurgery 2018.

6. Slangen R, Faber CG, Schaper NC, et al. A Trial-Based Economic Evaluation Comparing Spinal Cord Stimulation With Best Medical Treatment in Painful Diabetic Peripheral Neuropathy. The journal of pain : official journal of the American Pain Society 2017;18:405-14.

APPENDIX A. SEARCH STRATEGIES

The detailed strategy below is presented in Medline and EMBASE syntax.

Search Strategy
(May 1, 2016 and June 29, 2018)
Limited to English language, human population

Database: PUBMED/MEDLINE

1.	"Spinal cord stimulation" OR "Spinal cord stimulation"[MeSH] OR "spinal cord stimulator" OR "spinal cord stimulators"
2.	#1 NOT "Case Reports"[Publication Type]

Database: EMBASE

'spinal cord stimulation'/exp OR 'spinal cord stimulator'/exp AND [humans]/lim AND [English]/lim AND [abstracts]/lim AND [5-1-2013]/sd NOT [12-1-2013]/sd AND [2010-2014]/py

Parallel strategies were used to search the Cochrane Library and others listed below. Keyword searches were conducted in the other listed resources.

Electronic Database Searches
The following databases have been searched for relevant information:
Cochrane Database of Systematic Reviews (through 2009, Issue 2)
PubMed (1975 through July 23, 2009)

Additional Economics, Clinical Guideline and Gray Literature Databases
Food and Drug Administration (FDA)
Google
ClinicalTrials.gov

APPENDIX B. CURRENT COMPARATIVE STUDIES IN ClinTrial.gov ASSESSING SCS (accessed July 25, 2018)

NCT Number	Tittle	Conditions	Interventions	Control	Enrollment	Funder	Start Date	Completion Date
NCT03595241	PANACEA Feasibility Study to Assess the Efficacy of BurstDR Spinal Cord Stimulation (SCS) (PANACEA)	• Abdominal Refractory Visceral Pain	• Burst DR SCS	• No intervention	30	• Other	July 30, 2018	December 1, 2019
NCT03586882	Effect of Spinal Cord Stimulation on Gait and Balance in Chronic Low Back Pain Patients	• Chronic Low Back Pain	• SCS	• No Intervention	100	• Other Industry	June 15, 2018	February 2020
NCT03546738	Spinal Cord Burst Stimulation for Chronic Radicular Pain Following Lumbar Spine Surgery	• Back Pain With Radiation • Pain, Postoperative	• Burst SCS	• Sham	50	• Other	June 15, 2018	February 8, 2023
NCT03470766	Sham-Controlled RCT on 10kHz High-Frequency Spinal Cord Stimulation for Chronic Neuropathic Low Back Pain (Modulate-LBP) (Modulate-LBP)	• Chronic Low Back Pain • Neuropathic Pain • Refractory Pain	• Nevro Senza • System (HF10 SCS Therapy)	• Sham	96	• Other	August 1, 2018	August 1, 2020
NCT03462147	Efficacy of Spinal Cord Stimulation in Patients With a Failed Back Surgery Syndrome. (HDS)	• Back Pain	• High Density SCS • Conventional SCS	• Sham	10	• Other	October 1, 2017	December 31, 2018
NCT03419312	PET Patterns, Biomarkers and Outcome in Burst SCS Treated FBSS Patients	• FBSS • Pain, Intractable • Low Back Pain • Radicular; Neuropathic, • Lumbar, Lumbosacral	• Burst SCS	• Sham	12	• Other	February 11, 2018	June 2019

NCT Number	Tittle	Conditions	Interventions	Control	Enrollment	Funder	Start Date	Completion Date
NCT03228420	Comparison of 10 kHz SCS Combined With CMM to CMM Alone in the Treatment of Neuropathic Limb Pain	• Painful Diabetic • Neuropathy	• Senza HF10 • SCS Therapy	• CMM	360	• Other	July 20, 2017	December 31, 2018
NCT01550575	Precision Retrospective Outcomes (PRO)	• Chronic Pain	• Non Boston • Scientific SCS • Boston Scientific • Precision Plus SCS	• CMM	10000	• Industry	March 2012	December 2022
NCT01162993	Effect of Spinal Cord Stimulation (SCS) in Painful Diabetic Polyneuropathy	• Diabetic Neuropathies	• SCS	• No Intervention	40	• Other	April 2010	January 2018

APPENDIX C. SUMMARY OF INCLUDED STUDIES

Author (year) Study type	Demographics	Results	Conclusion	Limitations Conflict of Interest
Al-Kaisy (2018)[1] Cross-over RCT	N = 30 Male: 16/24 (66.7%) Age: 47.9 (range, 33 - 60) F/U: 12-weeks (3-weeks per frequency) % F/U: 80% (24/30) Diagnosis: FBSS Intervention vs. control • 1200 Hz @ 180 µsec vs. • 3030 Hz @ 60 µsec vs. • 5882 Hz @ 30 µsec vs. • Sham	VAS back pain score (Mean ± SD)* • Sham: 4.83 ± 2.45 • 1200 Hz: 4.51 ± 1.87 • 3030 Hz: 4.57 ± 2.09 • 5882 Hz: 3.22 ± 1.98 Pairwise comparison of VAS back pain scores • 5882 Hz vs. sham: mean difference = 1.61, adjusted p-value = 0.003 • 1200 Hz vs. sham: NS • 3030 Hz vs. sham: NS Mean % reduction in VAS back pain scores • Sham: 34.9% • 1200 Hz: 40.6% • 3030 Hz: 39.8% • 5882 Hz: 57.1% Mean average leg pain scores • Sham: 2.51 • 1200 Hz: 2.37 • 3030 Hz: 2.20 • 5882 Hz: 1.81 (NS difference between groups, p=0.367) Patient Preference (reported either very satisfied or somewhat satisfied w/ therapy) • Sham: NR • 1200 Hz: 63% • 3030 Hz: 63% • 5882 Hz: 75% (p NR) Patients' Global Impression of Change	This randomized crossover study demonstrated that 5882 Hz stimulation can produce significant pain relief for axial low back pain compared with lower frequencies and sham stimulation. Sham stimulation produced similar analgesic effects to 1200 Hz and 3030 Hz and this effect may influence future neuromodulation clinical trial designs.	• Differences in charge per second may have partially influenced the outcome • Blinding cannot be guaranteed • Prior to randomization, 3 subjects were withdrawn by the study investigators for no specified reason • No wash out period between cross-overs • Short follow-up of 3-weeks • Potential for recall bias Adnan Al-Kaisy received travel sponsorship and speaker fees from Medtronic and Nevro Corp, he is the principal investigator in separate studies sponsored by Medtronic, Nevro Corp and Abbot and he has financial interest in Micron Device LLC. Stefano Palmisani received speaker fees and sponsorships to attend professional meetings from Nevro Corp and Medtronic; David Pang received sponsorship to attend professional meetings from Medtronic and Nevro Corp. Ye Tan and Sheryl McCammon are employees of Medtronic.

Author (year) Study type	Demographics	Results	Conclusion	Limitations Conflict of Interest
		• Sham: - No change: 9/24 (37.5%) - Somewhat better: 10/24 (41.7%) - Better: 5/24 (20.8%) • 1200 Hz: - No change: 6/24 (25%) - Somewhat better: 14/24 (58.3%) - Better: 4/24 (16.7%) • 3030 Hz: - No change: 4/24 (16.7%) - Somewhat better: 14/24 (58.3%) - Better: 4/24 (16.7%) • 5882 Hz: - No change: 2/24 (8.3%) - Somewhat better: 12/24 (50%) - Better: 10/24 (41.7%) (Freidman's test, p-value = 0.007) <u>Patients chosen stimulation frequency at the end of the 12-week cross-over period</u> • Sham: 12.5% • 1200 Hz: 21% • 3030 Hz: 12.5% • 5882 Hz: 29% Reverted to traditional simulation: 25% **Safety:** <u>Pain at implanted pulse generator site</u> 3/24 (12.5%) (1 subject required lead replacement)		

Author (year) Study type	Demographics	Results	Conclusion	Limitations Conflict of Interest
		Minor lead migration (radiologically confirmed) 3/24 (12.5%) Skin heating during recharging 1/24 (4.2%) Intercostal pain 1/24 (4.2%) Infection 0/24 (0%) Adverse neurological sequelae 0/24 (0%)		
Duarte (2016)[2] RCT	N = 60 Male: 38/60 (63%) Age: 59 (SD, 11) F/U: 6-months % F/U: 90% (54/60) Diagnosis: Refractory diabetic neuropathic pain in the lower extremities Intervention vs. control • CMP + SCS vs. • CMP alone	Reduction in pain intensity, %Δ from baseline (SCS vs. CMP) • CMP + SCS - Minimally clinically important (10-30%): 4/36 (11%) - Moderately important (30-50%): 3/36 (8%) - Substantial clinical difference (≥50%): 24/36 (67%) - NR: 5/36 (14%) • CMP alone - Minimally clinically important (10-30%): 6/18 (33%) - Moderately important (30-50%): NR - Substantial clinical difference (≥50%): 1/18 (6%) - NR: 11/18 (61%) VAS for Pain Intensity (Mean (SD)) • CMP + SCS: 29 (27) • CMP alone: 66 (22) - (SCS vs. CMP mean difference = -37, 95% CI -52 to -22, p < 0.001) EQ-5D index (Mean (SD))†	SCS resulted in significant improvement in pain intensity and QoL in patients with PDN, offering further support for SCS as an effective treatment for patients suffering from PDN. From a methodological point of view, different results would have been obtained if QALY calculations were not adjusted for baseline EQ-5D scores, highlighting the need to account for imbalances in baseline QoL.	• Did not employ ITT (6 patients not included in 6-month follow-up analysis • Statistically significant differences in baseline QALY score for which investigators had to adjust for retrospectively. • Open label design • Lack of placebo None

Author (year) Study type	Demographics	Results	Conclusion	Limitations Conflict of Interest
		• CMP + SCS: 0.65 (0.28) • CMP alone: 0.44 (0.33) (SCS vs. CMP mean difference = 0.21, 95% CI 0.04 to 0.39, p < 0.05) EQ-VAS (Mean (SD)) • CMP + SCS: 61 (23) • CMP alone: 41 (20) (SCS vs. CMP alone mean difference = 20, 95% CI -7 to -34, p < 0.01) QALYS – unadjusted for baseline EQ-5D score • CMP + SCS: 0.226 • CMP alone: 0.220 (Difference = 0.006, 95% CI 0.070 to 0.085, p = NS) QALYS – adjusted for baseline EQ-5D score • CMP + SCS: 0.258 • CMP alone: 0.178 (Difference = 0.080, 95% CI 0.044 to 0.114, p < 0.001) Between group differences in EQ-5D dimensions (Mobility, Self-care, Usual Activities, Pain/Discomfort, Anxiety/Depression) • NS for all dimensions except Pain/Discomfort (p < 0.001) Proportion of CMP alone patients choosing to cross-over to the CMP + SCS group after 6-months 14/18 (78%) Proportion of CMP + SCS patients choosing to continue CMP + SCS therapy after 6-months 34/36 (94%)		
Kriek (2017)[4] ISRCTN 36655259 Cross-over RCT	N = 33 Male: 4/29 (14%) Age: 42.55 (SD, 12.83)	VAS (mean (SE) [95% CI]) • Standard 40 Hz SCS: 39.83 (4.7) [30.19–49.47]; p<0.05 vs. sham	The results from this trial allow to conclude that stimulation with 40, 500, 1200 Hz and burst	• Did not employ ITT (4 patients not included in follow-up analysis) • Short wash out period of 2 days

Author (year) Study type	Demographics	Results	Conclusion	Limitations Conflict of Interest
	F/U: 10-weeks (2-weeks per frequency) % F/U: 88% (29/33) Diagnosis: CRPS Intervention vs. control • Standard 40 Hz SCS vs. • 500 Hz SCS vs. • 1200 Hz SCS vs. • Burst SCS vs. • Placebo (sham)	• 500 Hz SCS: 40.13 (4.94) [30.02–50.24]; p<0.05 vs. sham • 1200 Hz SCS: 42.89 (4.79) [33.09–52.70] ; p<0.05 vs. sham • Burst SCS: 47.98 (5.26) [37.22–58.75] ; p<0.05 vs. sham • Placebo (sham): 63.74 (3.51) [56.56–70.91] P<0.05 for all SCS groups vs. sham McGill average pain score (mean (SE) [95% CI])‡ • Standard 40 Hz SCS: 4.70 (0.40) [3.89–5.50] • 500 Hz SCS: 5.10 (0.45) [4.18–6.03] • 1200 Hz SCS: 5.31 (0.46) [4.36–6.26] • Burst SCS: 5.66 (0.49) [4.65–6.66] • Placebo (sham): 7.07 (0.28) [6.50–7.63] p<0.05 for all SCS groups vs. sham GPE for Satisfaction (mean (SE) [95% CI])§ • Standard 40 Hz SCS: 5.28 (0.29) [4.69–5.86] • 500 Hz SCS: 5.31 (0.27) [4.76–5.86] • 1200 Hz SCS: 4.97 (0.26) [4.43–5.50] • Burst SCS: 4.72 (0.34) [4.02–5.43] • Placebo (sham): 3.52 (0.35) [2.79–4.24] p<0.05 for all SCS groups vs. sham GPE for Improvement (mean (SE) [95% CI])§ • Standard 40 Hz SCS: 4.93 (0.20) [4.53–5.34]; p<0.05 vs. sham • 500 Hz SCS: 5.00 (0.23) [4.53–5.47]; p<0.05 vs. sham • 1200 Hz SCS: 4.72 (0.21) [4.29–5.15]; p=NS vs. sham • Burst SCS: 4.55 (0.24) [4.06–5.05]; p=NS vs. sham • Placebo (sham): 3.79 (0.27) [3.24–4.34]	are equally effective in relieving neuropathic pain related to CRPS and are significantly better than placebo. Some patients prefer standard stimulation over the newer, non-standard stimulation settings. However, even though higher frequencies and burst SCS are promising, we should not discard standard stimulation as a therapeutic option. More importantly, standard SCS therapy has proven to be safe and effective when used for prolonged periods of time. The best solution for the future is to incorporate all the various stimulation modalities into one device so that the patient can receive the stimulation which provides the best pain relief and user-friendliness and to make it possible for them to switch between various frequency settings if needed, either during the trial-SCS period of	• All patients were pre-treated with standard SCS prior to entering crossover period; may not be generalizable to patients naïve to stimulation • Blinding cannot be ensured considering placebo and burst SCS did not elicit paresthesia, and the differences in charging time per each frequency • Potential for recall This investigator-initiated study was supported by a grant from St. Jude Medical (Plano, TX, USA). The design, performance, analysis and submission of this trial were independently performed by our research group. FH is a paid consultant for Grunenthal GmbH; DdR has a patent on burst stimulation and is a paid consultant for St. Jude Medical.

Author (year) Study type	Demographics	Results	Conclusion	Limitations Conflict of Interest
		Preferred Stimulation • Standard 40 Hz SCS: 14/29 (48.3%) • 500 Hz SCS: 6/29 (20.7%) • 1200 Hz SCS: 4/29 (13.8%) • Burst SCS: 4/29 (13.8%) • Placebo (sham): 1 (3.4%) p=NR Best user-friendliness • Standard 40 Hz SCS: 14/29 (48.3%) • 500 Hz SCS: 8/29 (27.6%) • 1200 Hz SCS: 1/29 (3.4%) • Burst SCS: 6/29 (20.7%) • Placebo (sham): 0/29 (0%) p=NR Most Comfortable • Standard 40 Hz SCS: 14/29 (48.3%) • 500 Hz SCS: 7/29 (24.1%) • 1200 Hz SCS: 4/29 (13.8%) • Burst SCS: 4/29 (13.8%) • Placebo (sham): 0/29 (0%) p=NR **Safety:** Serious adverse events 0/29 (0%) Electrode dislocation 3/29 (10.3%) (n=1, lead revised and continued trial; n=2 lead revised but did not continue trial) Electrode reconfiguration required 8 events Itching and/or rash 2/29 (6.9%)	during regular SCS therapy. Ultimately, the field of neuromodulation should move towards customized individual patient care.	

Author (year) Study type	Demographics	Results	Conclusion	Limitations Conflict of Interest
		Axial paresthesia 1/29 (3.4%) Headache 4 events		
Nissen (2018)[5] Case series (retrospective)	N = 175 (224 patients enrolled, 49 did not experience adequate pain relief during trial period and did not receive a permanent SCS) Male: 52% Age: median 48 (22-83) years F/U: 6 (0-18) years Diagnosis: FBSS Intervention: SCS	**Safety:** • Device explantation: 26% (45/175) ○ Inefficient pain relief: 76% (34/45) ○ IPG depletion: 6% (3/45) ○ No further need for SCS: 6% (3/45) ○ Surgical site infection**:** 2% (1/45) (permanent explanation) ○ Electrode migration: 2% (1/45) ○ IPG region discomfort: 2% (1/45) ○ Need for MRI: 2% (1/45) ○ Unsuccessful implantation: 2% (1/45) • Revision: 37% (64/175) (70 total revisions)** • Revision due to complications: 14% (25/175) (26 total revisions) ○ Deep infection: 24% (6/25) (7 total: 6 revisions, 1 removal) ○ Hardware malfunction (extension lead, electrode or IPG replacement; SCS removal and re-implantation): 40% (10/25) (11 total revisions) ○ Subcutaneous hematoma: 4% (1/25) ○ Discomfort over pulse generator: 12% (3/25) (4 total: 3 revisions, 1 removal) ○ Electrode migration: 8% (2/25) (3 total: 2 revisions, 1 removal) • Revision due to inadequate pain relief: 11% (19/175) (22 total revisions) ○ Electrode repositioning: 15 revisions ○ Electrode replaced: 2 revisions ○ Explantation and new trial: 3 revisions	**Safety Summary:** • Two out of 3 patients with permanent SCS after the trial did not need additional surgery during the follow-up period. • The complication rate was 14%, which is markedly less than the 30% to 40% reported previously. Complications were mainly minor and did not lead to serious neurological sequelae. • The infection rate (3%) was in line with previous studies, reporting 3% to 6% infection rates. All infections appeared less <1 month after an operation, indicating that long-term subclinical infections are rare. Only 1 patient had a permanent	• During the study, neurosurgeons performing implantations changed • Criteria for permanent SCS implantation changed over the course of the study • Most patients in the study received an electrode that is not used presently. Funding was from a Government Research Fund. Dr Nissen has received travel funding from the Medtronic, Boston Scientific and Abbott St Jude Medical. Ms Ikäheimo, Dr Huttunen, and Dr von und zu Fraunberg have received travel funding from the Medtronic and Abbott St Jude Medical. Dr Leinonen has no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

Author (year) Study type	Demographics	Results	Conclusion	Limitations Conflict of Interest
		○ Explantation and immediate new SCS: 2 revisions • Revision due to IPG battery depletion: 11% (20/175) (22 total revisions) • Infection (overall): 3.1% Neurological injuries requiring surgical intervention: 0%	explantation due to an infection.	
Slangen (2017)[6] Cost-utility Study	N = 36 Male: 24/36 (66.7%) Age (mean ± SD): SCS, 57.1 ± 12.4 years; BMT, 56.5 ± 8.0 years F/U: 3, 6, and 12 months % F/U: 3-months, 32/36 (88.9%); 6-months, 33/36 (91.7%); 12-months, 17/22 (77.3%)†† Diagnosis: Diabetic Peripheral Neuropathy Intervention vs. control • SCS + BMT (n=22) vs. • BMT (n=14) Cost-utility analysis • Perspective: Societal and Payer • Time Horizon: 12-months • Performed alongside multi-center RCT • QALY calculated using utility scores from the EuroQol 5	**Economic**: **Societal Perspective** ICER (SCS + BMT relative to BMT) • €94,159.56 Total Costs at 12-months • SCS + BMT: €26,539.18 vs. • BMT: €5,313.45 Effectiveness at 12-months (QALY) • SCS + BMT: .58 vs. • BMT: .36 Probability Cost Effective with a WTP Threshold = €80,000 • 46% **Healthcare Perspective** ICER (SCS + BMT relative to BMT) • €34,518.85 Total Costs at 12-months • SCS + BMT: €18,742.18 vs. • BMT: €2,173.13 Effectiveness at 12-months (% Successfully treated pts.) • SCS + BMT: 55% vs. • BMT: 7% Probability Cost Effective with a WTP Threshold = €80,000	SCS was not cost effective compared with BMT at the 12-month follow-up, mainly because of the high initial investment costs of SCS. Secondary analyses showed that the ICER decreased considerably when correcting for baseline differences in costs, and extending the depreciation period of the SCS material to 4 years.	• In 3 patients, only baseline data was present (although ITT was employed) • Part of the cost data were collected retrospectively (potential for recall bias) • Data of the BMT group were linearly extrapolated up to 12 months, assuming no change between 6- and 12- months in this group • Short-term cost-utility only, no long-term data None

Author (year) Study type	Demographics	Results	Conclusion	Limitations Conflict of Interest
	• Primary outcome: ≥50% pain relief or a score of ≥6 on GPE scale at 12 months§ • Cost discounted at 4%/year • Cost in 2012€ • Nonparametric bootstrap analysis and sensitivity performed	• NR		

Abbreviations: BMT, Best Medical Treatment; CMP, Conventional Medical Practice; CRPS, Complex Regional Pain Syndrome; EQ-5D, Euro Qualified 5 Dimensions; FBSS, Failed Back Surgery Syndrome; GPE, Global Perceived Effect; ICER, Incremental Cost Effectiveness Ratio; IPG, Implantable Pulse Generator; ITT, Intention to Treat; NR, Not Reported; NS, Not significant; QALY; Quality Adjusted Life Years; SCS, Spinal Cord Stimulation; VAS, Visual Analog Scale; WTP, Willingness to Pay.

* The average pain scores for back pain from the last three days of complete diary data during the last week of each blinded crossover assignment was the primary efficacy outcome.

† EQ-5D utility scores at baseline were ALSO statistically significantly different between SCS and CMP groups.

‡ The McGill Pain Questionnaire recorded the Numerical Rating Scale (NRS) of average pain, minimum pain, maximum pain and pain during exertion (scale 0–10: 0 = no pain and 10 = worst pain ever).

§ The GPE score reporting satisfaction and the improvement on a 7-point Likert scale. Lower GPE scores are indicative for more severe conditions (satisfaction scale: 7 = very satisfied to 1 = not at all satisfied; improvement scale: 7 = completely recovered to 1 = worse than ever).

** Study is unclear in defining how removals differ from revisions. Data has been abstracted as it was presented in the article.

†† Patients in the BMT group (n=14) were not evaluated at 12-month follow-up because after 6 months they were offered SCS.

APPENDIX D. LIST OF EXCLUDED ARTICLES AFTER FULL-TEXT REVIEW

Study	Reason for Exclusion:
Systematic Reviews	
Aiyer R, Barkin RL, Bhatia A, Gungor S. A systematic review on the treatment of phantom limb pain with spinal cord stimulation. Pain management 2016;7:59-69.	No new RCTs since previous report
Amirdelfan K, Webster L, Poree L, Sukul V, McRoberts P. Treatment Options for Failed Back Surgery Syndrome Patients With Refractory Chronic Pain: An Evidence Based Approach. Spine 2017;42 Suppl 14:S41-s52.	No new RCTs since previous report
Bicket MC, Dunn RY, Ahmed SU. High-Frequency Spinal Cord Stimulation for Chronic Pain: Pre-Clinical Overview and Systematic Review of Controlled Trials. Pain medicine (Malden, Mass) 2016;17:2326-36.	Comparison of different SCS modalities, no non-SCS controls
Cho JH, Lee JH, Song KS, et al. Treatment Outcomes for Patients with Failed Back Surgery. Pain physician 2017;20:E29-e43.	No new RCTs since previous report
Cruccu G, Garcia-Larrea L, Hansson P, et al. EAN guidelines on central neurostimulation therapy in chronic pain conditions. European journal of neurology 2016;23:1489-99.	No new RCTs since previous report
Deer TR, Campos LW, Pope JE. Evaluation of Abbott's BurstDR stimulation device for the treatment of chronic pain. Expert review of medical devices 2017;14:417-22.	Comparison of different SCS modalities, no non-SCS controls
Dy SM, Bennett WL, Sharma R, et al. AHRQ Comparative Effectiveness Reviews. Preventing Complications and Treating Symptoms of Diabetic Peripheral Neuropathy. Rockville (MD): Agency for Healthcare Research and Quality (US); 2017.	No new RCTs since previous report
Grider J. Effectiveness of spinal cord stimulation in chronic spinal pain: a systematic review. Pain physician 2016;19:E33-E54.	No new RCTs since previous report
Hou S, Kemp K, Grabois M. A Systematic Evaluation of Burst Spinal Cord Stimulation for Chronic Back and Limb Pain. Neuromodulation : journal of the International Neuromodulation Society 2016;19:398-405.	Comparison of different SCS modalities, no non-SCS controls
Kapural L, Peterson E, Provenzano DA, Staats P. Clinical Evidence for Spinal Cord Stimulation for Failed Back Surgery Syndrome (FBSS): Systematic Review. Spine 2017;42 Suppl 14:S61-s6.	No new RCTs since previous report
Tajti J, Szok D, Majlath Z, Csati A, Petrovics-Balog A, Vecsei L. Alleviation of pain in painful diabetic neuropathy. Expert opinion on drug metabolism & toxicology 2016;12:753-64.	No new RCTs since previous report
Visnjevac O, Costandi S, Patel BA, et al. A Comprehensive Outcome-Specific Review of the Use of Spinal Cord Stimulation for Complex Regional Pain Syndrome. Pain practice : the official journal of World Institute of Pain 2017;17:533-45.	No new RCTs since previous report

Study	Reason for Exclusion:
Waszak PM, Modric M, Paturej A, et al. Spinal Cord Stimulation in Failed Back Surgery Syndrome: Review of Clinical Use, Quality of Life and Cost-Effectiveness. Asian spine journal 2016;10:1195-204.	No new RCTs since previous report
Zyluk A, Puchalski P. Effectiveness of complex regional pain syndrome treatment: A systematic review. Neurologia i neurochirurgia polska 2018.	No new RCTs since previous report
RCTs	
Amirdelfan K, Yu C, Doust MW, et al. Long-term quality of life improvement for chronic intractable back and leg pain patients using spinal cord stimulation: 12-month results from the SENZA-RCT. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 2018.	Comparison of different SCS modalities, no non-SCS controls
De Andres J, Monsalve-Dolz V, Fabregat-Cid G, et al. Prospective, Randomized Blind Effect-on-Outcome Study of Conventional vs High-Frequency Spinal Cord Stimulation in Patients with Pain and Disability Due to Failed Back Surgery Syndrome. Pain medicine (Malden, Mass) 2017;18:2401-21.	Comparison of different SCS modalities, no non-SCS controls
Deer T, Slavin KV, Amirdelfan K, et al. Success Using Neuromodulation With BURST (SUNBURST) Study: Results From a Prospective, Randomized Controlled Trial Using a Novel Burst Waveform. Neuromodulation : journal of the International Neuromodulation Society 2018;21:56-66.	Comparison of different SCS modalities, no non-SCS controls
Deer TR, Levy RM, Kramer J, et al. Dorsal root ganglion stimulation yielded higher treatment success rate for complex regional pain syndrome and causalgia at 3 and 12 months: a randomized comparative trial. Pain 2017;158:669-81.	Comparison of SCS to DRG stimulation
Kapural L, Yu C, Doust MW, et al. Comparison of 10-kHz High-Frequency and Traditional Low-Frequency Spinal Cord Stimulation for the Treatment of Chronic Back and Leg Pain: 24-Month Results From a Multicenter, Randomized, Controlled Pivotal Trial. Neurosurgery 2016;79:667-77.	Comparison of different SCS modalities, no non-SCS controls
Tjepkema-Cloostermans MC, de Vos CC, Wolters R, Dijkstra-Scholten C, Lenders MW. Effect of Burst Stimulation Evaluated in Patients Familiar With Spinal Cord Stimulation. Neuromodulation : journal of the International Neuromodulation Society 2016;19:492-7.	Comparison of different SCS modalities, no non-SCS controls
Safety	
Bendel MA, O'Brien T, Hoelzer BC, et al. Spinal Cord Stimulator Related Infections: Findings From a Multicenter Retrospective Analysis of 2737 Implants. Neuromodulation : journal of the International Neuromodulation Society 2017;20:553-7.	Case Series with inadequate follow-up (<5 years)
van Buyten JP, Wille F, Smet I, et al. Therapy-Related Explants After Spinal Cord Stimulation: Results of an International Retrospective Chart Review Study. Neuromodulation : journal of the International Neuromodulation Society 2017;20:642-9.	Case Series with inadequate follow-up (<5 years)

Study	Reason for Exclusion:
Chan AK, Winkler EA, Jacques L. Rate of perioperative neurological complications after surgery for cervical spinal cord stimulation. Journal of neurosurgery Spine 2016;25:31-8.	Case Series with inadequate follow-up (<5 years)
Dupre DA, Tomycz N, Whiting D, Oh M. Spinal Cord Stimulator Explantation: Motives for Removal of Surgically Placed Paddle Systems. Pain practice : the official journal of World Institute of Pain 2018;18:500-4.	Case Series with inadequate follow-up (<5 years)
Fitzgibbon DR, Stephens LS, Posner KL, et al. Injury and Liability Associated with Implantable Devices for Chronic Pain. Anesthesiology 2016;124:1384-93.	Case Series with inadequate follow-up (<5 years); also looking at liability claims, relevant outcomes not reported
Hoelzer BC, Bendel MA, Deer TR, et al. Spinal Cord Stimulator Implant Infection Rates and Risk Factors: A Multicenter Retrospective Study. Neuromodulation : journal of the International Neuromodulation Society 2017;20:558-62.	Duplicate study (see Bendel et al 2017 above); case Series with inadequate follow-up (<5 years)
Khan H, Kumar V, Ghulam-Jelani Z, et al. Safety of Spinal Cord Stimulation in Patients Who Routinely Use Anticoagulants. Pain medicine (Malden, Mass) 2017.	Case Series with inadequate follow-up (<5 years)
Kleiber JC, Marlier B, Bannwarth M, Theret E, Peruzzi P, Litre F. Is spinal cord stimulation safe? A review of 13 years of implantations and complications. Revue neurologique 2016;172:689-95.	Case Series with unclear follow-up
Maldonado-Naranjo AL, Frizon LA, Sabharwal NC, et al. Rate of Complications Following Spinal Cord Stimulation Paddle Electrode Removal. Neuromodulation : journal of the International Neuromodulation Society 2017.	Case Series with inadequate follow-up (<5 years)
Moeschler SM, Warner NS, Lamer TJ, et al. Bleeding Complications in Patients Undergoing Percutaneous Spinal Cord Stimulator Trials and Implantations. Pain medicine (Malden, Mass) 2016;17:2076-81.	Case Series with inadequate follow-up (<5 years)
Moufarrij NA. Epidural hematomas after the implantation of thoracic paddle spinal cord stimulators. Journal of neurosurgery 2016;125:982-5.	Case Series with unclear follow-up; highlights several case reports
Pope JE, Deer TR, Falowski S, et al. Multicenter Retrospective Study of Neurostimulation With Exit of Therapy by Explant. Neuromodulation : journal of the International Neuromodulation Society 2017;20:543-52.	Case Series with unclear follow-up; relevant outcomes NR
Sanchis-Lopez N, Romero-Garcia C, De Andres-Ibanez J, et al. Medical Device Related Pressure Injury in the Treatment of Chronic Pain: An Early Sign of Explantation in Suspected Infection. Pain physician 2018;21:E235-e46.	Mixed SCS (63%) and intrathecal drug delivery (ITDD) pumps (37%), outcomes not reported separately; case series with unclear f/u
Yusuf E, Bamps S, Thuer B, et al. A Multidisciplinary Infection Control Bundle to Reduce the Number of Spinal Cord Stimulator Infections. Neuromodulation : journal of the International Neuromodulation Society 2017;20:563-6.	Case series with inadequate f/u; focus is to evaluate an intervention to reduce SCS infections

Study	Reason for Exclusion:
Economic Studies	
Farber SH, Han JL, Elsamadicy AA, et al. Long-term Cost Utility of Spinal Cord Stimulation in Patients with Failed Back Surgery Syndrome. Pain physician 2017;20:E797-e805.	Not a full economic study
Han JL, Murphy KR, Hussaini SMQ, et al. Explantation Rates and Healthcare Resource Utilization in Spinal Cord Stimulation. Neuromodulation : journal of the International Neuromodulation Society 2017;20:331-9.	Not a full economic study
Hoelscher C, Riley J, Wu C, Sharan A. Cost-Effectiveness Data Regarding Spinal Cord Stimulation for Low Back Pain. Spine 2017;42 Suppl 14:S72-s9.	Search date included time period of previous report

Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy: An Evidence Update

Evidence Update for the Washington State Health Technology Assessment Program

December 2018

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This health technology assessment report is based on research conducted by the Center for Evidence-based Policy (Center) under contract to the Washington State Health Care Authority (HCA). This report is an independent assessment of the technology question(s) described based on accepted methodological principles. The findings and conclusions contained herein are those of the authors, who are responsible for the content. These findings and conclusions do not necessarily represent the views of the Washington HCA and thus, no statement in this report shall be construed as an official position or policy of the HCA.

The information in this assessment is intended to assist health care decision makers, clinicians, patients, and policy makers in making evidence-based decisions that may improve the quality and cost-effectiveness of health care services. Information in this report is not a substitute for sound clinical judgment. Those making decisions regarding the provision of health care services should consider this report in a manner similar to any other medical reference, integrating the information with all other pertinent information to make decisions within the context of individual patient circumstances and resource availability.

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Conflict of Interest Disclosures: No authors have conflicts of interest to disclose. All authors have completed and submitted the Oregon Health & Science University form for Disclosure of Potential Conflicts of Interest, and none were reported.

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Bottom Line

This evidence update includes studies published since the original evidence review conducted in 2012 that informed the coverage policy for stereotactic radiation surgery (SRS) and stereotactic body radiation therapy (SBRT), as adopted by the Washington State Health Technology Clinical Committee (HTCC) in March 2013. After summarizing the eligible studies in this evidence update, we have determined that they would likely not change the conclusions of the 2012 evidence report.

The guidelines from the National Comprehensive Cancer Network (NCCN) include recommendations to consider the use of SRS and SBRT for the cancers covered in the HTCC 2013 decision: central nervous system (CNS) cancers and medically inoperable early-stage non-small cell lung cancer (NSCLC). The NCCN guidelines recommend consideration of treatment using SRS or SBRT for a number of additional indications, including cancers of the liver, pancreas, and prostate.

A review of coverage policies from a Medicare Local Coverage Determination (LCD) applying to Washington and three private payers (Aetna, Cigna, and Regence) found that all 4 of these payers provide coverage for the cancers covered in the HTCC 2013 decision. Each of these 4 payers provides coverage for additional indications, although there is little consistency among these 4 payers for which indications are covered.

Background

The Washington State HTCC commissioned an evidence review in 2012 on the effectiveness of SRS and SBRT for treating various cancers.[1] On March 22, 2013, using that evidence review to guide decision making, the committee adopted the following coverage determination:

- SRS for CNS primary and metastatic tumors is a covered benefit for adults and children when the following criteria are met:
  - Patient functional status score (i.e., Karnofsky score) is greater than or equal to 50; and
  - Evaluation includes multidisciplinary team analysis (e.g., tumor board), including surgical input.
- SBRT is covered for adults and children for the following conditions when the following criteria are met:
  - For cancers of spine/paraspinal structures; or
  - For inoperable NSCLC, stage 1; and
  - Evaluation includes multidisciplinary team analysis, including surgical input.[2]
- All other indications are non-covered

The Washington Health Technology Assessment program contracted with the Center for Evidence-based Policy (Center) in 2016 to conduct an updated evidence search on this topic and produce a brief on the included eligible studies to help determine whether the previous

coverage policy decision should be reviewed. The Center completed an evidence update in January 2017,[3] and the Washington State Health Care Authority did not find the evidence sufficient to commission an updated full review on the topic. This document is a second evidence update, commissioned in October 2018. This evidence update is based on a search for studies published since the 2017 evidence update report search and summarizes the findings of all relevant studies published since the 2012 full evidence review.

Methods

To identify studies published since the 2017 evidence update, Center researchers conducted Ovid searches of MEDLINE, the Cochrane Database of Systematic Reviews, and the Cochrane Controlled Trials Register database. The search strategies are in Appendix A. Studies were included if they met the criteria outlined in the PICO below. We also examined NCCN's recommended treatment algorithms for recommendations on the use of SRS, SBRT, or stereotactic ablative radiotherapy (SABR) for all cancers. We assessed coverage policies for Medicare and 3 private payers: Aetna, Cigna, and Regence. The U.S. National Library of Medicine's data on clinical studies (ClinicalTrials.gov) was searched for phase 3 and phase 4 trials that assess the effectiveness of SRS, SBRT, or SABR.

For each indication, we determined a bottom-line conclusion that was based on our assessment of the likelihood that studies published since 2012 would change the conclusion of the prior evidence review. For indications that are covered in the HTCC's current 2013 decision, we looked for evidence that the treatment is not as effective or safe as a comparator. For indications that are not covered in the HTCC's current decision, we looked for evidence of a significant benefit or harm favoring SRS or SBRT. If we found new evidence that might change the conclusion regarding any indication covered in the 2012 report, then we would recommend that the HTCC commission a full update of the report. If we found that the new evidence would likely not change the conclusion of the 2012 report for any indication, then we would recommend that the HTCC not commission a full update of the report at this time.

PICO

Populations

Adults and children with CNS and non-CNS malignancies where treatment by radiation therapy is appropriate

Interventions

SRS or SBRT with devices such as Gamma Knife, CyberKnife, TomoTherapy

Comparators

Conventional (conformal) external beam therapy (EBRT), surgery, no treatment

Outcomes

Survival rate, duration of symptom-free remission, quality of life, harms including radiation exposure and complications, cost, cost-effectiveness

Key Questions

1) What is the evidence of efficacy and effectiveness for SRS and SBRT compared to conventional EBRT for the following patients:

a. Patients with CNS tumors
b. Patients with non-CNS cancers

2) What are the potential harms of SRS and SBRT compared to conventional EBRT? What is the incidence of these harms? This includes consideration of progression of treatment in unnecessary or inappropriate ways.

3) What is the evidence that SRS and SBRT have differential efficacy, effectiveness, or safety issues in subpopulations including differences by:

a. Gender
b. Age
c. Site and type of cancer
d. Stage and grade of cancer
e. Setting, provider characteristics, equipment, quality assurance standards, and procedures

4) What is the evidence of cost and cost-effectiveness of SRS and SBRT compared to EBRT?

For Key Questions 1 to 3, the following inclusion criteria were applied to individual studies:

- Treatments delivered in 10 or fewer fractions
- Published, peer-reviewed, English-language articles
- Comparative study designs (prospective, retrospective, and randomized or controlled clinical trials)
- Other specific inclusion criteria for individual studies:
  - CNS cancers: eligible study design with a minimum sample size of 20 participants
  - Cancers of the breast, colon, head, neck, lung, prostate: eligible study design with a minimum sample size of 50 participants
  - Other non-CNS cancers: eligible study design with a minimum sample size of 20 participants

These exclusion criteria were applied to all studies:

- Does not include patient-important outcomes
- Does not meet sample size criteria
- Treatments delivered in 11 or more fractions

- Data for treatment planning (e.g., dosing) or treatment delivery (e.g., accuracy)
- Non-cancer indications (e.g., trigeminal neuralgia)
- Non-English publication
- Study conducted in a location that is not sufficiently representative of the U.S. (i.e., in a lower or middle income country)
- Study does not include human subjects

For Key Question 4, studies providing comparative cost data and relevant economic evaluations, cost-effectiveness analyses, and other economic simulation modeling studies were included. The exclusion criteria above apply to the economic studies considered for Key Question 4.

Findings

After deduplication, 2,331 documents were found in the searches. After title and abstract screening, 265 were identified for full-text review. After full-text review, 69 studies were eligible for this evidence update, as shown in Figure 1. Table 1 shows the number of included articles by cancer and study design. The list of studies excluded at the full-text level, with exclusion reasons, is in Appendix D.

Figure 1. PRISMA Study Flow Diagram

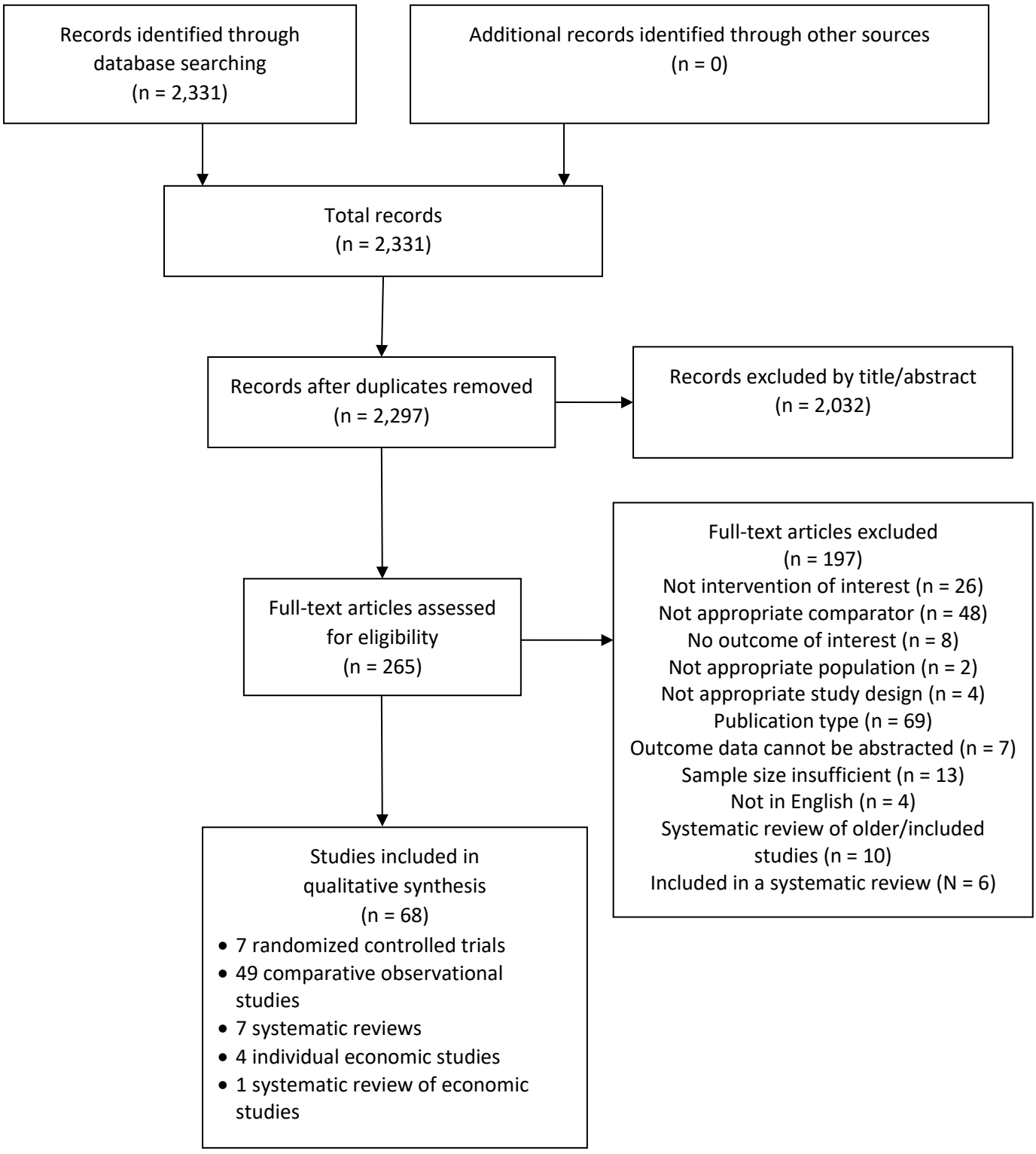

Table 1. Number of Included Studies by Study Type and Indication: 2018 Update

	Systematic Review	Randomized Controlled Trial	Comparative Observational	Economic
Brain cancer	2	4	22	0
Spinal cancer	0	2	0	0
Lung cancer	3	1	12	1
Pancreatic cancer	1	0	5	0
Prostate cancer	0	0	3	1
Liver cancer	0	0	2	2
Head and neck cancer	0	0	4	0
Bone metastases	1	0	0	0
Adrenal cancer	0	0	1	0
TOTAL	7	7	49	4 + 1 SR*

*Abbreviation. SR: systematic review. Note. *SR includes economic studies of brain, bone, liver, lung, pancreas, and prostate cancers.*

In the 2017 update, 1,968 records were identified after deduplication, and 66 of those publications were included in this update. Combining the search results from both updates yielded 135 studies published since the 2012 evidence review. Table 2 shows the number of studies by indication and study type across these 2 evidence updates. A summary of the findings of these studies is presented below for each indication.

Table 2. Number of Included Studies by Study Type and Indication: Update Since 2012

	Systematic Review	Randomized Controlled Trial	Comparative Observational	Economic
Brain cancer	10	6	37	2
Spinal cancer	0	2	2	0
Lung cancer	7	3	27	1
Pancreatic cancer	2	0	6	0
Prostate cancer	1	0	8	1
Liver cancer	0	0	5	2
Head and neck cancer	0	0	4	0
Bone metastases	1	0	0	0
Adrenal cancer	1	0	1	0
Meningioma/Schwannoma	0	0	2	0
TOTAL	22	11	92	6 + 1 SR*

*Abbreviation. SR: systematic review. Note. *SR includes economic studies of brain, bone, liver, lung, pancreas, and prostate cancers.*

Brain Cancer

The identified new studies of effectiveness and safety are unlikely to change the conclusions of the 2012 evidence review for brain cancer because additional studies have been published since 2012 confirming that survival rates for SRS were the same or improved compared to conventional radiotherapy without additional risk of harms.

The updated searches identified 10 systematic reviews[4-13] published since the 2012 update; 2 of these systematic reviews were published in 2017.[8,13]

- Khan et al.[8] published a 2017 systematic review comparing SRS alone to whole brain radiation therapy (WBRT) alone and SRS plus WBRT. The authors conducted a meta-analysis of 5 RCTs (N = 763).[8] WBRT had a decreased overall survival rate compared to SRS plus WBRT, although the difference was not statistically significant (hazard ratio [HR], 1.19; 95% CI, 0.96 to 1.43; *P* = .12).[8] Local control was statistically significantly worse in WBRT compared to SRS plus WBRT (HR, 2.05; 95% CI, 1.36 to 3.09, *P* < .001).[8] There were no statistically significant differences in adverse events when comparing the SRS plus WBRT group to the WBRT alone group (odds ratio [OR], 1.16; 95% CI, 0.77 to 1.76; *P* = .48).[8]
- Yuan et al.[13] published a network meta-analysis in 2017 generating an indirect comparison of SRS, SRS plus WBRT, and WBRT. In the indirect comparisons, SRS alone had a statistically significantly improved 1-year survival rate than WBRT alone (OR, 2.54; 95% CI, 1.56 to 4.58). Adding SRS to WBRT improved the 1-year survival rate compared to WBRT alone (OR WBRT alone vs. WBRT + SRS, 0.48; 95% CI, 0.27 to 0.81).[13]

Our search identified 6 additional RCTs showing mixed results.

- Patients aged 3 to 25 years with benign and low-grade brain tumors (N = 100) were randomly assigned to receive SRS or conventional radiotherapy.[14] Full-scale intelligence quotient scores during the 5-year follow-up period were significantly greater in the SRS group compared to the control group (mean difference, 1.48; *P* = .04).[14] Overall survival at 5 years was not statistically significantly different between groups (86% vs. 91%; *P* = .54).[14]
- SRS was compared to WBRT after total or subtotal resection in an RCT of patients with single brain metastasis (N = 59).[15] Overall survival at 2 years was significantly worse in the SRS group compared to the WBRT group (10% vs. 37%; *P* = .046).[15]
- Additional analyses of the 2016 RCT by Kepka et al.[15] were conducted on quality of life outcomes, and 37 of the 59 participants were eligible for analyses.[16] At 2 months, quality of life scores were statistically significantly better in the SRS groups compared to WBRT groups for drowsiness (19.9 vs. 36.2; *P* = .048) and for appetite loss (8.9 vs. 30.2; *P* = .03).[16]
- SRS was compared to observation of patients treated with chemotherapy for asymptomatic cerebral oligometastases from NSCLC in an RCT (N = 105).[17] The median overall survival times were not statistically significantly different between the SRS and observation groups (14.6 months; 95% CI, 9.2 to 20.0 vs. 15.3 months; 95% CI, 7.2 to 23.4; *P* = .42).[17]

- Patients with resected brain metastases (1 to 3 brain metastases) were randomly assigned to SRS or observation (N = 132).[18] Absence of local recurrence at 12 months was statistically significantly greater in the SRS group compared to the control group (72% vs. 43%; HR, 0.46; 95% CI, 0.24 to 0.88; *P* = .02).[18]
- SRS + WBRT was compared to WBRT alone in an RCT of participants with 1 to 3 brain metastases (N = 331).[19] Overall, there was no statistically significant difference in median overall survival time between the 2 groups, but among participants with graded prognostic assessment 3.5 to 4, median overall survival time was statistically significantly longer in the SRS plus WBRT group compared to the WBRT alone group (21.0 months vs. 10.3 months; *P* = .05).[19]

Our search identified 37 comparative observational studies.[20-56]

Economic Studies

The identified new studies of economic outcomes are unlikely to change the conclusions of the 2012 evidence review for brain cancer because additional studies have been published since 2012 confirming that SRS is cost-effective compared to conventional radiotherapy. The systematic review by Lester-Coll[57] included 5 economic studies of brain cancer that compared SRS to WBRT or surgery, and our search identified 2 additional economic studies comparing SRS to surgery.[58,59] All of these studies showed SRS to be cost-effective relative to the comparators.[57-59]

Spinal Cancer

The identified new studies of effectiveness and safety are unlikely to change the conclusions of the 2012 evidence review for spinal cancer because 2 RCTs and 2 comparative observational studies have been published since 2012 confirming that mean overall survival duration or overall survival rates for SRS were the same or better compared to conventional radiotherapy without additional risk of harms.[60-63]

The 2 RCTs analyzed data from the same study, examining pain outcomes[60] and quality of life outcomes.[61]

- Pain response measured on the visual analog scale (VAS) was assessed in patients with spinal metastases (N = 55) randomly assigned to receive SBRT or 3-D conformal radiotherapy.[60] At 6 months, the SBRT group had significantly lower VAS scores (13.7 vs. 21.4; *P* = .002).[60]
- Quality of life outcomes were assessed at 3 and 6 months, comparing the SBRT group to the 3-D conformal radiotherapy group (N = 55).[61] At both time points, there were no significant differences between cohorts on functional impairment, psychosocial aspects, or fatigue (*P* > .05 for all).[61]

In the 2 comparative observational studies, the SBRT groups had statistically significantly improved survival rates compared to conventional radiotherapy groups.[62,63]

- SRS was compared to conventional radiotherapy in patients treated for spinal metastasis from hepatocellular carcinoma (N = 59).[63] Mean overall survival duration was statistically significantly greater in the SRS group compared to the conventional radiotherapy group (7 months vs. 3 months; *P* = .04).[63]
- In a retrospective cohort study, participants who received SRS were matched to those who received EBRT (N = 13 pairs). All participants were treated for spinal metastasis from renal cell carcinoma and followed for 6 months.[62] At 6 months, there was a statistically significantly improved progression-free survival rate for participants treated with SRS compared to those treated with EBRT (*P* = .01).[62]

Economic Studies

The identified new studies of economic outcomes are unlikely to change the conclusions of the 2012 evidence review. One economic study by Kim et al.[64] has been published since the 2012 evidence review, which was included in the systematic review by Lester-Coll et al.[57] This U.S. study compared SBRT to EBRT, using a willingness-to-pay threshold of $100,000 per QALY gained, and the study found SBRT to not be cost-effective relative to EBRT, with an incremental cost-effectiveness ratio (ICER) of $124,552 per QALY.[64]

Lung Cancer

The identified new studies of effectiveness and safety are unlikely to change the conclusions of the 2012 evidence review for inoperable early-stage NSCLC because additional studies have been published since 2012 confirming that overall survival rates were the same or improved for SBRT compared to conventional radiotherapy without additional risk of harms.

Three systematic reviews that summarized observational studies for inoperable, early stage NSCLC were published in 2017[65-67] and 1 systematic review was published in 2015.[68] All 4 of these systematic reviews concluded that SBRT was more effective than observation or other forms of radiotherapy.[65-67] Two comparative observational studies were identified that showed improved overall survival rates for SBRT compared to no treatment.[69,70] The one published RCT by Nyman et al.[71] in 2016 showed improved overall survival rates for SBRT versus conventional radiotherapy, although this difference was not statistically significant.

- In the RCT by Nyman et al.,[71] SBRT was compared to conventional 3-D radiotherapy among patients with inoperable stage I NSCLC (N = 102). The median follow-up period was 37 months, and there was no statistically significant difference in overall survival rates (HR, 0.75; 95% CI, 0.43 to 1.30).[71] There was no significant difference in pneumonitis (19% vs. 34%; *P* = .26), and statistically significantly less esophagitis in the SBRT group compared to the control group (8% vs. 30%; *P* = .006).[71]

The identified new studies of effectiveness and safety are unlikely to change the conclusions of the 2012 evidence review for operable early-stage NSCLC because studies published since 2012 showed mixed results. Two publications reported on RCTs among operable NSCLC patients.[72,73]

- Chang et al.[73] reported results combining data from 2 RCTs in 2015 among operable stage I NSCLC patients (N = 58), comparing SABR to lobectomy with mediastinal lymph node dissection or sampling. The SABR group had an improved overall survival rate compared to the lobectomy group (HR, 0.14; 95% CI, 0.02 to 1.19).[73] Whether this difference is statistically significant is uncertain. The authors reported inconsistent results with a *P* value of .037 (statistically significant) and a 95% CI with the null effect (HR = 1; not statistically significant).[73]
- Louie et al.[72] reported quality of life outcomes from the Dutch ROSEL trial (N = 22), which was 1 of the 2 RCTs in the study by Chang et al.[73] The SABR group scored better on 22 of the 25 quality of life measures, although global health status was the only measure that was statistically significantly better in the SABR group compared to surgery (HR, 0.19; 95% CI, 0.04 to 0.91; *P* = .04).[72]

We identified 5 systematic reviews that assessed survival rates for SBRT vs. surgery in operable early-stage NSCLC patients. The 2014 systematic review by Zhang et al.[74] showed that the SBRT group had statistically significantly decreased overall survival rate compared to the surgical group (HR, 1.82; 95% CI, 1.38 to 2.40; *P* < .001), and the other 4 systematic reviews concluded that there was no evidence that SBRT had improved survival outcomes compared to surgery.[65,66,75,76] Our search identified 22 additional comparative observational studies that compared SBRT to surgery.[77-98]

The identified new studies of effectiveness and safety are unlikely to change the conclusions of the 2012 evidence review for patients with lung metastases because no RCTs have been published since 2012. The update searches identified 3 comparative observations studies.[99-101]

- SBRT was compared to surgery among patients with lung oligometastases from colorectal cancer (N = 170). [99] In a multivariable analysis, there was no statistically significant difference in overall survival rates in the SBRT group compared to the surgery group (HR, 1.71; 95% CI, 0.82 to 3.54; *P* = .15).[99]
- SBRT was compared to conventional radiotherapy among patients with lung metastases from a variety of cancers (N = 182). [100] The local failure rates did not statistically significantly differ between the 2 groups (HR, 0.60; 95% CI, 0.25 to 1.41; *P* = .24).[100]
- SRS was compared to surgical resection in patients who developed pulmonary metastasis after diagnosis with nonmetastatic osteosarcoma of the extremity (N = 58).[101] Overall survival at 2 years did not significantly differ between the 2 groups (40.7% vs. 48.3%; *P* > .05).[101]

Economic Studies

The identified new studies of economic outcomes are unlikely to change the conclusions of the 2012 evidence review because studies published since 2012 showed mixed results. Five economic studies of lung cancer were included in the systematic review by Lester-Coll[57] and were

published since 2012.[57] These studies compared SBRT to conventional radiotherapy or surgery with mixed results.[57]

One additional cost-effectiveness analysis was published in 2018 that compared SBRT to surgery for operable early-stage NSCLC.[102] The analyses showed that the costs of SBRT were €1,492.84 (approximately $1,700) less than surgery, and patients treated with SBRT had 0.54 QALYs more than surgery patients, so SBRT was both more effective and less costly than surgery.[102]

Pancreatic Cancer

The identified new studies of effectiveness and safety are unlikely to change the conclusions of the 2012 evidence review for pancreatic cancer because no RCTs have been published since 2012. Two systematic reviews were published since the 2012 evidence review.[103,104] The American Society of Clinical Oncology conducted a systematic review to inform 2016 guidelines on locally advanced, unresectable pancreatic cancer.[103] This systematic review included only RCTs, and the 2 RCTs on SRS and SBRT were included in the 2012 evidence review. Buwenge et al.[104] published a systematic review of robotic SBRT in 2015 that included 5 single-arm studies of patients with unresectable or locally advanced adenocarcinoma (total N = 99).[104] The authors concluded that the outcomes of SBRT were similar to the outcomes in previous studies of chemo-radiation with conventional fractionation, and that gastrointestinal toxicity is a concern with robotic SBRT, especially at the duodenal level.[104]

Our searches identified 6 comparative observational studies published since the 2012 evidence review.[105-110] Three comparative observational studies compared SBRT to intensity-modulated radiation therapy (IMRT), and all found no statistically significant differences between the groups in terms of survival and other outcomes.[105,107,108]

- A 2017 study of patients with unresectable stage I to III pancreatic adenocarcinoma (N = 270) compared SBRT to IMRT and found no statistically significant differences between groups in overall survival rates, local or distant failure, or rates of subsequent resection.[108]
- SBRT was compared to IMRT for patients with borderline resectable and locally advanced pancreatic cancer (N = 91), and the study found no statistically significant differences between the groups on resection, perioperative outcomes, and survival outcomes.[105]
- A comparative study (N = 41) of SBRT and IMRT for patients with locally advanced unresectable pancreatic cancer found no significant difference in overall survival rates (P = .13), although SBRT showed a significantly improved local disease-free survival rate compared to IMRT (P = .004).[107]

Three other studies analyzed data from the National Cancer Database (NCDB). Two of these NCDB studies found that the SBRT groups had significantly decreased overall survival rates compared to groups treated with conventionally fractionated radiation therapy.[109,110] The other study found significantly longer median survival time among the SBRT group compared to the

EBRT group, but no statistically significant difference between SBRT and IMRT in overall survival rates.[106]

- A 2018 study using the NCDB assessed overall survival among patients with inoperable pancreatic cancer who were treated with chemotherapy, with or without definitive radiation therapy (N = 13,004).[110] Compared to the chemotherapy alone group, patients receiving SBRT had a decreased overall survival rate (HR, 0.71; 95% CI, 0.64 to 0.80) than those receiving conventional radiation (HR, 0.80; 95% CI, 0.77 to 0.84).[110]
- SBRT was compared to conventionally fractionated radiation therapy in a study among patients with cT2-4/N0-1/M0 adenocarcinoma of the pancreas (N = 8,450).[109] The SBRT group had an improved overall survival rate compared to the conventional radiation group in a multivariable analysis (HR, 0.84; 95% CI, 0.75 to 0.93; *P* < .001).[109]
- A 2017 study using the NCDB compared SBRT, EBRT, and IMRT among patients with unresected pancreatic cancer who also received chemotherapy (N = 14,331).[106] The unadjusted median survival time for SBRT, EBRT, and IMRT was 13.9 months, 10.9 months, and 12.0 months.[106] In a matched analyses, SBRT remained superior to EBRT (log-rank *P* = .02), but was not statistically significantly different compared to IMRT (log-rank *P* = .049).[106]

Economic Studies

The identified new studies of economic outcomes are unlikely to change the conclusions of the 2012 evidence review. Our search and a review of studies in the systematic review by Lester-Coll et al.[57] identified 1 economic study of SBRT for pancreatic cancer published since 2012.[111] This Taiwanese study by Leung et al.[111] compared treatment using gemcitabine to gemcitabine plus SBRT and gemcitabine plus IMRT.[111] The gemcitabine plus SBRT group had a lower ICER than gemcitabine plus IMRT, but neither of these groups had an ICER below the World Health Organization standard for being cost-effective (3 times the per-capita gross domestic product).[111]

Prostate Cancer

The identified new studies of effectiveness and safety are unlikely to change the conclusions of the 2012 evidence review for prostate cancer because no RCTs have been published since 2012. The 1 identified systematic review included only data from uncontrolled studies (n = 14 studies) with a total of 1,472 participants.[112] We identified 9 comparative observational studies.[113-121] Most of these studies generally found better outcomes in the SBRT groups than comparator groups (EBRT, IMRT, brachytherapy, prostatectomy).

Among the 8 comparative observational studies, 7 included participants with localized or low-risk prostate cancer.[113,115-121] Two of these studies assessed gastrointestinal or genitourinary toxicity.[120,121]

- The Surveillance, Epidemiology, and End Results Program (SEER)-Medicare linked data were used to identify men with localized prostate cancer who were treated with SBRT, IMRT, or brachytherapy (N = 33,597).[121] SBRT had equivalent gastrointestinal toxicity compared to

brachytherapy and IMRT, and SBRT had a statistically significantly higher rate of erectile dysfunction than brachytherapy and IMRT at 2-year follow-up ($P < .001$).[121] The SBRT group had a higher rate of urinary incontinence than IMRT ($P < .001$) and a lower rate of urinary incontinence compared with brachytherapy ($P < .001$).[121]

- SBRT was compared to IMRT among a national sample of Medicare beneficiaries with prostate cancer in 1 study (N = 4,005).[120] Genitourinary toxicity was significantly higher in the SBRT group compared to the IMRT group at 6 months (15.6% vs. 12.6%; OR, 1.29; 95% CI, 1.05 to 1.53; $P = .009$) and 24 months after treatment (43.9% vs. 36.3%; OR, 1.38; 95% CI, 1.12 to 1.63; $P = .001$.[120]

Another study assessed prostate-specific antigen (PSA) slope, which is a chemical marker and thus an indirect outcome.[113]

- One study (N = 75) compared SBRT to conventionally fractionated EBRT for patients with low- to low-intermediate-risk prostate cancer.[113] The rate of decline in PSA was statistically significantly greater in the SBRT group compared to the conventionally fractionated EBRT group ($P < .05$) at 2 and 3 years after treatment, although the PSA slopes for the 2 groups were not significantly different during the first year ($P > .05$).[113]

Four additional studies assessed quality of life outcomes among participants with localized prostate cancer.[115-118]

- One study (N = 803) included a multi-institutional pooled cohort analysis of patient-reported quality of life before and after SBRT, IMRT, or brachytherapy for localized prostate cancer.[115] In a multivariable analysis, quality of life outcomes were not significantly different between the SBRT and IMRT groups in urinary irritation or obstruction ($P = .55$), urinary incontinence ($P = .74$), and sexual function ($P = .57$), but SBRT was associated with a better bowel score than IMRT (+6.7 points; 95% CI, 3.2 to 10; $P < .001$).[115]
- SABR was compared to high-dose rate brachytherapy plus hypofractionated EBRT in a study that investigated quality of life in patients (N = 207) treated for localized prostate cancer.[116] For the percentage of patients with a minimally clinical important change, SABR had significantly better quality of life, showing better outcomes in urinary function (20% vs. 54%; $P < .001$), bowel function (31% vs. 37%; $P = .02$), and sexual function (34% vs. 53%; $P = .03$).[116]
- Another study (N = 339) assessed quality of life in patients treated for clinically localized prostate cancer with SBRT or radical prostatectomy.[118] The largest differences in quality of life occurred in the first 6 months after treatment.[118] There were larger declines in the surgery group compared to the SBRT group in urinary and sexual quality of life measures, and a larger decline in the SBRT group compared to the surgery group for bowel-related quality of life (*P* values not reported).[118]
- Quality of life was assessed among patients (N = 912) with clinically localized prostate cancer treated with SBRT or moderate hypofractionation radiotherapy.[117] The SBRT group

was significantly less likely to experience worsening in bowel symptoms at 2 years (25.3% vs. 37.4%; P = .002) and urinary symptoms (14.0% vs. 32.8%; P < .001).[117] No significant differences were found in sexual symptom scores between the 2 groups.[117]

We identified 1 study of participants with advanced prostate cancer.[114]

- Among patients (N = 63) with oligometastatic recurrence of hormone-sensitive prostate cancer, treatment with SBRT was compared to treatment not including SBRT.[114] The time from first diagnosis of metastasis to the start of androgen deprivation therapy was significantly longer in the SBRT group compared to the control group (17.3 months; 95% CI, 13.7 to 20.9 vs. 4.19 months; 95% CI, 0.0 to 9.0; P < .001.[114] The mean time between diagnosis of metastasis to disease progression during androgen deprivation therapy was significantly longer for the SBRT group compared to the control group (66.6 months; 95% CI, 53.5 to 79.8 vs. 36.41 months; 95% CI, 26.0 to 46.8; P = .02).[114]

Economic Studies

The identified new studies of economic outcomes are unlikely to result in a rating of either low-quality or stronger evidence of cost-effectiveness. The systematic review by Lester-Coll et al.[57] included 5 economic studies for prostate cancer published from 2012 to 2106, and our search identified 1 additional economic study published in 2017.[122] All identified studies in the review by Lester-Coll et al. compared SBRT to IMRT, finding that SBRT was dominant over IMRT in ICER analyses, or that SBRT was cost saving compared to IMRT.[57] The additional study from 2017 was a cost-utility analysis of SBRT versus low-dose rate brachytherapy for localized prostate cancer and found SBRT to be dominant over brachytherapy with a reduction in cost of $2,615.[122]

Liver Cancer

The identified new studies of effectiveness and safety are unlikely to change the conclusions of the 2012 evidence review for liver cancer because no RCTs have been published since 2012. No systematic reviews were identified, and 5 comparative observational studies were identified.[123-127] All 5 comparative observational studies were among patients with hepatocellular carcinoma.[123-127] Two of these studies compared SBRT to radiotherapy or resection, and none of these studies found any statistically significant differences in overall survival rates.[126,127]

- SBRT was compared to selective internal radiotherapy in a study (N = 189) of hepatocellular carcinoma.[126] After adjusting for confounding factors, there was no significant difference between groups in overall survival rates (HR, 0.72; 95% CI, 0.49 to 1.07; P = .11).[126]
- SABR was compared to liver resection for patients with small hepatocellular carcinoma with 1 or 2 nodules (N = 117).[127] After propensity score matching, there were no statistically significant differences between the SABR and resection groups in overall survival at 1 year (100% vs. 96.7%), 3 years (91.8% vs. 89.3%), or 5 years (74.3% vs. 69.2%) (log-rank test P = .41).[127]

Two comparative observational studies compared SBRT plus transarterial chemoembolization (TACE) to TACE alone,[123,124] and another compared SBRT to palliative care.[125] These 3 studies all found that adding SBRT improved survival outcomes.[123-125]

- SBRT combined with TACE was compared to TACE alone for small, solitary, hypervascular hepatocellular carcinoma (N = 365).[124] Mean disease-free survival time for patients without previous treatments in the SBRT plus TACE group was significantly higher than that of the TACE-alone group (15.7 months vs. 4.2 months; *P* = .03)[124]
- SBRT alone, SBRT plus TACE, and TACE alone were compared among patients with primary hepatocellular carcinoma (N = 121).[123] Median survival time was 3 months for the SBRT group, 7 months for the TACE group, and 20 months for the SBRT plus TACE group (*P* < .001).[123]
- Short-term survival after SBRT or palliative care was compared among patients with hepatocellular carcinoma with portal vein tumor thrombosis (N = 138).[125] The median overall survival time was longer in the SBRT group compared to the palliative care group (6.1 months; 95% CI, 4.71 to 7.49 vs. 3.0 months; 95% CI, 2.72 to 3.28; *P* = .003).[125]

Economic Studies

The identified new studies of economic outcomes are unlikely to result in a rating of either low-quality or stronger evidence of cost-effectiveness. One economic study of liver cancer[128] was included in the systematic review by Lester-Coll et al.,[57] and 2 other economic studies were identified on our search.[129,130]

- The cost-effectiveness of SBRT was compared to sorafenib for patients with advanced hepatocellular carcinoma in a Taiwanese study.[128] Using a willingness-to-pay threshold according to World Health Organization guidelines (3 times the per-capita gross domestic product), the probability of cost-effectiveness was 100% for SBRT and 0% for sorafenib.[128]
- In a U.S. study, cost-effectiveness was assessed for SBRT and radiofrequency ablation (RFA) among patients with hepatocellular carcinoma.[130] Four treatment strategies were simulated: SBRT followed by SBRT for local progression, RFA followed by RFA, RFA followed by SBRT, and SBRT followed by RFA.[130] Using a willingness-to-pay threshold of $100,000 per QALY, among the 4 treatments, RFA followed by SBRT was preferred in 65.8% of simulations.[130]
- SBRT was compared to RFA in a cost-effectiveness analysis of treating unresectable liver metastases in colorectal cancer patients, using a willingness-to-pay threshold of $100,000 per QALY gained.[129] SBRT was not cost-effective relative to RFA, with an ICER of $164,660 per QALY gained.[129]

Head and Neck Cancers

The identified new studies of effectiveness and safety are unlikely to change the conclusions of the 2012 evidence review for head or neck cancer because no new RCTs have been published. The updated searches identified 4 comparative observational studies with mixed results.

- Patients with recurrent head and neck cancers (N = 176) were treated with SBRT, IMRT, or charged particle radiotherapy.[131] One-year overall survival rates were not statistically significantly different for the SBRT group compared to the charged particle radiotherapy group (55% vs. 68%; *P* value not reported).[131]
- Patients with T1-2N0-3 oropharyngeal carcinoma (N = 250) were treated with IMRT followed by a boost with SBRT or brachytherapy.[132] After 3 years, there were no significant differences between the SBRT and brachytherapy groups in local control (97% vs. 94%; *P* = .33), disease-free survival (92% vs. 86%; *P* = .15), or overall survival (81% vs. 83%; *P* = .83).[132]
- Treatment of nasopharyngeal carcinoma patients (N = 329) was compared for chemotherapy and chemotherapy plus SRS.[133] The 2-year overall survival rate was significantly higher in the chemotherapy plus SRS group compared to the chemotherapy alone group (91.51% vs. 76.32%; *P* = .003).[133]
- SBRT was compared to charged particle radiotherapy among patients undergoing reirradiation for head and neck cancers (N = 50).[134] The 1-year overall survival rates were significantly lower for the SBRT group compared to the charged particle radiotherapy group (36.3% vs. 67.1%; *P* < .001).[134]

Economic Studies

No economic studies were identified since the 2012 report.

Adrenal Cancer

The identified new studies of effectiveness and safety are unlikely to change the conclusions of the 2012 evidence review for adrenal cancer because no new RCTs have been published. The update searches identified 1 systematic review[135] of non-comparative studies, 1 comparative observational study,[136] and no RCTs.

- The systematic review of non-comparative studies for the treatment of adrenal metastases included 9 studies of SBRT with a total of 178 patients, and no statistical analyses were performed.[135] The authors concluded that if therapy is in the patient's interest, then surgery appears to be the best option and SABR is a reasonable alternative in inoperable patients.[135]
- In the 2017 study by Yuan et al.,[136] patients with adrenal gland metastases from hepatocellular carcinoma (N = 144) were treated with helical tomotherapy or conventional radiotherapy (2-D or 3-D conformal radiotherapy). Cumulative survival probability was significantly higher in the helical tomotherapy group compared to the conventional radiotherapy group (*P* = .47), although this difference was not statistically significant in a multivariable analysis (*P* value not reported).[136]

Economic Studies

No economic studies were identified since the 2012 report.

Other Cancers

For bone metastases, a single systematic review was identified, conducted to inform a 2017 American Society for Radiation Oncology guideline on palliative radiation therapy for bone metastases.[137] The included studies of SBRT were all non-comparative, and no statistical analyses were conducted.[137]

A single comparative observational study was identified for recurrent atypical meningiomas.[138] In this study, patients with recurrent atypical meningiomas (N = 46) were followed for 20 years after treatment using SRS or surgery.[138] The disease-free intervals were not statistically significantly different between the 2 groups (*P* value not reported).[138]

There was 1 study on the risk of malignancy anywhere in the body after SRS or non-SRS treatments for meningioma or schwannoma.[139] Patients treated with SRS were identified from a University of Florida database for patients treated for meningiomas (N = 640) or intracranial schwannomas (N = 705).[139] The cancer rates for these SRS-treated patients were compared with cancer rates in non-SRS-treated patients identified from the SEER database.[139] The cancer rate in meningioma patients treated with SRS was 3.96% (binomial 95% CI, 1.85 to 7.94) compared to the expected rate of 10%, and the cancer rate in schwannoma patients treated with SRS was 4.93% (binomial 95% CI, 2.61 to 8.89) compared to the expected rate of 12.5%.[139]

Guidelines

Each guideline from NCCN was reviewed for discussion of various terms used to refer to stereotactic radiosurgery: usually SRS, SBRT, or SABR. Recommendations in NCCN guidelines are categorized based on levels of evidence (determined by number of trials, trial design, and consistency of data) and consensus:

- Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate
- Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate
- Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate
- Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate[140]

A summary of each of the NCCN guidelines that discuss stereotactic radiosurgery is presented below (with the specific term for stereotactic radiosurgery used from the guideline), followed by a list of the NCCN guidelines that did not discuss these procedures. The NCCN guidelines recommend consideration of SRS and SBRT for the indications covered in the 2013 HTCC decision. The NCCN guidelines recommend consideration of SRS and SBRT for a number of other indications that are not covered in the 2013 HTCC decision, including cancers of the liver, pancreas, and prostate.

Bone Cancer

- SRS, IMRT, or particle beam therapy (proton, carbon ion, or other heavy ions) should be considered to allow high-dose therapy while maximizing the sparing of normal tissues. (category 2A)[141]

Central Nervous System Cancers

- SRS is preferred when safe, to both the resection cavity and any non-resected brain metastases, especially for low tumor volumes. (category 2A)[142]
- For surgical candidates, SRS plus WBRT is recommended if only 1 brain lesion is involved. (category 1)[142]
- In limited brain metastases, SRS may be equally effective as WBRT, while providing significant cognitive protection.[142] The definition of limited brain metastases is evolving and depends on the specific clinical situation. (category 2A)[142]
- With extensive brain metastases, SRS can be considered. (category 2A)[142]
- SRS and SBRT are appropriate for recurrence of metastatic spine cancer after previous radiation, and may be preferred for patients with oligometastatic disease with the goal of tumor ablation, and in tumors considered radioresistant. (category 2A)[142]
- SRS can be considered for recurrence of spine or brain cancers. (category 2A)[142]
- SRS is a treatment option for meningioma. (category 2A)[142]
    - SRS is recommended for World Health Organization grade I meningioma when using tight margins or close to critical structures. (category 2A)[142]
- It has not been established that SRS has a role in management of low-grade gliomas. (category 2A)[142]
    - Stereotactic radiotherapy may be a palliative option with anaplastic gliomas and glioblastomas for select patients with good performance status and small recurrent tumors. (category 2A)[142]

Cervical Cancer

- SBRT is not an appropriate, routine alternative to brachytherapy. (category 2A)[143]
- SBRT may be applied to isolated metastatic sites and can be considered for reirradiation of limited disease. (category 2A)[143]

Anal Carcinoma, Colon Cancer, Rectal Cancer

- With anal carcinoma, SBRT can be considered for treatment of primary and nodal recurrence in low volume metastatic disease.[144] With low volume liver oligometastasis, SBRT may be appropriate, depending upon response to systemic therapy. (category 2A)[144]
- In colon cancer patients, for resectable synchronous or metachronous liver of lung metastases, resection is preferred over SBRT or image-guided ablation. (category 2A)[145]

- For patients with a limited number of liver or lung metastases, SBRT, IMRT, or 3-D conformal radiotherapy can be considered in highly selected cases. (category 2A)[145]

- For rectal cancer, resection is preferred over SBRT or image-guided ablation. (category 2A)[146]
  - SBRT is an option when resection is not feasible. (category 2A)[146]
  - SBRT can be considered for liver or lung oligometastases. (category 2A)[146]

Gestational Trophoblastic Neoplasia

- Stereotactic brain radiotherapy can be considered for patients with high-risk gestational trophoblastic neoplasia, FIGO stages II-III, and prognostic score ≥ 7 or stage IV. (category 2A)[147]

Head and Neck Cancers

- There is insufficient evidence to recommend SBRT for head and neck cancers. (category 2A)[148]
  - However, palliative radiation with SBRT, IMRT, or 3D conformation radiotherapy should be considered for advanced cancers when curative intent is not appropriate. (category 2A)[148]
  - Reirradiation with SBRT is advised only for patients who do not have circumferential carotid involvement. (category 2A)[148]

Hepatobiliary Cancers

- All tumors may be amenable to radiotherapy (SBRT, IMRT, or 3D conformation radiotherapy). (category 2A)[149]
- SBRT can be considered when ablation/embolization techniques have failed or are contraindicated. (category 2A)[149]

Kidney Cancer

- SBRT can be considered for relapse or Stage IV kidney cancer. (category 2A)[150]

Lung Cancer

- Early Stage, medically inoperable NSCLC patients may be candidates for SABR. (category 2A)[151,152]
- Selected patients with small cell lung cancer stage I-IIa (T1-2, N0, M0) who are medically inoperable may be candidates for SABR. (category 2A)[151]
- NCCN found insufficient data to make a recommendation on the use of SBRT in select patients with limited-stage small cell lung cancer.[151]

Occult Primary

- SBRT is an option for localized adenocarcinoma or carcinoma not otherwise specified with lung nodules. (category 2A)[153]

- SABR can be considered for localized disease with 1 to 3 metastases and pulmonary metastases. (category 2A)[153]

Pancreatic Adenocarcinoma

- SBRT is an option for first-line or second-line therapy for pancreatic adenocarcinoma with good performance status. (category 2A)[154]
- After resection, SBRT is an option when there is local recurrence in the pancreatic operative bed, respecting normal organ tolerances. (category 2A)[154]
- SBRT should be delivered at a high-volume center or as part of a clinical trial. (category 2A)[154]
- SBRT should be avoided if CT, MRI, or endoscopy shows direct invasion of the bowel or stomach. (category 2A)[154]

Prostate Cancer

- With prophylactic nodal radiation in intermediate- to high-risk patients, SBRT combined with androgen deprivation therapy can be considered when longer courses of EBRT would cause medical or social hardship. (category 2A)[155]
- SBRT can be considered for oligometastatic and palliative radiotherapy. (category 2A)[155]
- Definitive SBRT is acceptable when there is appropriate technology, physics, and clinical expertise. (category 2A)[155]

Skin Cancers

- With cutaneous melanoma, SBRT may offer more durable local control with ablative treatment for intact extracranial metastases. (category 2A)[156]
- With uveal melanoma, SRS is the non-preferred form of radiotherapy for primary or recurrent intraocular tumors. (category 2A)[157]
    - SRS is an option for uveal melanoma with largest diameter > 18mm, thickness > 10 mm, or thickness > 8 mm with optic nerve involvement. (category 2A)[157]
    - For distant metastatic disease, SRS can be considered for limited or symptomatic disease. (category 2A)[157]
- In squamous cell skin cancer, SBRT may be appropriate in palliative therapy for symptomatic sites in select patients. (category 2A)[158]

Soft Tissue Sarcoma

- SBRT is an option in head or neck, extremity or superficial trunk stage IV cancers involving a single organ and limited tumor bulk that are amenable to local therapy, and for isolated regional disease or nodes. (category 2A)[159]
- SBRT is a palliative option when there are disseminated metastases. (category 2A)[159]

Thymomas and Thymic Carcinomas

- For limited focal metastases, SBRT may be appropriate. (category 2A)[160]

Thyroid Carcinoma

- For CNS metastases, either resection or SRS is preferred for CNS lesions. (category 2A)[161]
- SBRT, EBRT, or surgical excision can be considered for symptomatic isolated skeletal metastases or asymptomatic metastases in weight-bearing sites. (category 2A)[161]

Uterine

- SBRT may be appropriate for patients with isolated metastases. (category 2A)[162]

The NCCN guidelines[163] for these cancers do not include discussion of SRS, SBRT, or SABR:

- Acute lymphoblastic leukemia
- Acute myeloid leukemia
- AIDS-related Kaposi sarcoma
- Bladder cancer
- Breast cancer
- Chronic lymphocytic leukemia/small lymphocytic lymphoma
- Chronic myeloid leukemia
- Esophageal and esophagogastric junction cancers
- Gastric cancer
- Hairy cell leukemia
- Hodgkin lymphoma
- Malignant pleural mesothelioma
- Multiple myeloma or other plasma cell neoplasms
- Myelodysplastic syndromes
- Myeloproliferative neoplasms
- Neuroendocrine and adrenal tumors
- Non-Hodgkin's lymphomas
- Ovarian cancer
- Penile cancer
- Systemic mastocytosis
- Testicular cancer
- Vulvar cancer

Policies

No Medicare National Coverage Determinations were found pertaining to SRS or SBRT. One LCD was found applying to the state of Washington. We searched for private payer policies from Aetna, Cigna, and Regence. The coverage polices for the Medicare LCD,[164] Aetna,[165] Cigna,[166]

Regence,[167] and the 2013 HTCC decision are summarized in Table 3. The full coverage policies are in Appendix B.

All 4 of these payers cover SRS and SBRT for CNS cancers, NSCLC, and a variety of benign cranial tumors (e.g., vestibular schwannomas and meningiomas). There is not consistency among the payers for the other cancer indications. Some of the policies cover a particular cancer only if it is metastatic or recurrent.

Table 3. Coverage of SRS and SBRT by Indication

Indication	Medicare LCD***	Aetna	Cigna	Regence	WA HTCC Decision
CNS cancers (brain, spinal)	Yes	Yes	Yes	Yes	Yes
Lung, NSCLC, inoperable	Yes	Yes	Yes	Yes	Yes
Lung, NSCLC, operable	Yes	No	Yes	No	No
Lung, other cancer types	Yes	Yes*	No	Yes*	No
Adrenal gland cancer	Yes	No	No	No	No
Bone cancer	No	No	Yes*	No	No
Breast cancer	No	No	Yes*	No	No
Cervical cancer	No	No	Yes**	No	No
Colorectal cancer	No	No	Yes*	No	No
Head and neck cancer	Yes**	Yes**	Yes**	No	No
Hepatocellular carcinoma	No	Yes	No	Yes	No
Hepatobiliary Cancer	No	No	Yes	No	No
Kidney cancer	Yes	No	No	No	No
Liver cancer	Yes	Yes*	No	Yes	No
Melanoma	No	No	Yes*	No	No
Ocular/uveal melanomas	No	Yes	No	Yes	No
Osteosarcoma	No	No	No	Yes*	No
Pelvic cancer	Yes*	No	No	No	No
Sarcoma	No	No	Yes*	No	No
Pancreatic cancer	Yes	No	Yes	No	No
Prostate cancer	In clinical trials only	Yes	Yes	Yes	No
Renal cancer	No	No	Yes*	No	No
Acoustic neuromas/vestibular schwannomas	Yes	Yes	Yes	Yes	No
Meningiomas	Yes	Yes	Yes	Yes	No
Pituitary adenomas	Yes	No	Yes	Yes	No
Pineocytomas	Yes	No	Yes		No
Craniopharyngiomas	Yes	Yes	Yes	Yes	No
Glomus tumors	Yes	No	Yes	Yes	No
Hemangioblastomas	Yes	Yes	Yes	Yes	No
Chordomas	No	No	No	Yes	No

*Note. *Metastatic only; **Recurrent only; ***The Medicare LCD covers SBRT for tumors of any type arising in or near previously irradiated regions when a high level of precision and accuracy is needed to minimize injury to surrounding normal tissues, or where a high dose per fraction treatment is indicated.*

Studies Registered at ClincalTrials.gov

We searched the ClinicalTrials.gov database for phase 3 and phase 4 trials related to the effectiveness of SRS, SBRT, or SABR on tumors and identified 67 registered trials. A list of these trials is in Appendix C. Of these trials, 14 are reported as active and have completion dates within the next 2 years (by the end of 2020). Among these 14 studies, there are 2 RCTs for pancreatic cancer and 1 RCT and 1 nonrandomized study for prostate cancer. The other studies are RCTs for indications currently covered in the 2013 HTCC decision: brain cancer (4 RCTs), spinal cancer (2 RCTs), and NSCLC (3 RCTs).

There are 27 studies with completion dates prior to 2018, 8 of which are marked as completed:

- One study is included in this evidence update.[17]
- One study was included in the 2012 evidence review.
- Two of the studies were published before the search dates of the 2012 evidence review.
- Four studies have no relevant associated publications that we could identify.

The unpublished studies may contribute to a possible publication bias for this topic. Of the remaining 19 studies, 9 have been terminated, 2 were withdrawn, and 8 have unknown status with no publications listed.

References

1. Gerrity M, Thielke A, Leof A, et al. *Stereotactic radiosurgery and stereotactic body radiation therapy: updated final evidence report.* Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2012

2. Health Technology Clinical Committee. *Findings and decision: stereotactic radiation surgery and stereotactic body radiation therapy.* Olympia, WA:2013.

3. Mosbaek C, King V, Harrod C. *Stereotactic radiosurgery and stereotactic body radiation therapy: an evidence update.* Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2017.

4. Cage TA, Clark AJ, Aranda D, et al. A systematic review of treatment outcomes in pediatric patients with intracranial ependymomas. *J Neurosurg Pediatr.* 2013;11(6):673-681. doi: http://dx.doi.org/10.3171/2013.2.PEDS12345.

5. Elaimy AL, Mackay AR, Lamoreaux WT, et al. Clinical outcomes of Gamma Knife radiosurgery in the salvage treatment of patients with recurrent high-grade glioma. *World Neurosurg.* 2013;80(6):872-878. doi: http://dx.doi.org/10.1016/j.wneu.2013.02.030.

6. Gans JH, Raper DM, Shah AH, et al. The role of radiosurgery to the tumor bed after resection of brain metastases. *Neurosurgery.* 2013;72(3):317-325; discussion 325-316. doi: http://dx.doi.org/10.1227/NEU.0b013e31827fcd60.

7. Goyal S, Silk AW, Tian S, et al. Clinical management of multiple melanoma brain metastases: a systematic review. *JAMA Oncol.* 2015;1(5):668-676. doi: http://dx.doi.org/10.1001/jamaoncol.2015.1206.

8. Khan M, Lin J, Liao G, et al. Comparison of WBRT alone, SRS alone, and their combination in the treatment of one or more brain metastases: review and meta-analysis. *Tumour Biol.* 2017;39(7):1010428317702903. doi: 10.1177/1010428317702903.

9. Patil CG, Pricola K, Sarmiento JM, Garg SK, Bryant A, Black KL. Whole brain radiation therapy (WBRT) alone versus WBRT and radiosurgery for the treatment of brain metastases. *Cochrane Database Syst Rev.* 2012;9:CD006121. doi: http://dx.doi.org/10.1002/14651858.CD006121.pub3.

10. Patil CG, Pricola K, Sarmiento MJ, Garg SK, Bryant A, Black KL. Whole brain radiation therapy (WBRT) alone versus WBRT and radiosurgery for the treatment of brain metastases. *Cochrane Database Syst Rev.* 2016;9. doi: 10.1002/14651858.CD006121.pub3.

11. Soon YY, Tham IW, Lim KH, Koh WY, Lu JJ. Surgery or radiosurgery plus whole brain radiotherapy versus surgery or radiosurgery alone for brain metastases. *Cochrane Database Syst Rev*. 2014;3:CD009454. doi: http://dx.doi.org/10.1002/14651858.CD009454.pub2.

12. Soon YY, Tham WI, Lim KH, Koh YW, Lu JJ. Surgery or radiosurgery plus whole brain radiotherapy versus surgery or radiosurgery alone for brain metastases. *Cochrane Database Syst Rev*. 2016;9. doi: 10.1002/14651858.CD009454.pub2.

13. Yuan X, Liu WJ, Li B, Shen ZT, Shen JS, Zhu XX. A Bayesian network meta-analysis of whole brain radiotherapy and stereotactic radiotherapy for brain metastasis. *Medicine*. 2017;96(34):e7698. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5571995/pdf/medi-96-e7698.pdf.

14. Jalali R, Gupta T, Goda JS, et al. Efficacy of stereotactic conformal radiotherapy vs conventional radiotherapy on benign and low-grade brain rumors: a randomized clinical trial. *JAMA Oncol*. 2017;3(10):1368-1376. https://jamanetwork.com/journals/jamaoncology/articlepdf/2629956/jamaoncology_Jalali_2017_oi_170022.pdf.

15. Kepka L, Tyc-Szczepaniak D, Bujko K, et al. Stereotactic radiotherapy of the tumor bed compared to whole brain radiotherapy after surgery of single brain metastasis: results from a randomized trial. *Radiother Oncol*. 2016;121(2):217-224. https://ac.els-cdn.com/S0167814016343419/1-s2.0-S0167814016343419-main.pdf?_tid=08c0e663-f955-4dc0-8d59-239ca1b2a0db&acdnat=1540495558_e879407a0bfbdc36eaad0d12a5e84739.

16. Kepka L, Tyc-Szczepaniak D, Osowiecka K, Sprawka A, Trabska-Kluch B, Czeremszynska B. Quality of life after whole brain radiotherapy compared with radiosurgery of the tumor bed: results from a randomized trial. *Clin Transl Oncol*. 2018;20(2):150-159. doi: 10.1007/s12094-017-1703-5.

17. Lim SH, Lee JY, Lee MY, et al. A randomized phase III trial of stereotactic radiosurgery (SRS) versus observation for patients with asymptomatic cerebral oligo-metastases in non-small-cell lung cancer. *Ann Oncol*. 2015;26(4):762-768. doi: http://dx.doi.org/10.1093/annonc/mdu584.

18. Mahajan A, Ahmed S, McAleer MF, et al. Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2017;18(8):1040-1048. https://ac.els-cdn.com/S147020451730414X/1-s2.0-S147020451730414X-main.pdf?_tid=2bcfbe6d-

3845-497c-afa7-d5817765f741&acdnat=1540508699_5e7e41c5fecb3a7af8515d61fec576a1.

19. Sperduto PW, Shanley R, Luo X, et al. Secondary analysis of RTOG 9508, a phase 3 randomized trial of whole-brain radiation therapy versus WBRT plus stereotactic radiosurgery in patients with 1-3 brain metastases; poststratified by the graded prognostic assessment (GPA). *Int J Radiat Oncol Biol Phys* 2014;90(3):526-531. doi: http://dx.doi.org/10.1016/j.ijrobp.2014.07.002.

20. Adas YG, Yazici O, Kekilli E, et al. Whole brain radiotherapy combined with stereotactic radiosurgery versus stereotactic radiosurgery alone for brain metastases. *Asian Pac J Cancer Prev.* 2015;16(17):7595-7597. http://journal.waocp.org/?sid=Entrez:PubMed&id=pmid:26625767&key=2015.16.17.7595.

21. Bates JE, Youn P, Peterson CR, et al. Radiotherapy for brain metastases from renal cell carcinoma in the targeted therapy era: the University of Rochester experience. *Am J Clin Oncol.* 2017;40(5):439-443. doi: 10.1097/COC.0000000000000186.

22. Baykara M, Kurt G, Buyukberber S, et al. Management of brain metastases from non-small cell lung cancer. *J Cancer Res Ther.* 2014;10(4):915-921. doi: http://dx.doi.org/10.4103/0973-1482.137939.

23. Bir SC, Patra DP, Maiti TK, Bollam P, Minagar A, Nanda A. Direct comparison of Gamma Knife radiosurgery and microsurgery for small size meningiomas. *World Neurosurg.* 2017;101:170-179. https://ac.els-cdn.com/S1878875017301286/1-s2.0-S1878875017301286-main.pdf?_tid=3a54a6a3-2d75-4a52-a760-1dc79960ae39&acdnat=1540509759_d20630ca9a61455dd13d1f86b6180a16.

24. Bougie E, Masson-Cote L, Mathieu D. Comparison between surgical resection and stereotactic radiosurgery in patients with a single brain metastasis from non-small cell lung cancer. *World Neurosurg.* 2015;83(6):900-906. doi: http://dx.doi.org/10.1016/j.wneu.2015.01.029.

25. Chen L, Shen C, Redmond KJ, et al. Use of stereotactic radiosurgery in elderly and very elderly patients with brain metastases to limit toxicity associated with whole brain radiation therapy. *Int J Radiat Oncol Biol Phys* 2017;98(4):939-947. https://ac.els-cdn.com/S0360301617304091/1-s2.0-S0360301617304091-main.pdf?_tid=0cf0ccc3-2d80-412b-991d-676f7649986e&acdnat=1540509632_ec9d42ed445a22ea2effae6fee8e4e6c.

26. Doherty MK, Korpanty GJ, Tomasini P, et al. Treatment options for patients with brain metastases from EGFR/ALK-driven lung cancer. *Radiother Oncol.* 2017;123(2):195-202. https://ac.els-cdn.com/S0167814017301032/1-s2.0-S0167814017301032-main.pdf?_tid=988558e8-5b98-43f9-ab85-7c26d42c4fec&acdnat=1540509452_1241ca284fb08c76d1af46c97c93ecc8.

27. Fauchon F, Hasselblatt M, Jouvet A, et al. Role of surgery, radiotherapy and chemotherapy in papillary tumors of the pineal region: a multicenter study. *J Neurooncol.* 2013;112(2):223-231. doi: http://dx.doi.org/10.1007/s11060-013-1050-5.

28. Gerber NK, Yamada Y, Rimner A, et al. Erlotinib versus radiation therapy for brain metastases in patients with EGFR-mutant lung adenocarcinoma. *Int J Radiat Oncol Biol Phys* 2014;89(2):322-329. doi: http://dx.doi.org/10.1016/j.ijrobp.2014.02.022.

29. Golfinos JG, Hill TC, Rokosh R, et al. A matched cohort comparison of clinical outcomes following microsurgical resection or stereotactic radiosurgery for patients with small- and medium-sized vestibular schwannomas. *J Neurosurg.* 2016;125(6):1472-1482. https://thejns.org/downloadpdf/journals/j-neurosurg/125/6/article-p1472.pdf.

30. Halasz LM, Uno H, Hughes M, et al. Comparative effectiveness of stereotactic radiosurgery versus whole-brain radiation therapy for patients with brain metastases from breast or non-small cell lung cancer. *Cancer.* 2016;122(13):2091-2100. https://onlinelibrary.wiley.com/doi/pdf/10.1002/cncr.30009.

31. Hsieh J, Elson P, Otvos B, et al. Tumor progression in patients receiving adjuvant whole-brain radiotherapy vs localized radiotherapy after surgical resection of brain metastases. *Neurosurgery.* 2015;76(4):411-420. doi: http://dx.doi.org/10.1227/NEU.0000000000000626.

32. Kann BH, Park HS, Johnson SB, Chiang VL, Yu JB. Radiosurgery for brain metastases: changing practice patterns and disparities in the United States. *J Natl Compr Canc Netw.* 2017;15(12):1494-1502. http://www.jnccn.org/content/15/12/1494.long.

33. Kao J, Timmins J, Ozao-Choy J, Packer S. Effects of combined sunitinib and extracranial stereotactic radiotherapy on bone marrow hematopoiesis. *Oncol Lett.* 2016;12(3):2139-2144. doi: 10.3892/ol.2016.4851.

34. Kim HJ, Huh JW, Jung TY, et al. Clinical outcome with Gamma-Knife surgery or surgery for brain metastases from colorectal cancer. *J Clin Neurosci.* 2013;20(10):1417-1421. doi: http://dx.doi.org/10.1016/j.jocn.2012.12.020.

35. Klingenstein A, Furweger C, Muhlhofer AK, et al. Quality of life in the follow-up of uveal melanoma patients after enucleation in comparison to CyberKnife treatment. *Graefes Arch Clin Exp Ophthalmol.* 2016;254(5):1005-1012. https://link.springer.com/content/pdf/10.1007%2Fs00417-015-3216-7.pdf.

36. Krema H, Heydarian M, Beiki-Ardakani A, et al. A comparison between 125 Iodine brachytherapy and stereotactic radiotherapy in the management of juxtapapillary choroidal melanoma. *Br J Ophthalmol.* 2013;97(3):327-332. doi: http://dx.doi.org/10.1136/bjophthalmol-2012-302808.

37. Li B, Dai ZX, Chen YD, et al. Systemic therapy after radiotherapy significantly reduces the risk of mortality of patients with 1-3 brain metastases: a retrospective study of 250 patients. *Chin Med J.* 2017;130(24):2916-2921. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5742918/pdf/CMJ-130-2916.pdf.

38. Li D, Weng JC, Zhang GJ, et al. Proposed treatment paradigm for intracranial chondrosarcomas based on multidisciplinary coordination. *World Neurosurg.* 2018;109:e517-e530. https://ac.els-cdn.com/S1878875017317400/1-s2.0-S1878875017317400-main.pdf?_tid=a2a21831-97c8-4b30-b8ad-cb29d289c5f7&acdnat=1540503776_ed931dc804c0ab0f8c06573cec681c77.

39. Lin CH, Hsu KH, Chang SN, et al. Increased survival with the combination of stereotactic radiosurgery and gefitinib for non-small cell lung cancer brain metastasis patients: a nationwide study in Taiwan. *Radiat Oncol.* 2015;10:127. doi: http://dx.doi.org/10.1186/s13014-015-0431-7.

40. Lin L, Zhao CH, Ge FJ, et al. Patients with brain metastases derived from gastrointestinal cancer: clinical characteristics and prognostic factors. *Clin Transl Oncol.* 2016;18(1):93-98. doi: http://dx.doi.org/10.1007/s12094-015-1341-8.

41. Liu X, Shan B, Wang M, Xu J. World Health Organization grade II meningiomas: the role of adjuvant/salvage Gamma Knife surgery after initial surgery and prognostic factor assessment. *World Neurosurg.* 2018;109:e352-e362. https://ac.els-cdn.com/S1878875017316947/1-s2.0-S1878875017316947-main.pdf?_tid=9c84ad5a-cc5d-40a5-ba68-9554346907f6&acdnat=1540503749_b8be58d718a2a24e519e4105ed810681.

42. Magnuson WJ, Lester-Coll NH, Wu AJ, et al. Management of brain metastases in tyrosine kinase inhibitor-naive epidermal growth factor receptor-mutant non-small-cell lung cancer: a retrospective multi-institutional analysis. *J Clin Oncol.* 2017;35(10):1070-1077. doi: 10.1200/JCO.2016.69.7144.

43. Mix M, Elmarzouky R, O'Connor T, Plunkett R, Prasad D. Clinical outcomes in patients with brain metastases from breast cancer treated with single-session radiosurgery or whole brain radiotherapy. *J Neurosurg*. 2016;125(Suppl 1):26-30. doi: 10.3171/2016.7.GKS161541.

44. Nanda A, Thakur JD, Sonig A, Missios S. Microsurgical resectability, outcomes, and tumor control in meningiomas occupying the cavernous sinus. *J Neurosurg*. 2016;125(2):378-392. https://thejns.org/downloadpdf/journals/j-neurosurg/125/2/article-p378.pdf.

45. Patel KR, Burri SH, Boselli D, et al. Comparing pre-operative stereotactic radiosurgery (SRS) to post-operative whole brain radiation therapy (WBRT) for resectable brain metastases: a multi-institutional analysis. *J Neurooncol*. 2017;131(3):611-618. https://link.springer.com/content/pdf/10.1007%2Fs11060-016-2334-3.pdf.

46. Patel KR, Prabhu RS, Kandula S, et al. Intracranial control and radiographic changes with adjuvant radiation therapy for resected brain metastases: whole brain radiotherapy versus stereotactic radiosurgery alone. *J Neurooncol*. 2014;120(3):657-663. doi: http://dx.doi.org/10.1007/s11060-014-1601-4.

47. Pintea B, Baumert B, Kinfe TM, Gousias K, Parpaley Y, Bostrom JP. Early motor function after local treatment of brain metastases in the motor cortex region with stereotactic radiotherapy/radiosurgery or microsurgical resection: a retrospective study of two consecutive cohorts. *Radiat Oncol*. 2017;12(1):177. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5683312/pdf/13014_2017_Article_917.pdf.

48. Rachinger W, Oehlschlaegel F, Kunz M, et al. Cystic craniopharyngiomas: microsurgical or stereotactic treatment? *Neurosurgery*. 2017;80(5):733-743. doi: 10.1093/neuros/nyx031.

49. Rades D, Janssen S, Bajrovic A, Khoa MT, Veninga T, Schild SE. A matched-pair analysis comparing whole-brain radiotherapy with and without a stereotactic boost for intracerebral control and overall survival in patients with one to three cerebral metastases. *Radiat Oncol*. 2017;12(1):69. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5402642/pdf/13014_2017_Article_804.pdf.

50. Rades D, Janssen S, Dziggel L, et al. A matched-pair study comparing whole-brain irradiation alone to radiosurgery or fractionated stereotactic radiotherapy alone in patients irradiated for up to three brain metastases. *BMC Cancer*. 2017;17(1):30. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5219794/pdf/12885_2016_Article_2989.pdf.

51. Rades D, Kueter JD, Meyners T, et al. Single brain metastasis: resection followed by whole-brain irradiation and a boost to the metastatic site compared to whole-brain irradiation plus radiosurgery. *Clin Neurol Neurosurg.* 2012;114(4):326-330. doi: http://dx.doi.org/10.1016/j.clineuro.2011.10.042.

52. Rades D, Veninga T, Hornung D, Wittkugel O, Schild SE, Gliemroth J. Single brain metastasis: whole-brain irradiation plus either radiosurgery or neurosurgical resection. *Cancer.* 2012;118(4):1138-1144. doi: http://dx.doi.org/10.1002/cncr.26379.

53. Sanghvi SM, Lischalk JW, Cai L, et al. Clinical outcomes of gastrointestinal brain metastases treated with radiotherapy. *Radiat Oncol.* 2017;12(1):43. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5331623/pdf/13014_2017_Article_774.pdf.

54. Skeie BS, Enger PO, Brogger J, et al. Gamma Knife surgery versus reoperation for recurrent glioblastoma multiforme. *World Neurosurg.* 2012;78(6):658-669. doi: http://dx.doi.org/10.1016/j.wneu.2012.03.024.

55. Tian LJ, Zhuang HQ, Yuan ZY. A comparison between CyberKnife and neurosurgery in solitary brain metastases from non-small cell lung cancer. *Clin Neurol Neurosurg.* 2013;115(10):2009-2014. doi: http://dx.doi.org/10.1016/j.clineuro.2013.06.006.

56. Troude L, Boucekine M, Montava M, Lavieille JP, Regis JM, Roche PH. Adjunctive Gamma Knife surgery or wait and scan policy after optimal resection of large vestibular schwannomas: clinical and radiologic outcomes. *World Neurosurg.* 2018;118:e895-e905. https://ac.els-cdn.com/S1878875018315717/1-s2.0-S1878875018315717-main.pdf?_tid=9d0c5686-417d-463b-b6c5-8ec414542b54&acdnat=1540503493_5eee5f3df9827a0fff917e8b7657467c.

57. Lester-Coll NH, Sher DJ. Cost-effectiveness of stereotactic radiosurgery and stereotactic body radiation therapy: a critical review. *Curr Oncol Rep.* 2017;19(6):41. https://link.springer.com/article/10.1007%2Fs11912-017-0599-0.

58. Vuong DA, Rades D, van Eck AT, Horstmann GA, Busse R. Comparing the cost-effectiveness of two brain metastasis treatment modalities from a payer's perspective: stereotactic radiosurgery versus surgical resection. *Clin Neurol Neurosurg.* 2013;115(3):276-284. doi: http://dx.doi.org/10.1016/j.clineuro.2012.05.005.

59. Vuong DA, Rades D, Le AN, Busse R. The cost-effectiveness of stereotactic radiosurgery versus surgical resection in the treatment of brain metastasis in Vietnam from the perspective of patients and families. *World Neurosurg.* 2012;77(2):321-328. doi: http://dx.doi.org/10.1016/j.wneu.2011.05.050.

60. Sprave T, Verma V, Forster R, et al. Randomized phase II trial evaluating pain response in patients with spinal metastases following stereotactic body radiotherapy versus three-dimensional conformal radiotherapy. *Radiother Oncol.* 2018(pagination). doi: 10.1016/j.radonc.2018.04.030.

61. Sprave T, Verma V, Forster R, et al. Quality of life following stereotactic body radiotherapy versus three-dimensional conformal radiotherapy for vertebral metastases: secondary analysis of an exploratory phase II randomized trial. *Anticancer Res.* 2018;38(8):4961-4968. http://ar.iiarjournals.org/content/38/8/4961.long.

62. Sohn S, Chung CK, Sohn MJ, et al. Stereotactic radiosurgery compared with external radiation therapy as a primary treatment in spine metastasis from renal cell carcinoma: a multicenter, matched-pair study. *J Neurooncol.* 2014;119(1):121-128. doi: http://dx.doi.org/10.1007/s11060-014-1455-9.

63. Chang UK, Kim MS, Han CJ, Lee DH. Clinical result of stereotactic radiosurgery for spinal metastasis from hepatocellular carcinoma: comparison with conventional radiation therapy. *J Neurooncol.* 2014;119(1):141-148. doi: http://dx.doi.org/10.1007/s11060-014-1463-9.

64. Kim H, Rajagopalan MS, Beriwal S, Huq MS, Smith KJ. Cost-effectiveness analysis of single fraction of stereotactic body radiation therapy compared with single fraction of external beam radiation therapy for palliation of vertebral bone metastases. *Int J Radiat Oncol Biol Phys* 2015;91(3):556-563. doi: http://dx.doi.org/10.1016/j.ijrobp.2014.10.055.

65. Videtic GMM, Donington J, Giuliani M, et al. Stereotactic body radiation therapy for early-stage non-small cell lung cancer: executive summary of an ASTRO evidence-based guideline. *Pract Radiat Oncol.* 2017;7(5):295-301. doi: 10.1016/j.prro.2017.04.014.

66. Murray P, Franks K, Hanna GG. A systematic review of outcomes following stereotactic ablative radiotherapy in the treatment of early-stage primary lung cancer. *Br J Radiol.* 2017;90(1071):20160732. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5601509/pdf/bjr.20160732.pdf.

67. Falkson CB, Vella ET, Yu E, et al. Radiotherapy with curative intent in patients with early-stage, medically inoperable, non-small-cell lung cancer: a systematic review. *Clin Lung Cancer.* 2017;18(2):105-121.e105. https://ac.els-cdn.com/S1525730416303515/1-s2.0-S1525730416303515-main.pdf?_tid=fafd0cc0-0a98-474f-9f75-bca60e3a87e7&acdnat=1540509396_38718902f790df3664f8c4bd647fd004.

68. Jones GC, Kehrer JD, Kahn J, et al. Primary treatment options for high-risk/medically inoperable early stage NSCLC patients. *Clin Lung Cancer*. 2015;16(6):413-430. doi: http://dx.doi.org/10.1016/j.cllc.2015.04.001.

69. Nanda RH, Liu Y, Gillespie TW, et al. Stereotactic body radiation therapy versus no treatment for early stage non-small cell lung cancer in medically inoperable elderly patients: a National Cancer Data Base analysis. *Cancer*. 2015;121(23):4222-4230. doi: http://dx.doi.org/10.1002/cncr.29640.

70. Jeppesen SS, Hansen NCG, Schytte T, Hansen O. Survival of localized NSCLC patients without active treatment or treated with SBRT. *Acta Oncol*. 2018;57(2):219-225. https://www.tandfonline.com/doi/pdf/10.1080/0284186X.2017.1374558?needAccess=true.

71. Nyman J, Hallqvist A, Lund JA, et al. SPACE - a randomized study of SBRT vs conventional fractionated radiotherapy in medically inoperable stage I NSCLC. *Radiother Oncol*. 2016;121(1):1-8. https://ac.els-cdn.com/S0167814016342797/1-s2.0-S0167814016342797-main.pdf?_tid=3d0852bd-754b-4a79-9394-9a454931e2e9&acdnat=1540494796_c24d818831ad65a234e1c998d5d6e113.

72. Louie AV, van Werkhoven E, Chen H, et al. Patient reported outcomes following stereotactic ablative radiotherapy or surgery for stage IA non-small-cell lung cancer: results from the ROSEL multicenter randomized trial. *Radiother Oncol*. 2015;117(1):44-48. doi: http://dx.doi.org/10.1016/j.radonc.2015.08.011.

73. Chang JY, Senan S, Paul MA, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Oncol*. 2015;16(6):630-637. doi: http://dx.doi.org/10.1016/S1470-2045(15)70168-3.

74. Zhang B, Zhu F, Ma X, et al. Matched-pair comparisons of stereotactic body radiotherapy (SBRT) versus surgery for the treatment of early stage non-small cell lung cancer: a systematic review and meta-analysis. *Radiother Oncol*. 2014;112(2):250-255. doi: http://dx.doi.org/10.1016/j.radonc.2014.08.031.

75. Zheng X, Schipper M, Kidwell K, et al. Survival outcome after stereotactic body radiation therapy and surgery for stage I non-small cell lung cancer: a meta-analysis. *Int J Radiat Oncol Biol Phys* 2014;90(3):603-611. doi: http://dx.doi.org/10.1016/j.ijrobp.2014.05.055.

76. Solda F, Lodge M, Ashley S, Whitington A, Goldstraw P, Brada M. Stereotactic radiotherapy (SABR) for the treatment of primary non-small cell lung cancer; systematic

review and comparison with a surgical cohort. *Radiother Oncol.* 2013;109(1):1-7. doi: http://dx.doi.org/10.1016/j.radonc.2013.09.006.

77. Bryant AK, Mundt RC, Sandhu AP, et al. Stereotactic body radiation therapy versus surgery for early lung cancer among US veterans. *Ann Thorac Surg.* 2017(pagination). doi: 10.1016/j.ijrobp.2017.06.2456.

78. Cornwell LD, Echeverria AE, Samuelian J, et al. Video-assisted thoracoscopic lobectomy is associated with greater recurrence-free survival than stereotactic body radiotherapy for clinical stage I lung cancer. *J Thorac Cardiovasc Surg.* 2017. doi: 10.1016/j.jtcvs.2017.07.065.

79. Crabtree TD, Puri V, Robinson C, et al. Analysis of first recurrence and survival in patients with stage I non-small cell lung cancer treated with surgical resection or stereotactic radiation therapy. *J Thorac Cardiovasc Surg.* 2014;147(4):1183-1191; discussion 1191-1182. doi: http://dx.doi.org/10.1016/j.jtcvs.2013.11.057.

80. Eba J, Nakamura K, Mizusawa J, et al. Stereotactic body radiotherapy versus lobectomy for operable clinical stage IA lung adenocarcinoma: comparison of survival outcomes in two clinical trials with propensity score analysis (JCOG1313-A). *Jpn J Clin Oncol.* 2016;46(8):748-753. doi: 10.1093/jjco/hyw058.

81. Ezer N, Veluswamy RR, Mhango G, Rosenzweig KE, Powell CA, Wisnivesky JP. Outcomes after stereotactic body radiotherapy versus limited resection in older patients with early-stage lung cancer. *J Thorac Oncol.* 2015;10(8):1201-1206. doi: http://dx.doi.org/10.1097/JTO.0000000000000600.

82. Hamaji M, Chen F, Matsuo Y, et al. Video-assisted thoracoscopic lobectomy versus stereotactic radiotherapy for stage I lung cancer. *Ann Thorac Surg.* 2015;99(4):1122-1129. doi: http://dx.doi.org/10.1016/j.athoracsur.2014.11.009.

83. Kastelijn EA, El Sharouni SY, Hofman FN, et al. Clinical outcomes in early-stage NSCLC treated with stereotactic body radiotherapy versus surgical resection. *Anticancer Res.* 2015;35(10):5607-5614. http://ar.iiarjournals.org/content/35/10/5607.full.pdf.

84. Koyi H, Hillerdal G, Kolbeck KG, Brodin D, Liv P, Branden E. Non-small cell lung cancer (NSCLC) in octogenarians in clinical practice. *Anticancer Res.* 2016;36(10):5397-5402. http://ar.iiarjournals.org/content/36/10/5397.full.pdf.

85. Matsuo Y, Chen F, Hamaji M, et al. Comparison of long-term survival outcomes between stereotactic body radiotherapy and sublobar resection for stage I non-small-cell lung

cancer in patients at high risk for lobectomy: a propensity score matching analysis. *Eur J Cancer.* 2014;50(17):2932-2938. doi: http://dx.doi.org/10.1016/j.ejca.2014.09.006.

86. Miyazaki T, Yamazaki T, Nakamura D, et al. Surgery or stereotactic body radiotherapy for elderly stage I lung cancer? a propensity score matching analysis. *Surg Today.* 2017;47(12):1476-1483. https://link.springer.com/article/10.1007%2Fs00595-017-1536-4.

87. Mokhles S, Nuyttens JJ, Maat AP, et al. Survival and treatment of non-small cell lung cancer stage I-II treated surgically or with stereotactic body radiotherapy: patient and tumor-specific factors affect the prognosis. *Ann Surg Oncol.* 2015;22(1):316-323. doi: http://dx.doi.org/10.1245/s10434-014-3860-x.

88. Mokhles S, Verstegen N, Maat AP, et al. Comparison of clinical outcome of stage I non-small cell lung cancer treated surgically or with stereotactic radiotherapy: results from propensity score analysis. *Lung Cancer.* 2015;87(3):283-289. doi: http://dx.doi.org/10.1016/j.lungcan.2015.01.005.

89. Nakagawa T, Negoro Y, Matsuoka T, Okumura N, Dodo Y. Comparison of the outcomes of stereotactic body radiotherapy and surgery in elderly patients with cT1-2N0M0 non-small cell lung cancer. *Respir Investig.* 2014;52(4):221-226. doi: http://dx.doi.org/10.1016/j.resinv.2014.01.002.

90. Parashar B, Port J, Arora S, et al. Analysis of stereotactic radiation vs. wedge resection vs. wedge resection plus Cesium-131 brachytherapy in early stage lung cancer. *Brachytherapy.* 2015;14(5):648-654. doi: http://dx.doi.org/10.1016/j.brachy.2015.04.001.

91. Paul S, Lee PC, Mao J, Isaacs AJ, Sedrakyan A. Long term survival with stereotactic ablative radiotherapy (SABR) versus thoracoscopic sublobar lung resection in elderly people: national population based study with propensity matched comparative analysis. *BMJ.* 2016;354:i3570. https://www.bmj.com/content/bmj/354/bmj.i3570.full.pdf.

92. Presley CJ, Soulos PR, Tinetti M, Montori VM, Yu JB, Gross CP. Treatment burden of Medicare beneficiaries with stage I non-small-cell lung cancer. *J Oncol Pract.* 2017;13(2):e98-e107. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5659117/pdf/JOP.2016.014100.pdf.

93. Puri V, Crabtree TD, Bell JM, et al. Treatment outcomes in stage I lung cancer: a comparison of surgery and stereotactic body radiation therapy. *J Thorac Oncol.* 2015;10(12):1776-1784. doi: http://dx.doi.org/10.1097/JTO.0000000000000680.

94. Rosen JE, Salazar MC, Wang Z, et al. Lobectomy versus stereotactic body radiotherapy in healthy patients with stage I lung cancer. *J Thorac Cardiovasc Surg.* 2016;152(1):44-

54.e49. https://ac.els-cdn.com/S0022522316300356/1-s2.0-S0022522316300356-main.pdf?_tid=c436f0ce-0b4d-437b-858c-816860a43bf7&acdnat=1540511830_cbb7646c9ef4dc8837efe5ae44da451b.

95. Shaverdian N, Wang PC, Steinberg M, Lee P. The patient's perspective on stereotactic body radiation therapy (SBRT) vs. surgery for treatment of early stage non-small cell lung cancer (NSCLC). *Lung Cancer*. 2015;90(2):230-233. doi: http://dx.doi.org/10.1016/j.lungcan.2015.07.009.

96. Shirvani SM, Jiang J, Chang JY, et al. Lobectomy, sublobar resection, and stereotactic ablative radiotherapy for early-stage non-small cell lung cancers in the elderly. *JAMA Surg*. 2014;149(12):1244-1253. doi: http://dx.doi.org/10.1001/jamasurg.2014.556.

97. van den Berg LL, Klinkenberg TJ, Groen HJ, Widder J. Patterns of recurrence and survival after surgery or stereotactic radiotherapy for early stage NSCLC. *J Thorac Oncol*. 2015;10(5):826-831. doi: http://dx.doi.org/10.1097/JTO.0000000000000483.

98. Wang P, Zhang D, Guo XG, et al. A propensity-matched analysis of surgery and stereotactic body radiotherapy for early stage non-small cell lung cancer in the elderly. *Medicine*. 2016;95(52). doi: 10.1097/MD.0000000000005723.

99. Filippi AR, Guerrera F, Badellino S, et al. Exploratory analysis on overall survival after either surgery or stereotactic radiotherapy for lung oligometastases from colorectal cancer. *Clin Oncol (R Coll Radiol)*. 2016;28(8):505-512. https://ac.els-cdn.com/S0936655516000650/1-s2.0-S0936655516000650-main.pdf?_tid=200de574-6757-4981-9f46-097a68623d96&acdnat=1540512828_62ca95ee02f705fd8d18cc6f3d78b3f6.

100. Fleming C, Rimner A, Foster A, Woo KM, Zhang Z, Wu AJ. Palliative efficacy and local control of conventional radiotherapy for lung metastases. *Ann Palliat Med*. 2017;6(Suppl 1):S21-S27. http://apm.amegroups.com/article/view/14062/16452.

101. Yu W, Tang L, Lin F, et al. Stereotactic radiosurgery, a potential alternative treatment for pulmonary metastases from osteosarcoma. *Int J Oncol*. 2014;44(4):1091-1098. doi: http://dx.doi.org/10.3892/ijo.2014.2295.

102. Paix A, Noel G, Falcoz PE, Levy P. Cost-effectiveness analysis of stereotactic body radiotherapy and surgery for medically operable early stage non small cell lung cancer. *Radiother Oncol*. 2018(pagination). doi: 10.1016/j.radonc.2018.04.013.

103. Balaban EP, Mangu PB, Khorana AA, et al. Locally advanced, unresectable pancreatic cancer: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol.* 2016;34(22):2654-2668. doi: 10.1200/JCO.2016.67.5561.

104. Buwenge M, Cellini F, Silvestris N, et al. Robotic radiosurgery in pancreatic cancer: a systematic review. *World J Gastroenterol.* 2015;21(31):9420-9429. doi: http://dx.doi.org/10.3748/wjg.v21.i31.9420.

105. Chapman BC, Gleisner A, Rigg D, et al. Perioperative outcomes and survival following neoadjuvant stereotactic body radiation therapy (SBRT) versus intensity-modulated radiation therapy (IMRT) in pancreatic adenocarcinoma. *J Surg Oncol.* 2018;117(5):1073-1083. https://onlinelibrary.wiley.com/doi/pdf/10.1002/jso.25004.

106. de Geus SWL, Eskander MF, Kasumova GG, et al. Stereotactic body radiotherapy for unresected pancreatic cancer: a nationwide review. *Cancer.* 2017;123(21):4158-4167. https://onlinelibrary.wiley.com/doi/pdf/10.1002/cncr.30856.

107. Lin JC, Jen YM, Li MH, Chao HL, Tsai JT. Comparing outcomes of stereotactic body radiotherapy with intensity-modulated radiotherapy for patients with locally advanced unresectable pancreatic cancer. *Eur J Gastroenterol Hepatol.* 2015;27(3):259-264. doi: http://dx.doi.org/10.1097/MEG.0000000000000283.

108. Park JJ, Hajj C, Reyngold M, et al. Stereotactic body radiation vs. intensity-modulated radiation for unresectable pancreatic cancer. *Acta Oncol.* 2017;56(12):1746-1753. https://www.tandfonline.com/doi/pdf/10.1080/0284186X.2017.1342863?needAccess=true.

109. Zhong J, Patel K, Switchenko J, et al. Outcomes for patients with locally advanced pancreatic adenocarcinoma treated with stereotactic body radiation therapy versus conventionally fractionated radiation. *Cancer.* 2017;123(18):3486-3493. https://onlinelibrary.wiley.com/doi/pdf/10.1002/cncr.30706.

110. Zhong J, Switchenko J, Behera M, et al. Chemotherapy with or without definitive radiation therapy in inoperable pancreatic cancer. *Ann Surg Oncol.* 2018;25(4):1026-1033. https://link.springer.com/content/pdf/10.1245%2Fs10434-017-6322-4.pdf.

111. Leung HW, Chan AL, Muo CH. Cost-effectiveness of gemcitabine plus modern radiotherapy in locally advanced pancreatic cancer. *Clin Ther.* 2016;38(5):1174-1183. https://ac.els-cdn.com/S0149291816301308/1-s2.0-S0149291816301308-main.pdf?_tid=52cefc2d-a747-4edd-a3b1-4858940a93b7&acdnat=1540512426_462300bdc5ef7c07bdfeca6cd25b3e3c.

112. Tan TJ, Siva S, Foroudi F, Gill S. Stereotactic body radiotherapy for primary prostate cancer: a systematic review. *J Med Imaging Radiat Oncol.* 2014;58(5):601-611. doi: http://dx.doi.org/10.1111/1754-9485.12213.

113. Anwar M, Weinberg V, Chang AJ, Hsu IC, Roach M, 3rd, Gottschalk A. Hypofractionated SBRT versus conventionally fractionated EBRT for prostate cancer: comparison of PSA slope and nadir. *Radiat Oncol.* 2014;9:42. doi: http://dx.doi.org/10.1186/1748-717X-9-42.

114. Bouman-Wammes EW, van Dodewaard-De Jong JM, Dahele M, et al. Benefits of using stereotactic body radiotherapy in patients with metachronous oligometastases of hormone-sensitive prostate cancer detected by [18F]fluoromethylcholine PET/CT. *Clin Genitourin Cancer.* 2017;15(5):e773-e782. https://ac.els-cdn.com/S155876731730071X/1-s2.0-S155876731730071X-main.pdf?_tid=faa78a3e-27c6-4ace-a3ca-1a2b0f5b177f&acdnat=1540509747_e357191fabec0b29e231779ef1d58285.

115. Evans JR, Zhao S, Daignault S, et al. Patient-reported quality of life after stereotactic body radiotherapy (SBRT), intensity modulated radiotherapy (IMRT), and brachytherapy. *Radiother Oncol.* 2015;116(2):179-184. doi: http://dx.doi.org/10.1016/j.radonc.2015.07.016.

116. Helou J, Morton G, Zhang L, et al. A comparative study of quality of life in patients with localized prostate cancer treated at a single institution: stereotactic ablative radiotherapy or external beam+high dose rate brachytherapy boost. *Radiother Oncol.* 2014;113(3):404-409. doi: http://dx.doi.org/10.1016/j.radonc.2014.10.013.

117. Johnson SB, Soulos PR, Shafman TD, et al. Patient-reported quality of life after stereotactic body radiation therapy versus moderate hypofractionation for clinically localized prostate cancer. *Radiother Oncol.* 2016;121(2):294-298. https://ac.els-cdn.com/S0167814016343559/1-s2.0-S0167814016343559-main.pdf?_tid=bc04234b-a786-48f2-b8f0-1326761e2308&acdnat=1540512608_16501f7d43d21dbccc39d10814a82aa5.

118. Katz A, Ferrer M, Suarez JF, Multicentric Spanish Group of Clinically Localized Prostate Cancer. Comparison of quality of life after stereotactic body radiotherapy and surgery for early-stage prostate cancer. *Radiat Oncol.* 2012;7:194. doi: http://dx.doi.org/10.1186/1748-717X-7-194.

119. Shaverdian N, Verruttipong D, Wang PC, et al. Exploring value from the patient's perspective between modern radiation therapy modalities for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2017;97(3):516-525. https://ac.els-cdn.com/S0360301616334290/1-s2.0-S0360301616334290-main.pdf?_tid=e622f02f-

d9c5-462d-9372-2bed90aaed85&acdnat=1540506742_07b6fa3c693f1fd958c7eadabc308af2.

120. Yu JB, Cramer LD, Herrin J, Soulos PR, Potosky AL, Gross CP. Stereotactic body radiation therapy versus intensity-modulated radiation therapy for prostate cancer: comparison of toxicity. *J Clin Oncol.* 2014;32(12):1195-1201. doi: http://dx.doi.org/10.1200/JCO.2013.53.8652.

121. Halpern JA, Sedrakyan A, Hsu WC, et al. Use, complications, and costs of stereotactic body radiotherapy for localized prostate cancer. *Cancer.* 2016;122(16):2496-2504. https://onlinelibrary.wiley.com/doi/pdf/10.1002/cncr.30101.

122. Helou J, Torres S, Musunuru HB, et al. Stereotactic body radiotherapy versus low dose rate brachytherapy for localised prostate cancer: a cost-utility analysis. *Clin Oncol (R Coll Radiol).* 2017;29(11):718-731. https://ac.els-cdn.com/S0936655517303527/1-s2.0-S0936655517303527-main.pdf?_tid=009fb77f-509f-4655-bcd6-71c47c1177ed&acdnat=1540509148_e47c9a0821a224bd0860402954cb1633.

123. Cai Y, Chang Q, Xiao E, Shang QL, Chen Z. Transcatheter arterial chemoembolization (TACE) combined with Gamma-Knife compared to TACE or Gamma-Knife alone for hepatocellular carcinoma. *Medicine.* 2018;97(22):e10890. doi: 10.1097/MD.0000000000010890.

124. Honda Y, Kimura T, Aikata H, et al. Stereotactic body radiation therapy combined with transcatheter arterial chemoembolization for small hepatocellular carcinoma. *J Gastroenterol Hepatol.* 2013;28(3):530-536. doi: http://dx.doi.org/10.1111/jgh.12087.

125. Lu XJ, Dong J, Ji LJ, Xiao LX, Ling CQ, Zhou J. Tolerability and efficacy of Gamma Knife radiosurgery on hepatocellular carcinoma with portal vein tumor thrombosis. *Oncotarget.* 2016;7(3):3614-3622. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4823131/pdf/oncotarget-07-3614.pdf.

126. Oladeru OT, Miccio JA, Yang J, Xue Y, Ryu S, Stessin AM. Conformal external beam radiation or selective internal radiation therapy-a comparison of treatment outcomes for hepatocellular carcinoma. *J Gastrointest Oncol.* 2016;7(3):433-440. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4880776/pdf/jgo-07-03-433.pdf.

127. Su TS, Liang P, Liang J, et al. Long-term survival analysis of stereotactic ablative radiotherapy versus liver resection for small hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2017;98(3):639-646. https://ac.els-cdn.com/S0360301617304984/1-s2.0-S0360301617304984-main.pdf?_tid=fbf8d07b-eaed-405f-b303-e08847ce4202&acdnat=1540506657_956ea3964fb729cf3f3bfd26018ee487.

128. Leung HW, Liu CF, Chan AL. Cost-effectiveness of sorafenib versus SBRT for unresectable advanced hepatocellular carcinoma. *Radiat Oncol.* 2016;11:69. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4870794/pdf/13014_2016_Article_644.pdf.

129. Kim H, Gill B, Beriwal S, Huq MS, Roberts MS, Smith KJ. Cost-effectiveness analysis of stereotactic body radiation therapy compared with radiofrequency ablation for inoperable colorectal liver metastases. *Int J Radiat Oncol Biol Phys* 2016;95(4):1175-1183. https://ac.els-cdn.com/S0360301616001784/1-s2.0-S0360301616001784-main.pdf?_tid=3a0dff13-2cbe-4ad2-8f33-920faec95e91&acdnat=1540512542_e0c77ed6e386ccd4211fbf96a998377b.

130. Pollom EL, Lee K, Durkee BY, et al. Cost-effectiveness of stereotactic body radiation therapy versus radiofrequency ablation for hepatocellular carcinoma: a Markov modeling study. *Radiology.* 2017;283(2):460-468. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5410949/pdf/radiol.2016161509.pdf.

131. Yamazaki H, Demizu Y, Okimoto T, et al. Reirradiation for recurrent head and neck cancers using charged particle or photon radiotherapy. *Strahlenther Onkol.* 2017;193(7):525-533. https://link.springer.com/article/10.1007%2Fs00066-017-1129-6.

132. Al-Mamgani A, Van Rooij P, Sewnaik A, et al. Brachytherapy or stereotactic body radiotherapy boost for early-stage oropharyngeal cancer: comparable outcomes of two different approaches. *Oral Oncol.* 2013;49(10):1018-1024. doi: http://dx.doi.org/10.1016/j.oraloncology.2013.07.007.

133. Shan GP, Wang BB, Zheng P, Du FL, Yang YW. Efficacy and safety of chemotherapy combined with stereotactic radiotherapy in the treatment of nasopharyngeal carcinoma. *Med Sci Monit.* 2017;23:5630-5636. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5716374/pdf/medscimonit-23-5630.pdf.

134. Yamazaki H, Demizu Y, Okimoto T, et al. Comparison of re-irradiation outcomes for charged particle radiotherapy and robotic stereotactic radiotherapy using CyberKnife for recurrent head and neck cancers: a multi-institutional matched-cohort analysis. *Anticancer Res.* 2016;36(10):5507-5514. http://ar.iiarjournals.org/content/36/10/5507.long.

135. Gunjur A, Duong C, Ball D, Siva S. Surgical and ablative therapies for the management of adrenal 'oligometastases'-a systematic review. *Cancer Treat Rev.* 2014;40(7):838-846. doi: http://dx.doi.org/10.1016/j.ctrv.2014.04.001.

136. Yuan BY, Hu Y, Zhang L, Chen YH, Dong YY, Zeng ZC. Radiotherapy for adrenal gland metastases from hepatocellular carcinoma. *Clin Transl Oncol.* 2017;19(9):1154-1160. https://link.springer.com/content/pdf/10.1007%2Fs12094-017-1654-x.pdf.

137. Lutz S, Balboni T, Jones J, et al. Palliative radiation therapy for bone metastases: update of an ASTRO evidence-based guideline. *Pract Radiat Oncol.* 2017;04. doi: 10.1016/j.prro.2016.08.001.

138. Talacchi A, Muggiolu F, De Carlo A, Nicolato A, Locatelli F, Meglio M. Recurrent atypical meningiomas: combining surgery and radiosurgery in one effective multimodal treatment. *World Neurosurg.* 2016;87:565-572. doi: http://dx.doi.org/10.1016/j.wneu.2015.10.013.

139. Rahman M, Neal D, Baruch W, Bova FJ, Frentzen BH, Friedman WA. The risk of malignancy anywhere in the body after linear accelerator (LINAC) stereotactic radiosurgery. *Stereotact Funct Neurosurg.* 2014;92(5):323-333. doi: http://dx.doi.org/10.1159/000365225.

140. National Comprehensive Cancer Network. NCCN categories of evidence and consensus. 2018; https://www.nccn.org/professionals/physician_gls/categories_of_consensus.aspx. Accessed December 27, 2018.

141. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: bone cancer-version 1.2019. 2018; https://www.nccn.org/professionals/physician_gls/pdf/bone.pdf. Accessed November 20, 2018.

142. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: central nervous system cancers-version 1.2018. 2018; https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed November 20, 2018.

143. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: cervical cancer-version 2.2019. 2018; https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf. Accessed November 20, 2018.

144. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: anal carcinoma-version 2.2018. 2018; https://www.nccn.org/professionals/physician_gls/pdf/anal.pdf. Accessed November 20, 2018.

145. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: colon cancer-version 4.2018. 2018; https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed November 20, 2018.

146. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: rectal cancer-version 3.2018. 2018; https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed November 20, 2018.

147. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: gestational trophoblastic neoplasia-version 1.2019. 2018; https://www.nccn.org/professionals/physician_gls/pdf/gtn.pdf. Accessed November 20, 2018.

148. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: head and neck cancers-version 2.2018. 2018; https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Accessed November 20, 2018.

149. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: hepatobiliary cancers-version 5.2018. 2018; https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf. Accessed November 20, 2018.

150. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: kidney cancer-version 2.2018. 2018; https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf. Accessed November 20, 2018.

151. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: non-small cell lung cancer-version 1.2019. 2018; https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed November 20, 2018.

152. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: small cell lung cancer-version 1.2019. 2018; https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf. Accessed November 20, 2018.

153. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: occult primary (cancer of unknown primary[CUP])-version 1.2019. 2018;

https://www.nccn.org/professionals/physician_gls/pdf/occult.pdf. Accessed November 20, 2018.

154. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: pancreatic adenocarcinoma-version 1.2019. 2018; https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed November 20, 2018.

155. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: prostate cancer-version 4.2018. 2018; https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed November 20, 2018.

156. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: cutaneous melanoma-version 1.2019. 2018; https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf. Accessed November 20, 2018.

157. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: uveal melanoma-version 1.2018. 2018; https://www.nccn.org/professionals/physician_gls/pdf/uveal.pdf. Accessed November 20, 2018.

158. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: squamous cell skin cancer-version 2.2019. 2018; https://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf. Accessed November 20, 2018.

159. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: soft tissue sarcoma-version 2.2018. 2018; https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf. Accessed November 20, 2018.

160. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: thymomas and thymic carcinomas-version 2.2018. 2018; https://www.nccn.org/professionals/physician_gls/pdf/thymic.pdf. Accessed November 20, 2018.

161. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: thyroid carcinoma-version 2.2018. 2018; https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf. Accessed November 20, 2018.

162. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: uterine neoplasms-version 1.2019. 2018; https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf. Accessed November 20, 2018.

163. National Comprehensive Cancer Network. NCCN Guidelines. 2018; https://www.nccn.org/professionals/physician_gls/default.aspx. Accessed November 20, 2018.

164. Centers for Medicare and Medicaid Services. Local coverage determination (LCD): stereotactic radiation therapy: stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) (L34151). 2018; https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34151&ver=24&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=sbrt&KeyWordLookUp=Title&KeyWordSearchType=And&articleId=52974&bc=gAAAACAAAAAA&. Accessed December 5, 2018.

165. Aetna. Stereotactic radiosurgery. 2018; http://www.aetna.com/cpb/medical/data/1_99/0083.html. Accessed November 18, 2018.

166. Cigna. Cigna medical coverage policies – radiation therapy 2018; https://www.evicore.com/cignaclinicalguidelines/cigna%20-%20radiation%20therapy_v1.0.2019_eff01.17.2019_pub10.19.2018.pdf. Accessed November 19, 2018.

167. Regence. Stereotactic radiosurgery and stereotactic body radiation therapy. 2018; http://blue.regence.com/trgmedpol/surgery/sur16.pdf. Accessed November 18, 2018.

Appendix A. Search Strategies

Databases:

- Ovid MEDLINE(R) <1946 to October Week 3 2018>
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <October 23, 2018>

Search Strategy:

1 exp Radiosurgery/

2 (Radiosurg* or (Stereotactic* adj3 (Radiation* or radiother* or irradiat*)) or Gamma Knife or cyberknif* or tomotherapy* or SBRT or SRS or (robot* adj2 (irradiat* or radiat*) adj2 surg*) or (LINAC adj3 surg*)).mp.

3 1 or 2

4 limit 3 to (controlled clinical trial or meta analysis or practice guideline or randomized controlled trial)

5 exp Cohort Studies/

6 exp case-control studies/

7 3 and 5

8 limit 7 to yr="2002 -Current"

9 3 and 6

10 limit 9 to yr="2002 -Current"

11 limit 3 to systematic reviews

12 4 or 11

13 exp economics/ or ec.fs. or exp socioeconomic factors/ or ((cost* or econom* or financ*) adj3 (effectiv* or benefi*)).mp.

14 3 and 13

15 8 or 10 or 12 or 14

16 limit 15 to yr="2002 -Current"

17 limit 16 to english language

18 Comparative Study/

19 3 and 18

20 limit 19 to (english language and humans and yr="2002 -Current")

21 20 not 17

22 (201612* or 2017* or 2018*).ed.

23 17 and 22

24 19 and 22

25 limit 24 to english language

26 23 or 25

27 animals/

28 humans/

29 27 not (27 and 28)

30 26 not 29

31 remove duplicates from 30

Databases:

- EBM Reviews - Cochrane Central Register of Controlled Trials <September 2018>,
- EBM Reviews - Cochrane Database of Systematic Reviews <2005 to October 24, 2018>

Search Strategy:

1 radiosurg$.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]

2 (gamma knif$ or cyberknife* or tomotherapy* or SBRT or SRS).mp.

3 (stereotac$ adj3 (radiation or irradiat* or radiother$)).mp.

4 sbrt.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]

5 1 or 2 or 3 or 4

6 (2017* or 2018*).up.

7 5 and 6

8 limit 7 to yr="2016 -Current"

9 remove duplicates from 8

Appendix B. Coverage Policies

Medicare LCD

The following text is directly excerpted from the Medicare LCD.[164]

Cranial Lesions

Indications for SRS and SBRT:

- Primary central nervous system malignancies, generally used as a boost or salvage therapy for lesions < 5 cm
- Primary and secondary tumors involving the brain or spine parenchyma, meninges/dura, or immediately adjacent bony structures
- Benign brain tumors and spinal tumors such as meningiomas, acoustic neuromas, other schwannomas, pituitary adenomas, pineocytomas, craniopharyngiomas, glomus tumors, hemangioblastomas
- Cranial arteriovenous malformations, cavernous malformations, and hemangiomas
- Other cranial non-neoplastic conditions such as trigeminal neuralgia and select cases of medically refractory epilepsy. As a boost treatment for larger cranial or spinal lesions that have been treated initially with external beam radiation therapy or surgery (e.g., sarcomas, chondrosarcomas, chordomas, and nasopharyngeal or paranasal sinus malignancies)
- Metastatic brain or spine lesions, with stable systemic disease, Karnofsky Performance Status 40 or greater (or expected to return to 70 or greater with treatment), and otherwise reasonable survival expectations, OR an Eastern Cooperative Oncology Group (ECOG) Performance Status of 3 or less (or expected to return to 2 or less with treatment)
- Relapse in a previously irradiated cranial or spinal field where the additional stereotactic precision is required to avoid unacceptable vital tissue radiation

SRS is not considered medically necessary (for cranial lesions only) under the following circumstances:

- Treatment for anything other than a severe symptom or serious threat to life or critical functions
- Treatment unlikely to result in functional improvement or clinically meaningful disease stabilization, not otherwise achievable
- Patients with wide-spread cerebral or extra-cranial metastases with limited life expectancy unlikely to gain clinical benefit within their remaining life
- Patients with poor performance status (Karnofsky Performance Status < 40 or an ECOG Performance > 3)
- Cobalt-60 pallidotomy is non-covered
- Basic dosimetry calculations are limited to 1 unit for each arc in a linear accelerator system and 1 unit for each shot in Cobalt-60 system with a maximum of 10 units

- Treatment devices, complex is limited to one unit for each collimator in a linear accelerator system or one for each helmet in a cobalt-60 system. If the total number of units exceeds 6 or the number of isocenters plus 3 when multiple isocenters are necessary, a detailed explanation of medical necessity must be documented in the medical record.

Other Indications for SBRT

SBRT is indicated for primary tumors of and tumors metastatic to the lung, liver, kidney, adrenal gland, or pancreas as well as for pelvic and head and neck tumors that have recurred after primary irradiation when and only when each of the following criteria are met, and each specifically documented in the medical record:

- The patient's general medical condition (notably, the performance status) justifies aggressive treatment to a primary cancer or, for the case of metastatic disease, justifies aggressive local therapy to one or more discrete deposits of cancer within the context of efforts to achieve total clearance or clinically beneficial reduction in the patient's overall burden of systemic disease
- Other forms of radiotherapy, including but not limited to external beam and IMRT, cannot be safely or effectively utilized
- The tumor burden can be completely targeted with acceptable risk to critical normal structures
- If the tumor histology is germ cell or lymphoma, effective chemotherapy regimens have been exhausted and external beam radiation is ineffective or inappropriate for the patient as fully explained in the medical record

For patients with tumors of any type arising in or near previously irradiated regions, SBRT may be appropriate when a high level of precision and accuracy is needed to minimize the risk of injury to surrounding normal tissues. Also, in other cases where a high dose per fraction treatment is indicated SBRT may be appropriate. The necessity should be documented in the medical record.

Coverage may be considered at the Redetermination (Appeal) level on an individual basis for lesions when documentation clearly supports the necessity for high radiation dose per fraction and the necessity to avoid surrounding tissue exposure.

Low or intermediate risk prostate cancer may be covered when the patient is enrolled in an IRB-approved clinical trial and which clinical trial meets the "standards of scientific integrity and relevance to the Medicare population" described in IOM 100-03, National Coverage Determinations Manual, Chap 1, Part 1, section 20.32, B3a-k (with l-m desirable). Similarly, enrollment in a clinical registry compliant with the principles established in AHRQ's "Registries for Evaluating Patient Outcomes: A User's Guide," such as the Registry for Prostate Cancer Radiosurgery, may qualify the treatment for coverage.

Primary treatment of lesions of bone, breast, uterus, ovary, and other internal organs not listed earlier in this LCD as covered is non-covered. The literature does not support an outcome advantage over other conventional radiation modalities. However, SBRT treatment in the setting of recurrence after conventional radiation modalities have been utilized may be covered.

SBRT is not considered medically necessary under the following circumstances for any condition:

- Treatment unlikely to result in clinical cancer control or functional improvement
- The tumor burden cannot be completely
- Patients with poor performance status (Karnofsky Performance Status < 40 or ECOG status of 3 or worse)

Aetna

The following text is directly excerpted from the Aetna policy on stereotactic readiosurgery.[165]

Cranial SRS with a CyberKnife, Gamma Knife, or linear accelerator is considered medically necessary when used for any of the following indications:

- For treatment of members with symptomatic, small (< 3 cm) arteriovenous malformations, aneurysms, and benign tumors (acoustic neuromas (vestibular schwannomas), craniopharyngiomas, hemangiomas, meningiomas, pituitary adenomas, and neoplasms of the pineal gland) if the lesion is unresectable due to its deep intracranial location or if the member is unable to tolerate conventional operative intervention
- For treatment of brain malignancies (primary tumors or metastatic lesions)

SBRT with a CyberKnife, Gamma Knife, or linear accelerator is considered medically necessary for localized malignant conditions within the body where highly precise application of high-dose radiotherapy is required and clinically appropriate.

SRS for treatment of brain malignancies (primary tumors or metastatic lesions) is considered medically necessary in members with a good performance status (a score between 80 and 100 on the Karnofsky Performance Scale [i.e., at a minimum, able to perform normal activity with effort]), controlled systemic disease (defined as extracranial disease that is stable or in remission), and no more than 4 metastatic lesions. For treatment to additional lesions, further clinical justification may be needed.

SRS is considered medically necessary for ocular melanomas that are not amenable to surgical excision or other conventional forms of treatment.

SBRT is considered medically necessary for localized malignant conditions within the body where highly precise application of high-dose radiotherapy is required and clinically appropriate, including:

- Hepatocellular carcinoma in individuals with unresectable disease that is considered to be extensive and not suitable for liver transplantation or for individuals with local disease only

with a good performance status (a score between 80 and 100 on the Karnofsky Performance Scale) but who are not amenable to surgery due to comorbidities

- Prostate cancer in individuals with organ-confined prostate cancer with Gleason score ≤ 8 and PSA < 20
- NSCLC for inoperable stage I or II tumors
- Inoperable primary spinal tumors with compression or intractable pain
- Recurrent metastatic disease in a previously irradiated area
- Recurrent localized head and neck cancer
- Metastatic lesions to the liver when they are the sole site of disease and cannot be surgically resected or undergo accepted ablation techniques
- Metastatic disease to the lung when clinically appropriate and on a case-by-case basis

All other clinical sites or indications are considered experimental and investigational but will be considered on a case-by-case basis.

Cigna

The following text is directly excerpted from the Cigna policy on radiation therapy.[166]

Brain Metastases

SRS is considered medically necessary for an individual when ALL of the following criteria are met:

- Karnofsky Performance Status ≥ 70
- Systemic disease is under control or good options for systemic treatment are available
- Absence of leptomeningeal disease
- Primary histology is not germ cell, small cell, or lymphoma

Initial treatment with SRS for brain metastases is considered medically necessary when both of the following conditions are met:

- No lesion > 5 cm and all lesions can be treated in a single treatment plan in a single fraction (for SRS) or up to 5 fractions (for fractionated SRS)
- All lesions present on imaging must be targeted as a single episode of care. If this cannot be accomplished in a maximum of 5 fractions, each fraction must be billed as 3D conformal or IMRT, depending on the planning, as the definition of SRS is not met

In an individual who has received prior SRS, retreatment with SRS is considered medically necessary when ALL of the following conditions are met:

- No lesion > 5 cm and all lesions can be treated in a single treatment plan in a single fraction (for SRS) or up to 5 fractions (for fractionated SRS)
- The individual has not been treated with more than two episode of SRS in the past 9 months

- All lesions present on imaging must be targeted as a single episode of care.
- If this cannot be accomplished in a maximum of 5 fractions, each fraction must be billed as 3D conformal or IMRT, depending on the planning, as the definition of SRS is not met
- Life expectancy > 6 months
- Submission of recent consultation note and recent restaging studies

In an individual who has received prior WBRT, SRS is considered medically necessary if the life expectancy is greater than 3 months.

Post-operative SRS is considered medically necessary for the treatment of a combination of up to 4 resected and unresected lesions that are each < 4 cm in size.

Spinal

SRS is considered medically necessary for the treatment of an inoperable primary spinal tumor with compression or intractable pain.

Bone metastases

SBRT will be considered in cases that require treatment to a portion of the spine that has been previously irradiated. SBRT will also be considered for treatment of sarcoma, melanoma, and renal cell carcinoma that have metastasized to the spine.

Cervical cancer

With locoregional recurrence, SBRT may be considered based on a history of previous radiation to the same or abutting region and inability to deliver therapeutic doses of radiation with other techniques.

Head and neck cancer

With re-treatment for salvage after prior radiation, SBRT may be medically necessary in an individual who has no evidence of metastatic disease

Hepatobiliary Cancer

In primary liver cancer, SBRT is considered medically necessary to treat concurrently one or more tumors when there is evidence of the ability to protect an adequate volume of uninvolved liver. SBRT is considered medically necessary for unresectable localized intrahepatic bile duct cancer. SBRT is considered not medically necessary for unresectable localized extrahepatic bile duct cancer. SBRT is considered not medically necessary for unresectable localized gallbladder cancer.

Lung Cancer

SBRT (with 3D or IMRT planning) is considered medically necessary for an individual with medically inoperable Stage I or II NSCLC.

Oligometastases

SBRT for extra-cranial oligometastases is considered medically necessary in the following clinical situations:

- For an individual with NSCLC who
  - Has had or who will undergo curative treatment of the primary tumor (based on T and N stage) and
  - Has 1 to 3 metastases in the synchronous setting
- For an individual with colorectal cancer who
  - Has had or who will undergo curative treatment of the primary tumor and
  - Presents with 1 to 3 metastases in the lung or liver in the synchronous setting and
  - For whom surgical resection is not possible
- For an individual with
  - A clinical presentation of one 1 to 3 adrenal gland, lung, liver or bone metastases in the metachronous setting when all the following criteria are met:
    - Histology is non-small cell lung, colon, breast, sarcoma, renal cell, or melanoma
    - Disease free interval of > 1 year from the initial diagnosis
    - Primary tumor received curative therapy and is controlled
    - No prior evidence of metastatic disease (cranial or extracranial)

SBRT is considered medically necessary in an individual with NSCLC who presents in the synchronous or metachronous setting, has 1 to 3 sites of disease, and good performance status, assuming SBRT can be delivered safely to the involved sites.

SBRT is considered medically necessary in an individual with colorectal cancer who presents in the synchronous or metachronous setting, has 1 to 3 sites of disease limited to the lung or liver, and good performance status, assuming surgical resection is not feasible.

SBRT is considered medically necessary in an individual with breast cancer who presents in the metachronous setting; has 1 to 3 sites of disease limited to the lung, liver, or bone, has a disease free interval of > 1 year; and received curative therapy to the primary tumor.

SBRT is considered medically necessary in an individual with sarcoma, renal, or melanoma metastasis who meets the following criteria: disease free interval of > 1 year from the initial diagnosis, primary tumor received curative therapy and is controlled, and no prior evidence of metastatic disease.

SBRT to > 3 sites or non-hematogenous sites of spread such as lymphatic regions is considered experimental/investigational.

SBRT used to stimulate the abscopal effect is considered not medically necessary.

SBRT is not routinely medically necessary in an individual with oligoprogressive disease.

Pancreatic Cancer

SBRT is considered medically necessary for either of the following:

- Definitive treatment for medically or surgically inoperable or locally advanced cases following a minimum of 2 cycles of chemotherapy and restaging in which there is no evidence of tumor progression and the disease volume can be entirely encompassed in the radiation treatment volume
- Postoperative (adjuvant) cases in which there is residual gross disease or positive microscopic margins that can be entirely encompassed in the radiation treatment volume

The use of SBRT as planned neoadjuvant treatment is considered experimental, investigational and unproven.

SBRT using up to 5 radiation treatment fractions will be considered for the following:

- Preoperative (neoadjuvant resectable or borderline resectable) cases following a minimum of 2 cycles of chemotherapy and restaging in which there is no evidence of tumor progression
- Definitive treatment for medically inoperable or locally advanced cases following a minimum of 2 cycles chemotherapy and restaging in which there is no evidence of tumor progression and the disease volume can be entirely encompassed in the radiation treatment volume

SBRT is not considered medically necessary in palliative situations.

Prostate

SBRT alone is medically necessary for:

- Low-, intermediate-, and high-risk prostate cancer
- Negative bone scan within the past 6 months, where applicable

Skin Cancer

SBRT to treat melanoma metastases, require individual review and must also satisfy criteria set forth in the guideline on Radiation Therapy for Oligometastases.

Soft tissues sarcomas

Palliative use of SBRT requires medical review.

SBRT is considered medically necessary to treat a locally recurrent soft tissue sarcoma that is within or immediately adjacent to an area that has received radiation treatments as part of the primary management.

Benign conditions

Surgery remains the standard treatment for acoustic neuroma (vestibular schwannoma). However, the use of single-fraction SRS and fractionated SRS is medically necessary for those cases in which surgery is declined or not indicated.

SRS is considered medically necessary for the treatment of the following benign conditions:

- Benign brain tumor including any of the following:
  - Craniopharyngioma

- Glomus tumor
- Hemangioblastoma
- Meningioma
- Pineocytoma
- Pituitary adenoma
- Schwannomas

Regence

The following text is directly excerpted from the Regence policy on SRS and SBRT.[167]

SRS, SBRT, and SABR may be considered medically necessary for initial treatment or treatment of recurrence for any of the following indications:

- Intracranial sites:
  - Primary neoplasms of the CNS, including but not limited to low grade gliomas and high-grade gliomas
  - Metastatic lesion(s) to the CNS (solitary or multiple) in patients with a current Karnofsky performance score ≥ 60 or a current ECOG score ≤ 2
  - Acoustic neuromas (vestibular schwannomas)
  - Chordomas and chondrosarcomas of the skull base
  - Craniopharyngiomas
  - Hemangioblastoma
  - Hemangiopericytoma
  - Glomus jugulare and Glomus tympanicum tumors
  - Meningiomas, benign, atypical, or malignant
  - Pituitary adenomas
  - Spinal or paraspinal tumors (primary or metastatic)
  - Uveal melanoma
- Extracranial sites:
  - Hepatic tumor (primary or metastatic) as palliative or curative treatment when both of the following are met:
    - Absence or minimal extra hepatic disease
    - Karnofsky performance score ≥ 60 or an ECOG score ≤ 2
  - Hepatocellular carcinoma when all of the following criteria are met:
    - Five or fewer hepatic lesions
    - Size of largest lesion ≤ 6 cm diameter
    - Karnofsky performance score ≥ 60 or an ECOG score ≤ 2
  - Lung metastases when both of the following criteria are met:

        - Five or fewer metastatic lung lesions
        - Karnofsky performance score ≥ 60 or an ECOG score ≤ 2
    - Primary NSCLC (node negative, tumor stage T1a, T1b, T2a, T2b)
    - Osteosarcoma, metastatic when all of the following criteria are met:
        - Five or fewer metastatic lesions
        - Karnofsky performance score ≥ 60 or an ECOG score ≤ 2
    - Prostate cancer, low- to intermediate-risk when all of the following criteria are met:
        - Stage < than T3a
        - PSA ≤ 20
        - Gleason Score < 8
    - Spinal or paraspinal tumors (primary or metastatic)

SRS, SBRT, and SABR are considered investigational for all other indications including but not limited to:

- Cavernous malformations
- Choroidal neovascularization
- Chronic pain
- Epilepsy
- Functional disorders other than trigeminal neuralgia
- Refractory symptoms of essential tremor or Parkinson's disease
- Seizures
- Primary tumors of the following sites or metastatic to the following sites:
    - Cervix
    - Endometrium
    - Esophagus
    - Hemangiomas
    - Kidney
    - Large bowel
    - Ovaries
    - Pancreas
    - Rectum
    - Small bowel

Appendix C. Studies Registered at ClincalTrials.gov: Phase 3 and 4 Trials

NCT Number Location	Title	Status	Completion Date
NCT00003916 Australia, France Germany, Netherlands	Standard Radiation Therapy With or Without Stereotactic Radiation Therapy in Treating Patients With Glioma	Completed	December 2001
NCT00002708 U.S.	Radiation Therapy With or Without Radiosurgery in Treating Patients With Brain Metastases	Completed	December 2004
NCT00075166 U.S.	Surgery Versus Radiosurgery to Treat Metastatic Brain Tumors	Completed	November 2005
NCT00460395 U.S.	Surgery Versus Stereotactic Radiosurgery in the Treatment of Single Brain Metastasis: A Randomized Trial	Completed	December 2005
NCT00268684 Israel	Comparison Study of WBRT and SRS Alone Versus With Temozolomide or Erlotinib in Patients With Brain Metastases of NSCLC	Unknown status	February 2006
NCT00104936 Germany, Netherlands, Switzerland	Radiotherapy or Radiosurgery Compared With Observation Alone in Treating Patients With Newly Diagnosed, Benign Meningioma That Has Been Partially Removed by Surgery	Terminated	November 2006
NCT00181350 Netherlands	Serial CT Scans in Fractionated Stereotactic Radiotherapy	Completed	July 2007
NCT00002899 Belgium, Finland	Adjuvant Radiation Therapy in Treating Patients With Brain Metastases	Terminated	November 2007
NCT00581113 U.S.	Neural Stem Cell Preserving Brain Radiation Therapy & Stereotactic Radiosurgery in Patients With 1-6 Brain Metastases	Terminated	June 2009
NCT00328510 U.S.	Comparing Two Forms of Head Immobilization for Stereotactic Radiotherapy	Completed	September 2009
NCT01169129 Brazil	Surgery and Whole Brain Radiotherapy (RT) Versus Whole Brain Radiotherapy (RT) and Radiosurgery for 1-3 Resectable Brain Metastases	Withdrawn	July 2010
NCT01130766 Korea	Asymptomatic Brain Metastasis in Non-small Cell Lung Cancer (NSCLC)	Unknown status	May 2011
NCT00096265 U.S.	Radiation Therapy and Stereotactic Radiosurgery With or Without Temozolomide or Erlotinib in Treating Patients With Brain Metastases Secondary to Non-Small Cell Lung Cancer	Terminated	April 2012

NCT Number Location	Title	Status	Completion Date
NCT00280475 Japan	A Trial of Postoperative Whole Brain Radiation Therapy vs. Salvage Stereotactic Radiosurgery Therapy for Metastasis	Completed	January 2013
NCT00840749 U.S.	Randomized Study to Compare CyberKnife to Surgical Resection In Stage I Non-small Cell Lung Cancer	Terminated	March 2013
NCT01301560 Korea	Chemotherapy With or Without Radiosurgery for Asymptomatic Oligo Brain Metastasis	Unknown status	May 2013
NCT01449604 Thailand	Stereotactic Radiation in Vestibular Schwannoma	Unknown status	October 2013
NCT01233544 Denmark, Sweden	Radiofrequency Ablation Versus Stereotactic Radiotherapy in Colorectal Liver Metastases	Terminated	December 2014
NCT01535209 Poland	Stereotactic Radiotherapy of Resection Cavity For Single Brain Metastasis Versus Whole-Brain Radiotherapy After Resection	Unknown status	December 2014
NCT01364259 U.S.	A Study of Amifostine for Prevention of Facial Numbness in Radiosurgery Treatment of Trigeminal Neuralgia	Terminated	January 2015
NCT01429493 Belgium	Biological Image Guided Antalgic Stereotactic Body Radiotherapy of Bone Metastases	Unknown status	December 2015
NCT00687986 Netherlands	Trial of Either Surgery or Stereotactic Radiotherapy for Early Stage (IA) Lung Cancer	Terminated	December 2015
NCT01318200 U.S.	Transarterial Chemoembolization (TACE) vs. CyberKnife for Recurrent Hepatocellular Carcinoma (HCC)	Withdrawn	February 2016
NCT01336894 U.S.	Surgery With or Without Internal Radiation Therapy Compared With Stereotactic Body Radiation Therapy in Treating Patients With High-Risk Stage I Non-Small Cell Lung Cancer	Terminated	March 2017
NCT02729558 Netherlands	Local Radiotherapy Following Complete Resection of a Brain Metastasis	Unknown status	May 2017
NCT00517959 India	SCRT Versus Conventional RT in Children and Young Adults With Low Grade and Benign Brain Tumors	Unknown status	June 2017
NCT01344356 U.S.	Stereotactic Body Radiotherapy for Head and Neck Tumors	Unknown status	July 2017
NCT02323360 Italy	A Trial on SBRT After Incomplete TAE or TACE Versus Exclusive TAE or TACE For Treatment of Inoperable HCC	Unknown status	May 2018
NCT01352598 U.S.	Stereotactic Body Radiotherapy for Prostate Cancer	Recruiting	June 2018

NCT Number Location	Title	Status	Completion Date
NCT02320825 U.S.	Randomized Study Comparing Local Tumor Control After Post-Operative Single-Fraction or Hypofractionated Stereotactic Radiosurgery in the Treatment of Spinal Metastases	Completed	August 2018
NCT01839994 Poland	Conformal Radiotherapy (CRT) Alone Versus CRT Combined With HDR BT or Stereotactic Body Radiotherapy for Prostate Cancer	Unknown status	December 2018
NCT02162537 France	Therapeutic Strategies in Patients With Non-squamous Non-small Cell Lung Cancer With Brain Metastases	Recruiting	January 2019
NCT02791503 Netherlands	CROSSFIRE Trial: Comparing the Efficacy of Irreversible Electroporation With Radiotherapy	Recruiting	May 2019
NCT01592968 U.S.	A Prospective Phase III Trial to Compare Stereotactic Radiosurgery Versus Whole Brain Radiation Therapy	Recruiting	August 2019
NCT01926197 U.S.	Phase III FOLFIRINOX (mFFX) +/- SBRT in Locally Advanced Pancreatic Cancer	Recruiting	September 2019
NCT02512965 Australia	Study Comparing Stereotactic Body Radiotherapy vs Conventional Palliative Radiotherapy (CRT) for Spinal Metastases	Recruiting	December 2019
NCT03056638 U.S.	Trial of ADT and SBRT Versus SBRT for Intermediate Prostate Cancer	Recruiting	February 2020
NCT00950001 U.S.	Resection Bed Post-Surgical Stereotactic Radiosurgery (SRS)	Active, not recruiting	August 2020
NCT01372774 U.S.	Stereotactic Radiosurgery or Whole-Brain Radiation Therapy in Treating Patients With Brain Metastases That Have Been Removed By Surgery	Active, not recruiting	November 2020
NCT02882984 China	Hypofractionated Brain Radiation In EGFR Mutated Adenocarcinoma Cranial Disease (Hybrid)	Recruiting	December 2020
NCT01014130 Australia	Hypofractionated Radiotherapy (Stereotactic) Versus Conventional Radiotherapy for Inoperable Early Stage I Non-small Cell Lung Cancer (NSCLC)	Active, not recruiting	December 2020
NCT02893332 China	Stereotactic Body Radiation Therapy (SBRT) in Newly Diagnosed Advanced Staged Lung Adenocarcinoma (Sindas)	Recruiting	December 2020
NCT02820194 Italy	A Trial on SBRT Versus MWA for Inoperable Colorectal Liver Metastases (CLM)	Recruiting	February 2021
NCT02762266 U.S.	Transarterial Chemoembolization Compared With Stereotactic Body Radiation Therapy or Stereotactic Ablative Radiation Therapy in Treating Patients With Residual or Recurrent Liver Cancer Undergone Initial Transarterial Chemoembolization	Recruiting	February 2021

NCT Number Location	Title	Status	Completion Date
NCT02759783 England	Conventional Care Versus Radioablation (Stereotactic Body Radiotherapy) for Extracranial Oligometastases	Recruiting	October 2021
NCT02055859 Italy	Cyberknife Radiosurgery for Patients With Neurinomas	Recruiting	November 2021
NCT01968941 Canada	Stereotactic Body Radiotherapy Versus Conventional Radiotherapy in Medically-Inoperable Non-Small Lung Cancer Patients	Recruiting	November 2021
NCT03256981 England	Stereotactic Body Radiotherapy for the Treatment of OPD	Recruiting	November 2021
NCT00922974 U.S.	Image-Guided Radiosurgery or Stereotactic Body Radiation Therapy in Treating Patients With Localized Spine Metastasis	Active, not recruiting	January 2022
NCT02794337 India	TACE vs TACE+SBRT for Unresectable Hepatocellular Cancer	Recruiting	January 2022
NCT03075072 U.S.	Whole Brain Radiation Versus Stereotactic Radiation (SRS) in Patients With 5-20 Brain Metastases: A Phase III, Randomized Clinical Trial	Recruiting	March 2022
NCT03727867 China	Efficacy of Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Combined With Early Stereotactic Body Radiation Therapy to the Primary Tumor in Advanced Non-small Cell Lung Cancer	Not yet recruiting	June 2022
NCT03550391 Canada	Stereotactic Radiosurgery Compared With Whole Brain Radiotherapy (WBRT) for 5-15 Brain Metastases	Recruiting	June 2022
NCT03741673 U.S.	Pre-operative SRS or Post-operative SRS in Treating Cancer Patients With Brain Metastases	Recruiting	July 2022
NCT01581749 U.S.	Evaluation of Truebeam for Low-Intermediate Risk Prostate Cancer	Recruiting	December 2022
NCT03338647 India	SBRT or TACE for Advanced HCC	Recruiting	December 2022
NCT02089100 France	Trial of Superiority of Stereotactic Body Radiation Therapy in Patients With Breast Cancer	Recruiting	February 2023
NCT03697343 Germany	Fractionated Stereotactic Radiotherapy vs. Single Session Radiosurgery in Patients With Larger Brain Metastases	Not yet recruiting	January 2024
NCT02468024 U.S.	JoLT-Ca Sublobar Resection (SR) Versus Stereotactic Ablative Radiotherapy (SAbR) for Lung Cancer	Recruiting	December 2024
NCT02685397 Canada	Management of Castration-Resistant Prostate Cancer With Oligometastases	Recruiting	April 2025

NCT Number Location	Title	Status	Completion Date
NCT01730937 U.S.	Sorafenib Tosylate With or Without Stereotactic Body Radiation Therapy in Treating Patients With Liver Cancer	Recruiting	June 2025
NCT03750227 U.S.	Pre-Operative or Post-Operative Stereotactic Radiosurgery in Treating Patients With Operative Metastatic Brain Tumors	Recruiting	November 2025
NCT01584258 England	Prostate Advances in Comparative Evidence	Recruiting	September 2026
NCT02364557 U.S.	Standard of Care Therapy With or Without Stereotactic Radiosurgery and/or Surgery in Treating Patients With Limited Metastatic Breast Cancer	Recruiting	December 2027
NCT03367702 U.S.	Stereotactic Body Radiation Therapy or Intensity-Modulated Radiation Therapy in Treating Patients With Stage IIA-B Prostate Cancer	Recruiting	December 2028
NCT03721341 Canada	Stereotactic Ablative Radiotherapy for Comprehensive Treatment of 4-10 Oligometastatic Tumors	Not yet recruiting	January 2029

Appendix D. Studies Excluded After Full-Text Review

Abdulkarim BS, Joseph K, Vos L, et al. A phase III randomized control trial comparing skin-sparing helical tomotherapy versus 3D-conformal radiation therapy in early-stage breast cancer: acute and late skin toxicity outcomes. International journal of radiation oncology. 2016;Conference: 58th annual meeting of the American Society for Radiation Oncology, ASTRO. 2016. United States 96(2 Supplement 1):S6. Exclusion reason: Publication type

Alghamdi M, Tseng CL, Myrehaug S, et al. Postoperative stereotactic body radiotherapy for spinal metastases. Chinese Clinical Oncology. 2017;6(Suppl 2):S18. Exclusion reason: Not appropriate comparator

Anderson ES, Postow MA, Young R, Chan TA, Yamada Y, Beal K. Initial report on safety and lesion response of melanoma brain metastases after stereotactic radiosurgery or hypofractionated radiation therapy in patients receiving concurrent pembrolizumab. International journal of radiation oncology biology physics. 2016;Conference: 58th annual meeting of the American Society for Radiation Oncology, ASTRO. 2016. United States 96(2 Supplement 1):E132. Exclusion reason: Publication type

Aouadi S, Vasic A, Paloor S, et al. Generation of synthetic CT using multi-scale and dual-contrast patches for brain MRI-only external beam radiotherapy. Physica Medica. 2017;42:174-184. Exclusion reason: Not intervention of interest

Astradsson A, Munck Af Rosenschold P, Feldt-Rasmussen U, et al. Visual outcome, endocrine function and tumor control after fractionated stereotactic radiation therapy of craniopharyngiomas in adults: findings in a prospective cohort. Acta Oncologica. 2017;56(3):415-421. Exclusion reason: Sample size insufficient

Badellino S, Muzio JD, Schivazappa G, et al. No differences in radiological changes after 3D conformal vs VMAT-based stereotactic radiotherapy for early stage non-small cell lung cancer. British Journal of Radiology. 2017;90(1078):20170143. Exclusion reason: Not intervention of interest

Baker S, Lim G, Nordal R, Surgeoner B, Kostaras X, Roa W. Provincial clinical practice guidelines for patients with 1-3 brain metastases. Radiotherapy and oncology Conference: CARO. 2016;120. Exclusion reason: Publication type

Ball D, Mai T, Vinod S, et al. A randomized trial of SABR vs conventional radiotherapy for inoperable stage I non-small cell lung cancer: tROG09.02 (CHISEL). Journal of thoracic oncology. 2017;Conference: 18th world conference on lung cancer of the international association for the study of lung cancer, IASLC. 2017. Japan 12(11 Supplement 2):S1853. Exclusion reason: Publication type

Ball D, Mai T, Vinod S, et al. A randomized trial of SABR vs conventional radiotherapy for inoperable stage I non-small cell lung cancer: TROG 09.02 (CHISEL). Journal of medical imaging and radiation oncology. 2017;Conference: 68th annual scientific meeting of the Royal Australian and New Zealand College of Radiologists, RANZCR. 2017. Australia 61(Supplement 1):33-34. Exclusion reason: Publication type

Bi N, Shedden K, Zheng X, Kong FS. Comparison of the Effectiveness of Radiofrequency Ablation With Stereotactic Body Radiation Therapy in Inoperable Stage I Non-Small Cell Lung Cancer: A Systemic Review and Pooled Analysis. International Journal of Radiation Oncology, Biology, Physics. 2016;95(5):1378-1390. Exclusion reason: Not appropriate comparator

Bibault JE, Dussart S, Pommier P, et al. Clinical Outcomes of Several IMRT Techniques for Patients With Head and Neck Cancer: a Propensity Score-Weighted Analysis. International journal of radiation oncology biology physics. 2017(pagination). Exclusion reason: Not intervention of interest

Blanchard P, Foulon S, Louvel G, Habibian M, Fizazi K. A randomized controlled trial of metastases-directed treatment in patients with metastatic prostate cancer using stereotactic body irradiation: a GETUG-AFU trial. Cancer/radiotherapie. 2017;21(6-7):491-494. Exclusion reason: Not in English

Borghetti P, Bonu ML, Roca E, et al. Radiotherapy and Tyrosine Kinase Inhibitors in Stage IV Non-small Cell Lung Cancer: Real-life Experience. In Vivo. 2018;32(1):159-164. Exclusion reason: Outcome data cannot be abstracted

Bosshard R, O'Reilly K, Ralston S, Chadda S, Cork D. Systematic reviews of economic burden and health-related quality of life in patients with acute myeloid leukemia. Cancer Treatment Reviews. 2018;69:224-232. Exclusion reason: Not intervention of interest

Bridges KJ, Jaboin JJ, Kubicky CD, Than KD. Stereotactic radiosurgery versus surgical resection for spinal hemangioblastoma: A systematic review. Clinical Neurology & Neurosurgery. 2017;154:59-66. Exclusion reason: Not appropriate comparator

Brown PD, Ballman KV, Cerhan J, et al. N107C/CEC.3: a phase III trial of post-operative stereotactic radiosurgery (SRS) compared with whole brain radiotherapy (WBRT) for resected metastatic brain disease. International journal of radiation oncology biology physics. 2016;Conference: 58th annual meeting of the American Society for Radiation Oncology, ASTRO. 2016. United States 96(5):937. Exclusion reason: Publication type

Brown PD, Ballman KV, Cerhan JH, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC.3): a multicentre, randomised, controlled, phase 3 trial. Lancet oncology. 2017;18(8):1049-1060. Exclusion reason: Included in a systematic review

Bryant AK, Mundt R, Sandhu APS, et al. Stereotactic body radiation therapy versus surgery for early non-small-cell lung cancer in the veterans affairs system. International journal of radiation oncology biology physics. 2017;Conference: 59th annual meeting of the American Society for Radiation Oncology, ASTRO. 2017. United States 99(2 Supplement 1):S7. Exclusion reason: Publication type

Chan OSH, Lee VHF, Mok TSK, Mo F, Chang ATY, Yeung RMW. The Role of Radiotherapy in Epidermal Growth Factor Receptor Mutation-positive Patients with Oligoprogression: A Matched-cohort Analysis. Clinical Oncology (Royal College of Radiologists). 2017;29(9):568-575. Exclusion reason: Not appropriate comparator

Chang JH, Shin JH, Yamada YJ, et al. Stereotactic Body Radiotherapy for Spinal Metastases: What are the Risks and How Do We Minimize Them? Spine. 2016;41 Suppl 20:S238-S245. Exclusion reason: Not appropriate comparator

Chapet O, De Laroche G, Dorel SB, et al. Prostate hypofractionated radiation therapy with a rectal spacer comparing moderate hypofractionation (62 Gy at 3.1 Gy per fraction) versus stereotactic irradiation (37.5 Gy at 7.5 Gy per fraction): acute toxicities from the rpah2 randomized trial. International journal of radiation oncology biology physics. 2017;Conference: 59th annual meeting of the American Society for Radiation Oncology, ASTRO. 2017. United States 99(2 Supplement 1):E218-E219. Exclusion reason: Publication type

Chaudhuri AA, Binkley MS, Rigdon J, et al. Pre-treatment non-target lung FDG-PET uptake predicts symptomatic radiation pneumonitis following Stereotactic Ablative Radiotherapy (SABR). Radiotherapy & Oncology. 2016;119(3):454-460. Exclusion reason: Not appropriate comparator

Chen H, Louie A, Boldt RG, Palma D, Nossent E, Senan S. Risks of SABR for early-stage non-small cell lung cancer with co-existing interstitial lung disease: a systematic review of literature. Radiotherapy and oncology Conference: CARO. 2016;120:S86-S87. Exclusion reason: Publication type

Chen H, Louie AV, Boldt RG, Rodrigues GB, Palma DA, Senan S. Quality of Life After Stereotactic Ablative Radiotherapy for Early-Stage Lung Cancer: A Systematic Review. Clinical Lung Cancer. 2016;17(5):e141-e149. Exclusion reason: Not appropriate comparator

Chen W, Lin Q, Sun X, et al. A propensity-matched analysis of stereotactic body radiotherapy and sublobar resection for stage I non-small cell lung cancer in patients at high risk for lobectomy. Journal of clinical oncology Conference. 2017;35(15 Supplement 1). Exclusion reason: Publication type

Chi A, Chen H, Wen S, Yan H, Liao Z. Comparison of particle beam therapy and stereotactic body radiotherapy for early stage non-small cell lung cancer: A systematic review and hypothesis-

generating meta-analysis. Radiotherapy & Oncology. 2017;123(3):346-354. Exclusion reason: Not appropriate comparator

Chi A, Wen S, Monga M, et al. Definitive Upfront Stereotactic Ablative Radiotherapy Combined with Image-Guided, Intensity Modulated Radiotherapy (IG-IMRT) or IG-IMRT Alone for Locally Advanced Non-Small Cell Lung Cancer. PLoS ONE [Electronic Resource]. 2016;11(9):e0162453. Exclusion reason: Sample size insufficient

Chin V, Nagrial A, Sjoquist K, et al. Chemotherapy and radiotherapy for advanced pancreatic cancer. Cochrane Database of Systematic Reviews. 2018(3). Exclusion reason: Not intervention of interest

Chmura SJ, Winter KA, Salama JK, et al. NRGBR002: a phase IIR/III trial of standard of care therapy with or without stereotactic body radiotherapy (SBRT) &/or surgical ablation for newly oligo-metastatic breast cancer. Cancer research Conference: 39th annual CTRC AACR san antonio breast cancer symposium United States. 2017;77(4 Supplement 1). Exclusion reason: Publication type

Cho WK, Noh JM, Ahn YC, Oh D, Pyo H. Radiation Therapy Alone in cT1-3N0 Non-small Cell Lung Cancer Patients Who Are Unfit for Surgical Resection or Stereotactic Radiation Therapy: Comparison of Risk-Adaptive Dose Schedules. Cancer Research & Treatment. 2016;48(4):1187-1195. Exclusion reason: Not intervention of interest

Choi J, Park SH, Khang SK, et al. Hemangiopericytomas in the Central Nervous System: a Multicenter Study of Korean Cases with Validation of the Usage of STAT6 Immunohistochemistry for Diagnosis of Disease. Annals of surgical oncology. 2016;23:954-961. Exclusion reason: Not intervention of interest

Choi JW, Kong DS, Seol HJ, et al. Outcomes of Gamma Knife Radiosurgery in Combination with Crizotinib for Patients with Brain Metastasis from Non-Small Cell Lung Cancer. World Neurosurgery. 2016;95:399-405. Exclusion reason: Sample size insufficient

Chung LK, Nguyen TP, Sheppard JP, et al. A Systematic Review of Radiosurgery Versus Surgery for Neurofibromatosis Type 2 Vestibular Schwannomas. World Neurosurgery. 2018;109:47-58. Exclusion reason: Not appropriate comparator

Churilla TM, Chowdhury I, Handorf E, et al. Comparison of local control of brain metastasis with stereotactic radiosurgery versus surgical resection: a secondary analysis of EORTC 22952-26001. International journal of radiation oncology biology physics. 2017;Conference: 59th annual meeting of the American Society for Radiation Oncology, ASTRO. 2017. United States 99(2 Supplement 1):S158-S159. Exclusion reason: Publication type

Conde-Moreno AJ, Herrando-Parreno G, Muelas-Soria R, et al. Whole-body diffusion-weighted magnetic resonance imaging (WB-DW-MRI) vs choline-positron emission tomography-

computed tomography (choline-PET/CT) for selecting treatments in recurrent prostate cancer. Clinical & translational oncology. 2017;19(5):553-561. Exclusion reason: Not intervention of interest

Cozzarini C, Noris Chiorda B, Sini C, et al. Hematologic Toxicity in Patients Treated With Postprostatectomy Whole-Pelvis Irradiation With Different Intensity Modulated Radiation Therapy Techniques Is Not Negligible and Is Prolonged: Preliminary Results of a Longitudinal, Observational Study. International Journal of Radiation Oncology, Biology, Physics. 2016;95(2):690-695. Exclusion reason: Not intervention of interest

Cui Y, Song J, Pollom E, et al. Quantitative Analysis of (18)F-Fluorodeoxyglucose Positron Emission Tomography Identifies Novel Prognostic Imaging Biomarkers in Locally Advanced Pancreatic Cancer Patients Treated With Stereotactic Body Radiation Therapy. International Journal of Radiation Oncology, Biology, Physics. 2016;96(1):102-109. Exclusion reason: Not intervention of interest

Da Silva I, Johnpulle RAN, Banks PD, et al. Incidence, features and management of radionecrosis (RN) in melanoma patients (pts) treated with cerebral radiotherapy (RT) and anti-PD-1 antibodies (PD1). Journal of clinical oncology Conference. 2017;35(15 Supplement 1). Exclusion reason: Not intervention of interest

Dabestani S, Marconi L, Bex A. Metastasis therapies for renal cancer. Current Opinion in Urology. 2016;26(6):566-572. Exclusion reason: Publication type

Dautruche A, Bolle S, Feuvret L, et al. Three-year results after radiotherapy for locally advanced sinonasal adenoid cystic carcinoma, using highly conformational radiotherapy techniques proton therapy and/or Tomotherapy. Cancer Radiotherapie. 2018;22(5):411-416. Exclusion reason: Sample size insufficient

De Ruysscher D, Faivre-Finn C, Moeller D, et al. European Organization for Research and Treatment of Cancer (EORTC) recommendations for planning and delivery of high-dose, high precision radiotherapy for lung cancer. Radiotherapy & Oncology. 2017;124(1):1-10. Exclusion reason: Publication type

Dess RT, Hartman HE, Soni PD, et al. Erectile function after stereotactic body radiation therapy for prostate cancer: a validated model-based comparison to nerve-sparing prostatectomy, conventional radiation therapy, and brachytherapy. International journal of radiation oncology biology physics. 2017;Conference: 59th annual meeting of the American Society for Radiation Oncology, ASTRO. 2017. United States 99(2 Supplement 1):E228. Exclusion reason: Publication type

Dohm A, McTyre ER, Chan MD, et al. Early or late radiotherapy following gross or subtotal resection for atypical meningiomas: Clinical outcomes and local control. Journal of Clinical Neuroscience. 2017;46:90-98. Exclusion reason: Not intervention of interest

Dong M, Liu J, Sun X, Xing L. Prognositc significance of SUV_{max} on pretreatment ¹⁸ F-FDG PET/CT in early-stage non-small cell lung cancer treated with stereotactic body radiotherapy: A meta-analysis. Journal of Medical Imaging & Radiation Oncology. 2017;61(5):652-659. Exclusion reason: Not appropriate comparator

De Goeje PL, Smit EF, Waasdorp C, et al. Stereotactic Ablative Radiotherapy Induces Peripheral T-Cell Activation in Patients with Early-Stage Lung Cancer. American Journal of Respiratory & Critical Care Medicine. 2017;196(9):1224-1227. Exclusion reason: Publication type

Ehlken C, Bohringer D, Agostini HT, Grundel B, Stech M. Potential selection bias in candidates for stereotactic radiotherapy for neovascular AMD. Graefe's archive for clinical and experimental ophthalmology. 2017. Exclusion reason: Not appropriate comparator

Eichorn D, Ali U, Lesenskyj A, et al. Retrospective analysis to determine the frequency of symptomatic new brain metastases during routine MRI surveillance post-SRS or-WBRT. Neuro oncology Conference: 21st annual scientific meeting and education day of the society for neuro oncology United States Conference start. 2016;18. Exclusion reason: Publication type

Elamin Y, Gomez DR, Papadimitrakopoulou V, et al. Local consolidation therapy (LCT) after first line tyrosine kinase inhibitor (TKI) for patients with EGFR mutant metastatic non-small cell lung cancer (NSCLC). Journal of clinical oncology Conference. 2017;35(15 Supplement 1). Exclusion reason: Publication type

Ellsworth SG, Rabatic BM, Chen J, et al. Principal component analysis identifies patterns of cytokine expression in non-small cell lung cancer patients undergoing definitive radiation therapy. PLoS ONE [Electronic Resource]. 2017;12(9):e0183239. Exclusion reason: No outcome of interest

Fenske DC, Price GL, Hess LM, John WJ, Kim ES. Systematic Review of Brain Metastases in Patients With Non-Small-Cell Lung Cancer in the United States, European Union, and Japan. Clinical Lung Cancer. 2017;18(6):607-614. Exclusion reason: No outcome of interest

Fetcko K, Lukas RV, Watson GA, Zhang L, Dey M. Survival and complications of stereotactic radiosurgery: A systematic review of stereotactic radiosurgery for newly diagnosed and recurrent high-grade gliomas. Medicine. 2017;96(43):e8293. Exclusion reason: Not appropriate comparator

Fietkau R. When is a nonsurgical approach possible for metastatic primary tumors and lymph node metastases of the urinary bladder and prostate? Der urologe. 2017. Exclusion reason: Not in English

Foley RW, Maweni RM, Jaafar H, McConn Walsh R, Javadpour M, Rawluk D. The Impact of Primary Treatment Strategy on the Quality of Life in Patients with Vestibular Schwannoma. World Neurosurgery. 2017;102:111-116. Exclusion reason: Outcome data cannot be abstracted

Frelinghuysen MD, Pignol JP, Nuyttens J. Linear accelerator or robotic sbrt for peripheral inoperable stage i non-small cell lung cancer: a cost-effectiveness analysis. International journal of radiation oncology biology physics. 2017;Conference: 59th annual meeting of the American Society for Radiation Oncology, ASTRO. 2017. United States 99(2 Supplement 1):E395-E396. Exclusion reason: Publication type

Fuentes R, Osorio D, Exposito Hernandez J, Simancas-Racines D, Martinez-Zapata JM, Bonfill Cosp X. Surgery versus stereotactic radiotherapy for people with single or solitary brain metastasis. Cochrane Database of Systematic Reviews. 2018(8). Exclusion reason: Systematic review of older/included studies

Furdova A, Sramka M, Chorvath M, Kralik G, Furda R, Gregus M. Clinical experience of stereotactic radiosurgery at a linear accelerator for intraocular melanoma. Melanoma Research. 2017;27(5):463-468. Exclusion reason: Not appropriate comparator

Fusco V, Parisi S, Andrea B, et al. Role of radiotherapy in the treatment of renal cell cancer: updated and critical review. Tumori. 2017;103(6):504-510. Exclusion reason: Publication type

George R, Sundararaj JJ, Govindaraj R, Chacko AG, Tharyan P. Interventions for the treatment of metastatic extradural spinal cord compression in adults. Cochrane Database of Systematic Reviews. 2018(7). Exclusion reason: Not intervention of interest

Goda J, Krishna U, Dutta D, et al. High precision stereotactic conformal radiotherapy (SCRT) improves the long term functional outcome in children and adolescent patients of craniopharyngioma: data from a prospective randomized trial. Neuro-oncology. 2018;Conference: 18th international symposium on pediatric neuro-oncology, ISPNO. 2018. United States 20(Supplement 2):i43. Exclusion reason: Publication type

Gonzalez-Motta A, Roach M. Stereotactic body radiation therapy (SBRT) for high-risk prostate cancer: Where are we now? Practical Radiation Oncology. 2018;8(3):185-202. Exclusion reason: Not appropriate comparator

Greco C, Pares O, Pimentel N, et al. Acute toxicity following single-dose radiation therapy in the management of intermediate risk prostate cancer: results from a phase 2 randomized trial. International journal of radiation oncology biology physics. 2017;Conference: 59th annual meeting of the American Society for Radiation Oncology, ASTRO. 2017. United States 99(2 Supplement 1):E236. Exclusion reason: Sample size insufficient

Groot VP, van Santvoort HC, Rombouts SJ, et al. Systematic review on the treatment of isolated local recurrence of pancreatic cancer after surgery; re-resection, chemoradiotherapy and SBRT. HPB. 2017;19(2):83-92. Exclusion reason: Not appropriate comparator

Grubb CS, Jani A, Wu CC, et al. Breast cancer subtype as a predictor for outcomes and control in the setting of brain metastases treated with stereotactic radiosurgery. Journal of Neuro-Oncology. 2016;127(1):103-110. Exclusion reason: Not appropriate comparator

Halasz LM, Uno H, Punglia RS. Reply to comparative effectiveness of stereotactic radiosurgery versus whole-brain radiation therapy for patients with brain metastases from breast or non-small cell lung cancer. Cancer. 2016;122(20):3244-3245. Exclusion reason: Publication type

Halpern JA, Sedrakyan A, Hsu WC, et al. Use, complications, and costs of stereotactic body radiotherapy for localized prostate cancer. Cancer. 2016;122(16):2496-2504. Exclusion reason: Included in a systematic review

Halvorsen PH, Cirino E, Das IJ, et al. AAPM-RSS Medical Physics Practice Guideline 9.a. for SRS-SBRT. Journal of Applied Clinical Medical Physics. 2017;18(5):10-21. Exclusion reason: Publication type

Hatiboglu MA, Tuzgen S, Akdur K, Chang EL. Treatment of high numbers of brain metastases with Gamma Knife radiosurgery: a review. Acta Neurochirurgica. 2016;158(4):625-634. Exclusion reason: Publication type

Helouc J, Morton G, Bezjak A, et al. A comparative study of quality of life in patients with low- and intermediate-risk prostate cancer: stereotactic radiotherapy vs. high dose-rate brachytherapy monotherapy vs. high dose-rate brachytherapy boost. Brachytherapy. 2018; Conference: American Brachytherapy Society annual meeting, ABS 2018. United States 17(4 Supplement 1):S57. Exclusion reason: Publication type

Henke L, Kashani R, Robinson C, et al. Phase I trial of stereotactic MR-guided online adaptive radiation therapy (SMART) for the treatment of oligometastatic or unresectable primary malignancies of the abdomen. Radiotherapy & Oncology. 2018;126(3):519-526. Exclusion reason: Not appropriate comparator

Hernandez-Duran S, Hanft S, Komotar RJ, Manzano GR. The role of stereotactic radiosurgery in the treatment of intramedullary spinal cord neoplasms: a systematic literature review. Neurosurgical Review. 2016;39(2):175-183; discussion 183. Exclusion reason: Not appropriate comparator

Huang CM, Huang MY, Tsai HL, et al. A retrospective comparison of outcome and toxicity of preoperative image-guided intensity-modulated radiotherapy versus conventional pelvic radiotherapy for locally advanced rectal carcinoma. Journal of Radiation Research. 2017;58(2):247-259. Exclusion reason: Not intervention of interest

Husain ZA, Sahgal A, De Salles A, et al. Stereotactic body radiotherapy for de novo spinal metastases: systematic review. Journal of Neurosurgery Spine. 2017;27(3):295-302. Exclusion reason: Not appropriate comparator

Ishihara T, Yamada K, Harada A, et al. Hypofractionated stereotactic radiotherapy for brain metastases from lung cancer: Evaluation of indications and predictors of local control. Strahlentherapie und Onkologie. 2016;192(6):386-393. Exclusion reason: Not appropriate comparator

Iyengar P, Tumati V, Gerber D, et al. Consolidative radiotherapy for limited metastatic nonesmall cell lung cancer: a randomized phase 2 trial. International journal of radiation oncology biology physics. 2017;Conference: 59th annual meeting of the American Society for Radiation Oncology, ASTRO. 2017. United States 99(5):1314. Exclusion reason: Sample size insufficient

Iyengar P, Wardak Z, Gerber DE, et al. Consolidative radiotherapy for limited metastatic non-small-cell lung cancer: a phase 2 randomized clinical trial. JAMA oncology. 2018;4(1). Exclusion reason: Sample size insufficient

Jacobs BL, Yabes JG, Lopa SH, et al. The early adoption of intensity-modulated radiotherapy and stereotactic body radiation treatment among older Medicare beneficiaries with prostate cancer. Cancer. 2017;123(15):2945-2954. Exclusion reason: No outcome of interest

Johnson SB, Stahl JM, Miccio JA, Kann BH, Kelly JR, Decker R. Stereotactic body radiation and adjuvant chemotherapy versus surgery and adjuvant chemotherapy for T1-2N0 small cell lung cancer. International journal of radiation oncology biology physics. 2018;Conference: 100th annual meeting of the American radium society. United States. 101(2 Supplement 1):E3. Exclusion reason: Publication type

Joseph K, Abdulkarim B, Vos L, et al. A phase III randomized control trial comparing skin sparing helical tomotherapy to 3D-conformal radiotherapy for adjuvant radiotherapy of early stage breast cancer. Radiotherapy and oncology Conference: CARO. 2016;120. Exclusion reason: Publication type

Jouglar E, Wagner A, Delpon G, et al. Can We Spare the Pancreas and Other Abdominal Organs at Risk? A Comparison of Conformal Radiotherapy, Helical Tomotherapy and Proton Beam Therapy in Pediatric Irradiation. PLoS ONE [Electronic Resource]. 2016;11(10):e0164643. Exclusion reason: Not intervention of interest

Kaidar-Person O, Zagar TM, Ewend M, Tzuk-Shina T, Marks LB. Frameless LINAC-based stereotactic radiation therapy to brain metastasis resection cavity without whole-brain radiation therapy: A systematic review. Practical Radiation Oncology. 2016;6(5):324-330. Exclusion reason: Not appropriate comparator

Kepka L, Tyc-Szczepaniak D, Osowiecka K, et al. Quality of life: result from a randomized trial that compared WBRT with radiosurgery of tumor cavity. Radiotherapy and oncology Conference. 2017;123:S327-S328. Exclusion reason: Publication type

Khoo V, Ahmed M, McDonald F, et al. CORE: a randomised trial of COnventional care versus Radioablation (stereotactic body radiotherapy) for Extracranial oligometastases. Lung cancer. 2017;Conference: 15th annual british thoracic oncology group conference, BTOG. 2017. Ireland 103(Supplement 1):S55-S56. Exclusion reason: Publication type

Kim H, Rajagopalan MS, Beriwal S, Smith KJ. Cost-effectiveness Analysis of Stereotactic Radiosurgery Alone Versus Stereotactic Radiosurgery with Upfront Whole Brain Radiation Therapy for Brain Metastases. Clinical oncology. 2017;07. Exclusion reason: Not appropriate comparator

Kirichenko V, Thai NV, Parda DS. Stereotactic body radiation therapy (SBRT) versus radiofrequency ablation (RFA) for unresectable colorectal cancer hepatic metastases: a cost-effectiveness analysis. International journal of radiation oncology. 2016;Conference: 58th annual meeting of the American Society for Radiation Oncology, ASTRO. 2016. United States 96(2 Supplement 1):S163. Exclusion reason: Publication type

Kobiela J, Spychalski P, Marvaso G, et al. Ablative stereotactic radiotherapy for oligometastatic colorectal cancer: Systematic review. Critical Reviews in Oncology-Hematology. 2018;129:91-101. Exclusion reason: Not appropriate comparator

Koffer PP, Savir G, Rava PS, et al. Local control and toxicity in single-fraction and fractionated stereotactic radiosurgery in the treatment of brain metastases: a case-matched analysis. International journal of radiation oncology. 2016;Conference: 58th annual meeting of the American Society for Radiation Oncology, ASTRO. 2016. United States 96(2 Supplement 1):E99. Exclusion reason: Not appropriate comparator

Kong FM, Zang Y, Pi W, et al. Stereotactic body radiation therapy to generate comparable survival to surgery in treating hepatocellular carcinoma (HCC): results of 756 patients. Journal of clinical oncology Conference. 2017;35(15 Supplement 1). Exclusion reason: Publication type

Kougioumtzopoulou A, Zygogianni A, Liakouli Z, Kypraiou E, Kouloulias V. The role of radiotherapy in bone metastases: A critical review of current literature. European Journal of Cancer Care. 2017;26(6). Exclusion reason: Not appropriate comparator

Krug D, Koder C, Hafner MF, et al. Acute toxicity of intensity-modulated radiotherapy with simultaneous integrated boost compared to 3D-conformal radiotherapy with sequential boost in the adjuvant treatment of breast cancer - Interim results from a randomized controlled trial. Strahlentherapie und onkologie. 2016;Conference: 22. Jahrestagung der deutschen gesellschaft fur radioonkologie, DEGRO. 2016. Germany 192(1 Supplement 1):31. Exclusion reason: Not intervention of interest

Kwint M, Walraven I, Burgers S, et al. Outcome of radical local treatment of non-small cell lung cancer patients with synchronous oligometastases. Lung Cancer. 2017;112:134-139. Exclusion reason: Not appropriate comparator

Lamba N, Muskens IS, DiRisio AC, et al. Stereotactic radiosurgery versus whole-brain radiotherapy after intracranial metastasis resection: a systematic review and meta-analysis. Radiation Oncology. 2017;12(1):106. Exclusion reason: Not appropriate comparator

Lancellotta V, Iacco M, Perrucci E, et al. Comparing four radiotherapy techniques for treating the chest wall plus levels III-IV draining nodes after breast reconstruction. British Journal of Radiology. 2018;91(1086):20160874. Exclusion reason: No outcome of interest

Lee K, Kim HR, Kim DK, et al. Post-recurrence survival analysis of stage I non-small-cell lung cancer. Asian Cardiovascular & Thoracic Annals. 2017;25(9):623-629. Exclusion reason: Not intervention of interest

Lester-Coll NH, Dosoretz AP, Magnuson WJ, Laurans MS, Chiang VL, Yu JB. Cost-effectiveness of stereotactic radiosurgery versus whole-brain radiation therapy for up to 10 brain metastases. Journal of Neurosurgery. 2016;125(Suppl 1):18-25. Exclusion reason: Not appropriate comparator

Lester-Coll NH, Rutter CE, Bledsoe TJ, Goldberg SB, Decker RH, Yu JB. Cost-effectiveness of surgery, stereotactic body radiation therapy, and systemic therapy for pulmonary oligometastases. International journal of radiation oncology biology physics. 2016;95(2):663-672. Exclusion reason: Included in a systematic review

Leung HW, Chan AL, Muo CH. Cost-effectiveness of Gemcitabine Plus Modern Radiotherapy in Locally Advanced Pancreatic Cancer. Clinical Therapeutics. 2016;38(5):1174-1183. Exclusion reason: Included in a systematic review

Leung HW, Liu CF, Chan AL. Cost-effectiveness of sorafenib versus SBRT for unresectable advanced hepatocellular carcinoma. Radiation Oncology. 2016;11:69. Exclusion reason: Included in a systematic review

Lin N. Spinal metastases: a comparison of stereotactic body radiotherapy (SBRT) and conventional radiotherapy. Journal of medical radiation sciences Conference: 12th annual scientific meeting of medical imaging and radiation therapy Australia. 2017;64(89). Exclusion reason: Publication type

Lin Q, Chen W, Sun X, et al. A propensity matched analysis of stereotactic body radiation therapy and sublobar resection for stage i non-small cell lung cancer in patients at high risk for lobectomy. International journal of radiation oncology biology physics. 2017;Conference: 59th annual meeting of the American Society for Radiation Oncology, ASTRO. 2017. United States 99(2 Supplement 1):E505. Exclusion reason: Publication type

Linney H, Barrett S. Stereotactic Body Radiation Therapy for Patients with Early-stage Prostate Cancer. Anticancer Research. 2018;38(3):1231-1240. Exclusion reason: Systematic review of older/included studies

Louie A, Chen H, Werkhoven EV, et al. Caro elekta quality of life following stereotactic ablative radiotherapy for early stage lung cancer: results from the ROSEL randomized controlled trial and a systematic review. Radiotherapy and oncology Conference: CARO. 2016;120:S57-S58. Exclusion reason: Publication type

Magnuson WJ, Amini A, Patil T, et al. Deferring radiation therapy for brain metastases in patients with EGFR-mutant non-small cell lung cancer: a multi-institutional analysis. International journal of radiation oncology. 2016;Conference: 58th annual meeting of the American Society for Radiation Oncology, ASTRO. 2016. United States 96(2 Supplement 1):S57-S58. Exclusion reason: Publication type

Mahajan A, Ahmed S, Li J, et al. Postoperative stereotactic radiosurgery versus observation for completely resected brain metastases: results of a prospective randomized study. International journal of radiation oncology. 2016;Conference: 58th annual meeting of the American Society for Radiation Oncology, ASTRO. 2016. United States 96(2 Supplement 1):S2. Exclusion reason: Publication type

Mbeutcha A, Chauveinc L, Bondiau PY, et al. Salvage prostate re-irradiation using high-dose-rate brachytherapy or focal stereotactic body radiotherapy for local recurrence after definitive radiation therapy. Radiation Oncology. 2017;12(1):49. Exclusion reason: Sample size insufficient

Mendez LC, Leung E, Cheung P, Barbera L. The Role of Stereotactic Ablative Body Radiotherapy in Gynaecological Cancers: A Systematic Review. Clinical Oncology (Royal College of Radiologists). 2017;29(6):378-384. Exclusion reason: Not appropriate comparator

Miao CW, Hu XD, Yu JM. Clinical application of helical tomotherapy in thoracic tumor. Chinese journal of cancer prevention and treatment. 2016;23(18):1268-1271 and 1276. Exclusion reason: Not in English

Miller JA, Balagamwala EH, Angelov L, et al. Spine stereotactic radiosurgery with concurrent tyrosine kinase inhibitors for metastatic renal cell carcinoma. Journal of Neurosurgery Spine. 2016;25(6):766-774. Exclusion reason: Not appropriate comparator

Miller JA, Kotecha R, Ahluwalia MS, et al. Overall survival and the response to radiotherapy among molecular subtypes of breast cancer brain metastases treated with targeted therapies. Cancer. 2017;123(12):2283-2293. Exclusion reason: Not appropriate comparator

Miller JA, Kotecha R, Suh JH. Comparative effectiveness of stereotactic radiosurgery versus whole-brain radiation therapy for patients with brain metastases from breast or non-small cell lung cancer. Cancer. 2016;122(20):3243-3244. Exclusion reason: Publication type

Minniti G, Paolini S, D'Andrea G, et al. Outcomes of postoperative stereotactic radiosurgery to the resection cavity versus stereotactic radiosurgery alone for melanoma brain metastases. Journal of Neuro-Oncology. 2017;132(3):455-462. Exclusion reason: Not appropriate comparator

Morrison J, Hood R, Yin FF, Salama JK, Kirkpatrick J, Adamson J. Is a single isocenter sufficient for volumetric modulated arc therapy radiosurgery when multiple itracranial metastases are spatially dispersed? Medical Dosimetry. 2016;41(4):285-289. Exclusion reason: Not intervention of interest

Murakami Y, Nakano M, Yoshida M, et al. Possibility of chest wall dose reduction using volumetric-modulated arc therapy (VMAT) in radiation-induced rib fracture cases: comparison with stereotactic body radiation therapy (SBRT). Journal of Radiation Research. 2018;59(3):327-332. Exclusion reason: No outcome of interest

Murray LJ, Lilley J, Hawkins MA, Henry AM, Dickinson P, Sebag-Montefiore D. Pelvic re-irradiation using stereotactic ablative radiotherapy (SABR): A systematic review. Radiotherapy & Oncology. 2017;125(2):213-222. Exclusion reason: Not appropriate comparator

Mutsaers A, Greenspoon J, Walker-Dilks C, Swaminath A. Systematic review of patient reported quality of life following stereotactic ablative radiotherapy for primary and metastatic liver cancer. Radiation Oncology. 2017;12(1):110. Exclusion reason: Not appropriate comparator

Myrehaug S, Sahgal A, Hayashi M, et al. Reirradiation spine stereotactic body radiation therapy for spinal metastases: systematic review. Journal of Neurosurgery Spine. 2017;27(4):428-435. Exclusion reason: Not appropriate comparator

Nadolski G, Kalbasi A, Soulen M, et al. Interim analysis of pilot randomized trial of transarterial chemoembolization with or without stereotactic body radiation therapy for hepatocellular carcinoma patients awaiting liver transplantation. Journal of vascular and interventional radiology. 2018;Conference: 43rd annual scientific meeting of the society of interventional radiology, SIR. 2018. United States 29(4 Supplement 1):S21-S22. Exclusion reason: Publication type

Nantavithya C, Gomez DR, Wei X, et al. Phase 2 Study of Stereotactic Body Radiation Therapy and Stereotactic Body Proton Therapy for High-Risk, Medically Inoperable, Early-Stage Non-Small Cell Lung Cancer. International journal of radiation oncology biology physics. 2018(pagination). Exclusion reason: Sample size insufficient

Navarria P, Ascolese A, Cozzi L, et al. Randomized double arm phase III study to evaluate feasibility and safety of gamma knife radiosurgery versus linac based (edge) radiosurgery in brain metastatic patients. Neuro oncology Conference: 12th meeting of the European Association of Neuro Oncology Germany Conference start. 2016;18. Exclusion reason: Publication type

Neubauer AS, Reznicek L, Minartz C, Ziemssen F. Economic Short-Term Cost Model for Stereotactic Radiotherapy of Neovascular AMD. Klinische monatsblatter fur augenheilkunde. 2016;233(8):951-957. Exclusion reason: Not appropriate comparator

Ng SP, Wang H, Fuller C, et al. Patient outcomes after re-irradiation of small skull base tumours using stereotactic body radiotherapy (SBRT), intensity modulated radiotherapy (IMRT) or proton therapy (PRT). Journal of medical imaging and radiation oncology. 2017;Conference: 68th annual scientific meeting of the Royal Australian and New Zealand College of Radiologists, RANZCR. 2017. Australia 61(Supplement 1):118. Exclusion reason: Publication type

Ng SP, Wang H, Fuller CD, et al. Reirradiation of small skull base tumors: a comparison of patient outcomes after stereotactic body radiotherapy, intensity-modulated radiotherapy, and proton therapy. Journal of neurological surgery, part B: skull base Conference: 28th annual meeting north american skull base society United States. 2018;79(Supplement 1). Exclusion reason: Publication type

Nguyen NP, Godinez J, Shen W, et al. Is surgery indicated for elderly patients with early stage nonsmall cell lung cancer, in the era of stereotactic body radiotherapy? Medicine. 2016;95(43):e5212. Exclusion reason: Publication type

Niibe Y, Nishimura T, Inoue T, et al. Oligo-recurrence predicts favorable prognosis of brain-only oligometastases in patients with non-small cell lung cancer treated with stereotactic radiosurgery or stereotactic radiotherapy: a multi-institutional study of 61 subjects. BMC Cancer. 2016;16(1):659. Exclusion reason: Not appropriate comparator

Nozawa H, Ishihara S, Kawai K, et al. Brain Metastasis from Colorectal Cancer: Predictors and Treatment Outcomes. Oncology. 2017;93(5):309-314. Exclusion reason: Outcome data cannot be abstracted

Oliver A. Stereotactic body radiation therapy versus conventional radiation therapy techniques for prostate cancer. Journal of medical radiation sciences. 2018;Conference: 13th national conference of the australian society of medical imaging and radiation therapy's, ASMIRT. 2018. Australia 65(Supplement 1):116. Exclusion reason: Publication type

Oskan F, Becker G, Bleif M. Specific toxicity after stereotactic body radiation therapy to the central chest: a comprehensive review. Strahlentherapie und Onkologie. 2017;193(3):173-184. Exclusion reason: Systematic review of older/included studies

Ost P, Reynders D, Decaestecker K, et al. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: a prospective, randomized, multicenter phase II trial. Journal of clinical oncology. 2018;36(5):446-453. Exclusion reason: Not intervention of interest

Padmanabhan R, Pinkawa M, Song DY. Hydrogel spacers in prostate radiotherapy: a promising approach to decrease rectal toxicity. Future Oncology. 2017;13(29):2697-2708. Exclusion reason: Not intervention of interest

Panje C, Andratschke N, Brunner TB, Niyazi M, Guckenberger M. Stereotactic body radiotherapy for renal cell cancer and pancreatic cancer: literature review and practice recommendations of

the DEGRO Working Group on Stereotactic Radiotherapy. Strahlentherapie und onkologie. 2016;192(12):875-885. Exclusion reason: Not appropriate comparator

Patil CG, Pricola K, Sarmiento JM, Garg SK, Bryant A, Black KL. Whole brain radiation therapy (WBRT) alone versus WBRT and radiosurgery for the treatment of brain metastases. Cochrane Database of Systematic Reviews. 2017;9:CD006121. Exclusion reason: Systematic review of older/included studies

Perrier L, Morelle M, Pommier P, et al. Cost Analysis of Complex Radiation Therapy for Patients With Head and Neck Cancer. International Journal of Radiation Oncology, Biology, Physics. 2016;95(2):654-662. Exclusion reason: Not intervention of interest

Pessina F, Navarria P, Cozzi L, et al. Outcome Evaluation of HER2 Breast Cancer Patients with Limited Brain Metastasis. Anticancer Research. 2017;37(12):7057-7062. Exclusion reason: Not appropriate comparator

Pessina F, Navarria P, Cozzi L, et al. Outcome appraisal of patients with limited brain metastases (BMs) from non small cell lung cancer (NSCLC) treated with different local therapeutic strategies: a single institute evaluation. British Journal of Radiology. 2017;90(1072):20170022. Exclusion reason: Outcome data cannot be abstracted

Petrelli F, Comito T, Ghidini A, Torri V, Scorsetti M, Barni S. Stereotactic Body Radiation Therapy for Locally Advanced Pancreatic Cancer: A Systematic Review and Pooled Analysis of 19 Trials. International Journal of Radiation Oncology, Biology, Physics. 2017;97(2):313-322. Exclusion reason: Not appropriate comparator

Phan VA, Le H, Singhal N, Nguyen N. Stereotactic ablative radiotherapy using EUS-guided fiducial placement for locally advanced pancreatic cancer: early experience in a tertiary center. Journal of gastroenterology and hepatology. 2017;Conference: Asian pacific digestive week, APDW. 2017. Hong Kong 32(Supplement 3):206. Exclusion reason: Publication type

Pillai A. Gamma Knife Surgery for Metastatic Brain Tumors from Gynecologic Cancer: Time for What Saves Time, Grants Time, and Is Tested By Time? World Neurosurgery. 2016;91:597-599. Exclusion reason: Publication type

Pokhrel D, Sood S, McClinton C, et al. Treatment planning strategy for whole-brain radiotherapy with hippocampal sparing and simultaneous integrated boost for multiple brain metastases using intensity-modulated arc therapy. Medical Dosimetry. 2016;41(4):315-322. Exclusion reason: Sample size insufficient

Pollard C, rd N, T. P N, et al. Clinical outcomes after local field conformal reirradiation of patients with retropharyngeal nodal metastasis. Head & Neck. 2017;39(10):2079-2087. Exclusion reason: Outcome data cannot be abstracted

Pollock BE, Link MJ, Stafford SL, Parney IF, Garces YI, Foote RL. The Risk of Radiation-Induced Tumors or Malignant Transformation After Single-Fraction Intracranial Radiosurgery: Results Based on a 25-Year Experience. International Journal of Radiation Oncology, Biology, Physics. 2017;97(5):919-923. Exclusion reason: Not appropriate comparator

Prins FM, Kerkmeijer LGW, Pronk AA, et al. Renal Cell Carcinoma: Alternative Nephron-Sparing Treatment Options for Small Renal Masses, a Systematic Review. Journal of Endourology. 2017;31(10):963-975. Exclusion reason: Not appropriate comparator

Qie S, Li Y, Shi HY, Yuan L, Su L, Zhang X. Stereotactic radiosurgery (SRS) alone versus whole brain radiotherapy plus SRS in patients with 1 to 4 brain metastases from non-small cell lung cancer stratified by the graded prognostic assessment: A meta-analysis (PRISMA) of randomized control trials. Medicine. 2018;97(33):e11777. Exclusion reason: Not appropriate comparator

Que JY, Lin LC, Lin CH, Lin KL, Lin YW, Yang CC. A preliminary analysis of robotic radiosurgery stereotactic body radiation therapy with or without sorafenib for hepatocellular carcinoma with portal vein tumor thrombosis. International journal of radiation oncology biology physics. 2017;Conference: 59th annual meeting of the American Society for Radiation Oncology, ASTRO. 2017. United States 99(2 Supplement 1):E180. Exclusion reason: Publication type

Rao G, Ahmed S, Hess K, Mahajan A. 215 Postoperative Stereotactic Radiosurgery vs Observation for Completely Resected Brain Metastases: results of a Prospective Randomized Study. Neurosurgery. 2016;63(Supplement 1):184. Exclusion reason: Publication type

Roman AA, Jodar C, Perez-Rozos A, Lupianez-Perez Y, Medina JA, Gomez-Millan J. The role of stereotactic body radiotherapy in reirradiation of head and neck cancer recurrence. Critical Reviews in Oncology-Hematology. 2018;122:194-201. Exclusion reason: Publication type

Samson P, Keogan K, Crabtree T, et al. Interpreting survival data from clinical trials of surgery versus stereotactic body radiation therapy in operable Stage I non-small cell lung cancer patients. Lung cancer. 2017;103:6-10. Exclusion reason: No outcome of interest

Santa Cruz O, Tsoutsou P, Castella C, et al. Locoregional Control and Toxicity in Head and Neck Carcinoma Patients following Helical Tomotherapy-Delivered Intensity-Modulated Radiation Therapy Compared with 3D-CRT Data. Oncology. 2018;95(2):61-68. Exclusion reason: Not appropriate comparator

Sapir E, Tao Y, Lin J, et al. Surgical resection or stereotactic body radiation therapy for sarcoma patients with pulmonary metastases. International journal of radiation oncology. 2016;Conference: 58th annual meeting of the American Society for Radiation Oncology, ASTRO. 2016. United States 96(2 Supplement 1):S26. Exclusion reason: Publication type

Sapir E, Tao Y, Schipper MJ, et al. Stereotactic Body Radiation Therapy as an Alternative to Transarterial Chemoembolization for Hepatocellular Carcinoma. International Journal of

Radiation Oncology, Biology, Physics. 2018;100(1):122-130. Exclusion reason: Not appropriate comparator

Sapisochin G, Goldaracena N, Laurence JM, et al. The extended Toronto criteria for liver transplantation in patients with hepatocellular carcinoma: a prospective validation study. Hepatology (baltimore, md). 2016;64(6):2077-2088. Exclusion reason: Not intervention of interest

Schulz D, Wirth M, Piontek G, et al. Improved overall survival in head and neck cancer patients after specific therapy of distant metastases. European Archives of Oto-Rhino-Laryngology. 2018;275(5):1239-1247. Exclusion reason: Outcome data cannot be abstracted

Schuster D, Sweeney AD, Stavas MJ, et al. Initial radiographic tumor control is similar following single or multi-fractionated stereotactic radiosurgery for jugular paragangliomas. American Journal of Otolaryngology. 2016;37(3):255-258. Exclusion reason: Sample size insufficient

Scorsetti M, Navarria P, Ascolese A, et al. Gammaknife versus linac based (EDGE) radiosurgery (SRS) for patients with limited brain metastases (BMS) from different solid tumor: a phase III randomized trial. Neuro-oncology. 2017;Conference: 5th quadrennial meeting of the world federation of neuro-oncology societies, WFNOS. Switzerland. 19(Supplement 3):iii5-iii6. Exclusion reason: Publication type

Shen CJ, Rigamonti D, Redmond KJ, Kummerlowe MN, Lim M, Kleinberg LR. The strategy of repeat stereotactic radiosurgery without whole brain radiation treatment for new brain metastases: Outcomes and implications for follow-up monitoring. Practical Radiation Oncology. 2016;6(6):409-416. Exclusion reason: Not appropriate comparator

Shaverdian N, Verruttipong D, Wang PC, et al. Exploring value from the patient's perspective between modern radiation therapy modalities for localized prostate cancer. Int J Radiat Oncol Biol Phys 2017;97(3):516-525. Exclusion reason: Not appropriate study design

Silva IL, Iskandarani M, Hotouras A, et al. A systematic review to assess the management of patients with cerebral metastases secondary to colorectal cancer. Techniques in Coloproctology. 2017;21(11):847-852. Exclusion reason: Systematic review of older/included studies

Sita TL, Petras KG, Wafford QE, Berendsen MA, Kruser TJ. Radiotherapy for cranial and brain metastases from prostate cancer: a systematic review. Journal of Neuro-Oncology. 2017;133(3):531-538. Exclusion reason: Not appropriate comparator

Siva S, Ellis RJ, Ponsky L, et al. Consensus statement from the International Radiosurgery Oncology Consortium for Kidney for primary renal cell carcinoma. Future Oncology. 2016;12(5):637-645. Exclusion reason: Publication type

Smith BW, Joseph JR, Saadeh YS, et al. Radiosurgery for Treatment of Renal Cell Metastases to Spine: A Systematic Review of the Literature. World Neurosurgery. 2018;109:e502-e509. Exclusion reason: Systematic review of older/included studies

Specht HM, Kessel KA, Oechsner M, Meyer B, Zimmer C, Combs SE. HFSRT of the resection cavity in patients with brain metastases. Strahlentherapie und Onkologie. 2016;192(6):368-376. Exclusion reason: Not appropriate comparator

Spina A, Boari N, Gagliardi F, Donofrio CA, Franzin A, Mortini P. The current role of Gamma Knife radiosurgery in the management of intracranial haemangiopericytoma. Acta Neurochirurgica. 2016;158(4):635-642. Exclusion reason: Not appropriate comparator

Steuber T, Sharma V, Decaestecker K, et al. Standard of care versus metastasis-directed therapy for nodal oligorecurrent prostate cancer following multimodality treatment: a case-control study. Journal of urology. 2017;Conference: 112th annual meeting of the American Urological Association, AUA. 2017. United States 197(4 Supplement 1):e717-e718. Exclusion reason: Publication type

Straube C, Scherb H, Gempt J, et al. Adjuvant stereotactic fractionated radiotherapy to the resection cavity in recurrent glioblastoma - the GlioCave study (NOA 17 - ARO 2016/3 - DKTK ROG trial). BMC cancer. 2018;18(1):15. Exclusion reason: Publication type

Tambas M, Agaoglu F, Iribas A, et al. Conventionally-fractionated VMAT vs. SBRT in prostate cancer: PSA kinetics, toxicity, quality of life. Radiotherapy and oncology Conference. 2016;119:S350-S351. Exclusion reason: Publication type

Tambas M, Agaoglu F, Iribas A, et al. Conventionally Fractionationed Volumetric Arc Therapy versus Hypofractionated Stereotactic Body Radiotherapy: Quality of Life, Side Effects, and Prostate-Specific Antigen Kinetics in Localized Prostate Cancer. Value in Health Regional Issues. 2016;10:91-99. Exclusion reason: Sample size insufficient

Taube S, Lazow SP, Yondorf M, et al. A matched-pair analysis of clinical outcomes of intracavitary cesium-131 brachytherapy versus stereotactic radiosurgery for resected brain metastases. International journal of radiation oncology. 2016;Conference: 58th annual meeting of the American Society for Radiation Oncology, ASTRO. 2016. United States 96(2 Supplement 1):E67. Exclusion reason: Publication type

Teng F, Tsien CI, Lawrence TS, Cao Y. Blood-tumor barrier opening changes in brain metastases from pre to one-month post radiation therapy. Radiotherapy & Oncology. 2017;125(1):89-93. Exclusion reason: No outcome of interest

Tian LX, Yu W, Li CL. Clinical research of gamma knife radiotherapy combined with yiqijieduxiaoliu decoction in patients with advanced hepatocellular carcinoma. Hepatology international. 2017;Conference: 26th annual conference of the asian pacific association for the

study of the liver, APASL. 2017. China 11(1 Supplement 1):S454. Exclusion reason: Publication type

Tran S, Jorcano S, Falco T, Lamanna G, Miralbell R, Zilli T. Oligorecurrent nodal prostate cancer: longterm results of an elective nodal irradiation approach. Radiotherapy and oncology Conference. 2017;123. Exclusion reason: Publication type

Trovo M, Furlan C, Polesel J, et al. Radical radiation therapy for oligometastatic breast cancer: results of a prospective phase II trial. Radiotherapy and oncology. 2017(pagination). Exclusion reason: Outcome data cannot be abstracted

Tsao MN, Xu W, Wong RK, et al. Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. Cochrane Database of Systematic Reviews. 2018;1:CD003869. Exclusion reason: Systematic review of older/included studies

Van Houtte P, Devriendt D. SBRT vs. WBRT. Journal of thoracic oncology. 2017;Conference: 18th world conference on lung cancer of the international association for the study of lung cancer, IASLC. 2017. Japan 12(11 Supplement 2):S1698-S1699. Exclusion reason: Publication type

Verbanck S, Hanon S, Schuermans D, et al. Mild Lung Restriction in Breast Cancer Patients After Hypofractionated and Conventional Radiation Therapy: a 3-Year Follow-Up. International journal of radiation oncology, biology, physics. 2016;95(3):937-945. Exclusion reason: Not intervention of interest

Verma V, Simone CB. Stereotactic body radiation therapy for metastases to the kidney in patients with non-small cell lung cancer: a new treatment paradigm for durable palliation. Annals of Palliative Medicine. 2017;6(2):96-103. Exclusion reason: Sample size insufficient

Waddle MR, Sio TT, Van Houten HK, et al. Photon and Proton Radiation Therapy Utilization in a Population of More Than 100 Million Commercially Insured Patients. International Journal of Radiation Oncology, Biology, Physics. 2017;99(5):1078-1082. Exclusion reason: No outcome of interest

Wang HH, Zhang CZ, Zhang BL, et al. Sublobar resection is associated with improved outcomes over radiotherapy in the management of high-risk elderly patients with Stage I non-small cell lung cancer: a systematic review and meta-analysis. Oncotarget. 2017;8(4):6033-6042. Exclusion reason: Systematic review of older/included studies

Wang YC, Li CC, Chien CR. Effectiveness of tomotherapy vs linear accelerator image-guided intensity-modulated radiotherapy for localized pharyngeal cancer treated with definitive concurrent chemoradiotherapy: a Taiwanese population-based propensity score-matched analysis. British Journal of Radiology. 2018;91(1086):20170947. Exclusion reason: Not intervention of interest

Warren B, Munoz-Schuffenegger P, Chan KKW, et al. Quantifying Health Utilities in Patients Undergoing Stereotactic Body Radiation Treatment for Liver Metastases for Use in Future Economic Evaluations. Clinical Oncology (Royal College of Radiologists). 2017;29(9):e141-e147. Exclusion reason: Not appropriate comparator

Weinberg U, Farber O, Bomzon Z, Giladi M, Kirson ED. 206TiP: METIS: a phase III study of radiosurgery with TTFields for 1-10 brain metastases from NSCLC. Journal of thoracic oncology. 2016;11(4):S146. Exclusion reason: Not intervention of interest

Wernicke AG, Yondorf MZ, Parashar B, et al. The cost-effectiveness of surgical resection and cesium-131 intraoperative brachytherapy versus surgical resection and stereotactic radiosurgery in the treatment of metastatic brain tumors. Journal of Neuro-Oncology. 2016;127(1):145-153. Exclusion reason: Included in a systematic review

Wilton L, Richardson M, Keats S, et al. Decreasing rectal dose in Prostate SBRT: an evaluation of two Rectal Displacement Devices (RDD). Journal of medical imaging and radiation oncology Conference: 67th annual scientific meeting of the Royal Australian and New Zealand College of Radiologists, RANZCR. 2016;60(49). Exclusion reason: Not intervention of interest

Wolf A, Donahue B, Silverman JS, Chachoua A, Lee JK, Kondziolka D. Stereotactic radiosurgery for focal leptomeningeal disease in patients with brain metastases. Journal of Neuro-Oncology. 2017;134(1):139-143. Exclusion reason: Not appropriate comparator

Xu Y, Chen W, Lin Q, et al. A propensity matched analysis of SBRT and sublobar resection for stage i non-small cell lung cancer in patients at high risk for lobectomy. Journal of thoracic oncology. 2017;Conference: 18th world conference on lung cancer of the international association for the study of lung cancer, IASLC. 2017. Japan 12(11 Supplement 2):S2336. Exclusion reason: Publication type

Zaorsky NG, Shaikh T, Murphy CT, et al. Comparison of outcomes and toxicities among radiation therapy treatment options for prostate cancer. Cancer Treatment Reviews. 2016;48:50-60. Exclusion reason: Systematic review of older/included studies

Zhong J, Ferris MJ, Switchenko J, et al. Postoperative stereotactic radiosurgery for resected brain metastases: A comparison of outcomes for large resection cavities. Practical Radiation Oncology. 2017;7(6):e419-e425. Exclusion reason: Not appropriate comparator

Zhou J, Yang B, Wang X, Jing Z. Comparison of the Effectiveness of Radiotherapy with Photons and Particles for Chordoma After Surgery: A Meta-Analysis. World Neurosurgery. 2018;117:46-53. Exclusion reason: Not appropriate comparator

Phase I/II trial evaluating carbon ion radiotherapy for salvaging treatment of locally recurrent nasopharyngeal carcinoma. Journal of cancer. 2016;7(7):774-783. Exclusion reason: Publication type

Stereotactic radiosurgery for treatment of brain metastases. Journal of oncology practice. 2016;12(8):703-712. Exclusion reason: Publication type

Quality of life following stereotactic ablative radiation therapy versus surgery for early-stage lung cancer: results from the rosel randomized controlled trial and a systematic review. International journal of radiation oncology. 2016;Conference: 58th Annual Meeting of the American Society for Radiation Oncology, ASTRO 2016. United States. 96(2 Supplement 1):S10-S11. Exclusion reason: Publication type

Clinical Trial Comparing Dose-intensified SBRT With Conventional Radiation Therapy for Spinal Metastases. Https://clinicaltrialsgov/show/nct02800551. 2016. Exclusion reason: Publication type

Cognitive Outcome After SRS or WBRT in Patients With Multiple Brain Metastases (CAR-Study B). Https://clinicaltrialsgov/show/nct02953717. 2016. Exclusion reason: Publication type

Phase II Trial of SBRT Compared With Conventional Radiotherapy for Oligometastatic Non-Small Cell Lung Cancer. Https://clinicaltrialsgov/show/nct02975609. 2016. Exclusion reason: Publication type

Correction to Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial (The Lancet Oncology (2017) 18 (1040-1048) (S147020451730414X), (10.1016/S1470-2045(17)30414-X)). Lancet oncology. 2017;18(8):e433. Exclusion reason: Publication type

2017 ASTRO Annual Meeting Late-Breaking Abstracts. International journal of radiation oncology biology physics Conference: 59th annual meeting of the American Society for Radiation Oncology, ASTRO. 2017;99(5). Exclusion reason: Publication type

Whole Brain Radiation Versus Stereotactic Radiation (SRS) in Patients With 5-20 Brain Metastases: a Phase III, Randomized Clinical Trial. Https://clinicaltrialsgov/show/nct03075072. 2017. Exclusion reason: Publication type

Effect of radiosurgery combined with temozolomide in the treatment of brain metastases of non-small cell lung cancer. Cancer research and clinic. 2018;30(1):17-22. Exclusion reason: Not in English

A Randomised Phase II Trial of Osimertinib With or Without SRS for EGFR Mutated NSCLC With Brain Metastases. Https://clinicaltrialsgov/show/nct03497767. 2018. Exclusion reason: Publication type