Health Technology Clinical Committee
Findings and Coverage Decision
Topic: **Positron Emission Tomography (PET) Scans for Lymphoma**
Meeting Date: **September 16th, 2011**
Final Adoption: **November 18th, 2011**

Number and Coverage Topic

20110916A – Positron Emission Tomography (PET) Scans for Lymphoma

HTCC Coverage Determination

Positron Emission Tomography (PET) scans for Lymphoma is a **covered benefit with conditions**

HTCC Reimbursement Determination

❖ Limitations of Coverage

- Positron Emission Tomography (PET) scans for Lymphoma is a covered benefit when the following conditions are met:
  - One scan for initial treatment planning;
  - Additional scans for restaging with clinical suspicion of disease progression or treatment failure subject to agency approval;
  - No coverage for routine surveillance

❖ Non-Covered Indicators

- N/A

❖ Agency Contact Information

Agency	Contact Phone Number
Labor and Industries	1-800-547-8367
Public Employees Health Plan	1-800-762-6004
Health and Recovery Services Administration	1-800-562-3022

Health Technology Background

The Positron Emission Tomography (PET) for Lymphoma was selected and published in December 2010 to undergo an evidence review process. The evidence based technology assessment report indicates that an estimated 74,000 US individuals will be diagnosed with lymphoma [about 65,500 non-Hodgkin lymphoma (NHL) and 8,500 Hodgkin lymphoma (HL)]. This makes NHL approximately eight times more frequent than HL.

Lymphoma is divided into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) based on the histological pattern of the malignancy. Hodgkin lymphoma is an uncommon malignancy involving lymph nodes and the lymphatic system. Two age ranges predominate — 15 to 30 years and over 55 years. Two types of Hodgkin lymphoma are identified — classic (CHL) (95%) and nodular lymphocyte-predominant (LPHL) (5%). Classic HL is further divided into four types — nodular sclerosis, mixed cellularity, lymphocyte depleted and lymphocyte rich. Non-Hodgkin lymphomas (NHL) are a heterogeneous group of lymphoproliferative malignancies originating in B-lymphocytes (80-85%), T-lymphocytes (15-20%) and natural killer lymphocytes (<1%). NHLs are separated into indolent, aggressive and highly aggressive categories based on their natural history. However, natural history of these lymphomas tends to correlate with histological cell type.

Positron emission tomography (PET) is a nuclear medicine diagnostic test that uses a positron emitting radioactive particle, currently fluorine-18 (^{18}F) as a radioactive tracer. For imaging of known or suspected cancer, ^{18}F is incorporated into a glucose molecule (^{18}FDG) and injected into the blood stream. ^{18}FDG preferentially accumulates in areas of high glucose metabolism including many cancer cells. Thus, areas of cancer are identified as areas of high radioactivity or “hot spots” on the scan image. The “hot spot” images from PET scanning have low spatial resolution so it may be difficult to determine the exact location of abnormal areas from the PET scan alone. As a result, in 2011 PET is usually performed on a combined PET-CT scanner where both the radioactive PET data and high spatial resolution CT data are recorded at the same time. This results in more precise localization of areas of abnormal glucose metabolism in the body. The claim for PET compared to other imaging methods such as MRI and CT is that uptake of ^{18}FDG by cancer cells is both more sensitive and specific for cancer than alterations in local anatomy and tissue properties that might be detected by MRI and CT. However, false negative PET scans can result from areas of cancer that may be too small or too metabolically inactive to accumulate enough ^{18}FDG to be detected by the PET scan. Alternatively, false positive PET scans can result from other causes of increased glucose metabolism such as hyperemia, infection, inflammation or tissue healing that may lead to abnormal accumulation of ^{18}FDG and then appear as “hot spots” on PET scans.

In July 2011, 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 Positron Emission Tomography (PET) for Lymphoma report is 80 pages.

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 September 16th, 2011, 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 Findings

Having considered the evidence based technology assessment report and the written and oral comments, the committee identified the following key factors and health outcomes, and evidence related to those health outcomes and key factors:

1. Evidence availability and technology features

The evidence based technology assessment report indicates:

- Positron emission tomography (PET) is a diagnostic imaging test using a positron emitting radioactive particle. In PET for cancer, the radioactive particle is currently ^{18}fluorine (^{18}F) which is incorporated into a glucose molecule ^{18}FDG. When injected into the blood stream, ^{18}FDG preferentially accumulates in areas of high glucose metabolism such as areas of active cancer. The PET scan produces areas of increased radioactivity (referred to as "hot spots") where cancer cells are metabolically active. Positron emission tomography is frequently performed after other imaging methods, such as CT or MRI, so it may not replace other imaging tests. In current practice, PET is normally performed on a fusion PET/CT scanner which produces PET "hot spot" data and CT anatomic data synchronously. The claim for PET is that the changes in glucose metabolism detected by PET are more sensitive and specific for presence of viable cancer than CT or MRI, which rely on changes in local anatomy and tissue properties.
- Lymphoma is a heterogeneous group of lympho-proliferative malignancies involving lymph nodes, bone marrow, spleen and other extra-lymphatic organs that affects approximately 74,000 individuals in the US annually. Lymphoma is divided into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). In turn, NHL is divided into many sub-types that are usually grouped into aggressive NHL (aNHL) and indolent NHL (iNHL).
- It is estimated that 74,000 US individuals will be diagnosed with lymphoma [about 65,500 non-Hodgkin lymphoma (NHL) and 8,500 Hodgkin lymphoma (HL)]. This makes NHL approximately eight times more frequent than HL. Depending on type and stage of lymphoma, five year survival rates are as high as 80 to 90%. Accurate information about diagnosis and staging is important for planning the most appropriate treatment strategy, response to treatment, and monitoring for recurrence. Histopathologic tissue examination is necessary for definitive diagnosis of HL or NHL. A patient's physical symptoms, palpation, biopsy, magnetic resonance imaging (MRI), computed tomography (CT), gallium, and positron emission tomography (PET and PET/CT) can be used to assess patients. Positron emission tomography and PET/CT (collectively PET) are increasingly performed to inform staging, restaging, and estimation of prognosis after treatment and surveillance for recurrence of cancer.
- Evidence included in the technology assessment review was obtained through a structured, systematic search of the medical literature; economic studies; and clinical guidelines. MEDLINE search retrieved 354 full citations from which 18 observational studies were included. Core source searched yielded 7 SRs and TAs, 3 cost or cost-effectiveness study designs and 6 clinical practice guidelines.
- The evidence based technology assessment report identified six expert treatment guidelines. CMS Decision Memo (2010): CMS did NOT issue a national coverage decision. CMS (2010) has a new PET framework:
    - Initial treatment strategy: NCD of one PET
    - Subsequent anti-tumor treatment strategy: left to local regional carriers to decide
    - Exception for lymphoma – cover all PET

- The committee also reviewed information provided by the state agencies, and public members; and heard comments from the evidence reviewer, clinical expert, HTA program, agency medical directors and the public.

2. Is the technology safe?

The committee discussed multiple key factors and health outcomes that were important for consideration in their overall decision on whether the technology is safe. Summary of committee considerations follows.

- The evidence based technology assessment report indicates that there is limited evidence on safety. Although, there is moderate radiation dose associated with each PET and PET/CT scan performed, lymphoma is a potentially lethal disease. Concern for the effects of radiation may be more important for younger patients and for repeated PET and CT studies during follow-up. The overall strength of evidence is low.
- The evidence based technology assessment report indicated that the Australia MSAC (2010) addressed the question of safety of PET. No evidence directly addressed safety of PET in lymphoma. Australia MSAC believed that data on safety for PET for other indications can be reasonably applied to PET for lymphoma. Australia MSAC concludes that PET for lymphoma is safe.
- The evidence based technology assessment report indicated that potential safety issues for PET would include contrast reactions, radiation dose levels and incidental findings. The radiopharmaceutical ^{18}FDG used for PET scanning is an analog of glucose. Intuitively, ^{18}FDG should be well tolerated as a glucose analog, and no contrast reactions have been noted for ^{18}FDG. Radiation dose from PET (and PET/CT) is significant. Radiation dose from PET is 10-30 mSv (approximately 300 chest x-ray equivalents). Dose from CT varies depending on whether the CT is a low-dose CT performed to anatomical correlation only or a standard CT. Dosage from standard CT is also 10-30 mSV (also equivalent to approximately 300 chest x-rays). Dosages from PET/CT must be added.

3. Is the technology effective?

The committee discussed multiple key factors and health outcomes that were important for consideration in their overall decision on whether the technology is effective. Summary of committee considerations follows.

- Screening and Diagnosis – the evidence based technology assessment report indicated that there is no evidence about the use of PET for either screening of asymptomatic patients or in making a diagnosis of lymphoma. The diagnosis of lymphoma always requires tissue sampling (biopsy) for histological diagnosis.
- Original Staging by PET (or PET/CT) Compared with Conventional Staging or as an Incremental Test to Conventional Staging –
    - *Hodgkin and Aggressive Non-Hodgkin Lymphoma (aNHL)*: the evidence based technology assessment report indicated that staging for HL and aNHL is normally performed after diagnosis and before primary treatment in order to determine the extent of disease. Staging is important because the detection of additional sites of HL or aNHL may alter both the stage and the planned treatment. The evidence based technology assessment reported that the Australian MSAC technology assessment *Positron Emission Tomography for Lymphoma* (2010) summarized four systematic reviews (Kwee, 2008; Facey, 2007; Pakos, 2005; Kirby, 2007) that address the use of PET for original staging. These systematic reviews evaluate PET compared to CT and/or to gallium scintigraphy. The Australian MSAC technology assessment also reviews two studies that evaluate PET as an incremental study to conventional staging. When

compared to CT or gallium, PET appears to consistently have higher sensitivity and specificity than CT or gallium for staging of HL and aNHL. The sensitivity for PET in detecting HL and aNHL at initial staging ranges from 88-100% compared to sensitivity for CT of 88% and for gallium of 20-93%. Specificity for PET ranges from 90-100% compared to 80% for the specificity of CT. The evidence based technology assessment reported indicated that no RCTs or other study designs were identified for original staging.

- *Indolent Non-Hodgkin Lymphoma (iNHL):* The evidence for PET staging is mixed. Positron emission tomography appears to detect additional disease compared to CT in a significant number of patients but also appears to miss disease detected by CT. The series by Fueger (2009) compared PET/CT to PET alone and CT alone and found that PET/CT performs better than either of the comparators. This is not surprising given the evidence from other series that PET and CT both detect disease missed by the other modality. The studies reported here did not clearly state the reference standard. This makes evaluation of the true sensitivity and specificity impossible. The quality of the case series is low and the overall strength of the evidence is low. The evidence for PET staging is mixed. Positron emission tomography appears to detect additional disease compared to CT in a significant number of patients but also appears to miss disease detected by CT. The series by Fueger (2009) compared PET/CT to PET alone and CT alone and found that PET/CT performs better than either of the comparators. This is not surprising given the evidence from other series that PET and CT both detect disease missed by the other modality. The studies reported here did not clearly state the reference standard. This makes evaluation of the true sensitivity and specificity impossible. The quality of the case series is low and the overall strength of the evidence is low. No RCTs were identified. Four case series report on accuracy of PET in original staging of iNHL. Fueger (2009) reported on 45 patients with iNHL who had PET/CT for original staging. Scott (2009) reported on 74 consecutive patients with iNHL who received PET after conventional staging; all 74 patients received PET and 16 patients also had gallium scans. Le Dortz (2010) retrospectively reviewed 45 patients with iNHL who underwent initial staging with CT and PET. Bodet-Milin (2010) retrospectively reviewed 45 patients with mantle cell lymphoma (iNHL) who underwent PET in addition to conventional scanning prior to treatment.

- Routine Staging after Primary Treatment – the evidence based technology assessment report indicated one scenario for staging after primary treatment is the “routine” evaluation of every patient to evaluate for persistent or non-responsive lymphoma. The evidence for diagnostic accuracy of PET for staging is mixed. Some of the evidence evaluates PET as a substitute for conventional staging and some as an incremental study added to conventional staging. The underlying studies mix HL and aNHL populations for which, on at least one study, PET has different accuracy. The studies often mix initial staging with staging after primary treatment. Positron emission tomography appears to have higher sensitivity and specificity than conventional staging for detection of sites of lymphoma. Positron emission tomography certainly identifies more sites than conventional imaging; this phenomenon is typical for “hot spot” imaging techniques which produce information for the entire body instead of just the areas chosen for imaging (e.g., CT of the chest, abdomen and pelvis). Additional sites identified by PET will include true positive and false positive results. PET appears to perform better for original staging than for staging after primary therapy.
  - The evidence based technology assessment report indicated that no RCTs were identified. One small, single center case series reported on PET for staging after primary treatment (Cerci, 2010).

- Evaluation of Residual Mass after Primary Treatment – the evidence based technology assessment report indicated no RCTs or other study designs were identified of residual mass after treatment. PET appears to have heterogeneous results in the evaluation of residual mass after completion of primary therapy. Both sensitivity and specificity have wide ranges of 40-100%. Facey (2007) concluded that PET has higher specificity than CT but similar sensitivity. In the evaluation of a residual mass, both sensitivity and specificity have a comparable bearing on further clinical management and sensitivities or specificities of 40% may not yield reliable information for changing treatment decisions. The three systematic reviews are all rated fair to good. The underlying studies are case reports and were noted by systematic review authors to have methodological flaws. Given the heterogeneous results, the strength of the evidence is low.
- Estimation of Prognosis after Primary Treatment – the evidence based technology assessment report indicated no RCTs or other study designs were identified. One systematic review based on two case series evaluates the ability of PET at the end of primary treatment to predict subsequent outcome. Positron emission tomography appears to have a reasonable sensitivity but heterogeneous specificity in two studies. It appears to outperform CT in predicting subsequent outcome. The evidence is based on two small case series and overall strength is considered low.
    - The evidence based technology assessment indicated that Australia MSAC (2010) reported two case series of 99 and 127 patients that evaluated the ability of PET to distinguish between “responders” and “non-responders”. These two case series compared PET results with 2-3 year progression-free survival (PFS).
- Estimation of Prognosis after Secondary Treatment – the evidence based technology assessment report No RCTs were identified. Three case series address the ability of PET to predict relapse or recurrence after salvage treatment (Moskowitz, 2010; Dodero, 2010 and Qiao, 2011). The statistics provided in the two systematic reviews and three case series make comparison difficult. It appears that PET has a lower sensitivity and specificity in predicting subsequent outcome after secondary treatment than after primary treatment. Likelihood ratios or hazard ratios of 3-4 and PPV and NPV of around 80% do not provide strong indication of subsequent outcome. As with estimation of prognosis after primary treatment, it is unclear if sensitivity, specificity and likelihood ratios values given here would alter subsequent management. Although the systematic review and case series are of moderate to good quality, the overall strength of the evidence is low.
    - The evidence based technology assessment report indicated two systematic reviews address the ability of PET to predict relapse or recurrence after salvage (secondary) treatment (Terasawa, 2010; Poulou, 2010).
- Surveillance of Asymptomatic Patients after Treatment – the evidence based technology assessment report indicated no systematic reviews or technology assessments that address PET in surveillance of patients without symptoms who are in remission after treatment for HL or aNHL. No RCTs were identified either. Five case series evaluate the value of PET during surveillance of patients with HL and aNHL in remission (Goldschmidt, 2011; Lee, 2010; Crocchiolo, 2009; Mocikova, 2010; and Petrausch, 2010). The evidence based technology assessment report indicated that the evidence for the use of PET for routine surveillance of patients in remission is consistent. Positron emission tomography performed on asymptomatic patients has a significant false positive rate. Clinical findings and original stage of HL or aNHL are good predictors of subsequent relapse or recurrence. Positron emission tomography does not appear to have a strong role in surveillance of asymptomatic patients. The evidence consists of five recent case series of poor to fair quality. The overall strength of the evidence is low.

- Monitoring of Response to Treatment during Treatment – the evidence based technology assessment report indicated that one systematic review and three case series investigated the ability of PET scan performed mid-cycle during primary treatment to predict subsequent outcome. Pooled sensitivity from Terasawa's meta-analysis was 81% for HL and 78% for aNHL; specificity was 97% for HL and 87% for aNHL. Results from the three case series are comparable. Results for PPV and NPV from the case series vary from study to study (one study evaluated HL and another aNHL). It is uncertain if the diagnostic efficacy results are strong enough to justify management changes in mid-treatment. The results are internally consistent and overall strength of evidence is considered moderate.
    - The evidence based technology assessment report indicated a systematic review by Terasawa (2009) which evaluated the ability of PET to predict disease progression or relapse when performed in mid-cycle of primary treatment for HL or aNHL.
- Estimation of Prognosis during or after Treatment – *Indolent Non-Hodgkin Lymphoma (iNHL):* the evidence based technology assessment report indicated that the evidence is limited to two small case series which suggest that PET findings are reasonably accurate in predicting early relapse of iNHL; a negative PET scan appears to be more valuable than a positive PET. The evidence is considered weak because of the small number of patients included in these case series, and the overall strength of evidence is low. No RCTs were identified.
- *Hodgkin and Aggressive Non-Hodgkin Lymphoma (aNHL)*: The evidence based technology assessment reported indicated no evidence was identified for the effect of PET on the reduction of other tests, patient survival or quality of life. There is limited evidence on changes in management. There is limited evidence on the effect of PET on patient management, quality of life or survival. The overall strength of evidence is considered low. *Indolent Non-Hodgkin Lymphoma (iNHL):* Positron emission tomography appears to have modest impact on clinical decision making. The evidence is based on one small case series and is considered of low strength. No RCTs were identified. Scott (2009) reported on change in management after PET staging in a case series of 74 patients with iNHL.

4. Special Populations?

- The evidence based technology assessment report indicated that no evidence on special populations was reported.

5. Is the technology cost-effective?

The committee discussed multiple key factors that were important for consideration in their overall decision on whether the technology has value and is cost-effective. Summary of committee considerations follows.

- The evidence based technology assessment report indicated that the evidence for costs of PET in lymphoma comes primarily from outside the United States. Several of the studies are valued in US dollars, but the medical delivery and payment systems are different than in the US. The evidence should therefore be interpreted with care. The cost data comes primarily from outside the US. The four studies identified use different cost assumptions. The savings from PET are small under any of the cost assumptions studied. The single US study found that routine surveillance imaging cost $100,000 and had an increased radiation dose of 147 mSv per recurrence detected. The overall strength of evidence is low.
- Australia MSAC (2010) identified no published studies that it considers relevant or of sufficient quality to include. The authors performed an economic analysis based on using PET in place of conventional methods for staging. Assuming PET is used, the Australia MSAC estimates a savings of Australian $150 (8%) per HL patient and Australian $210 for NHL.

- The evidence based technology assessment report identified no RCTs.

6. Medicare Decision and Expert Treatment Guidelines

Committee reviewed and discussed the expert guidelines as identified and reported in the technology assessment report.

- Centers for Medicare and Medicaid Services (CMS) – no NCD policy addressing children.
  - The evidence based technology assessment report indicated that in 2010, CMS issued a decision not to make a national coverage decision (NCD) for PET scanning in malignancies. This leaves ultimate coverage decisions on ^{18}FDG PET to local Medicare carriers. In the Decision Memo, CMS (2010) created a two-part framework for analysis of PET use in malignancies—initial treatment strategy and subsequent anti-tumor strategy.
    - For Initial Treatment Strategy, CMS will "nationally" cover lymphoma and other solid malignancies for one FDG PET study for determining the optimal location to perform an invasive biopsy and to determine stage of the tumor. Moreover, CMS allows local Medicare contractors to make local decisions for coverage of additional PET scans for therapeutic purposes related to initial treatment strategy.
    - For Subsequent Anti-tumor Treatment Strategy, lymphoma is considered separately from other malignancies. Positron emission tomography is covered "nationally" without exception.
- Guidelines – the evidence based technology assessment report identified a total of nine guidelines in the core source search, and no additional guidelines were identified in the MEDLINE search. Of the original nine guidelines, four were excluded because they did not address PET scanning. The remaining guidelines include one from the *International Harmonization Project in Lymphoma (IHPL)* and two each from the *National Comprehensive Cancer Network (NCCN)* and the *American College of Radiology (ACR)*. The guidelines from NCCN and ACR were rated as fair quality and the guideline from IHPL was rated as poor quality. Poor quality ratings are primarily the result of undisclosed literature search methods for cited literature and for potential conflicts of interest of authors.
  - The evidence based technology assessment report indicated that the NCCN (2011a; 2011b) guidelines recommend the use of PET for initial staging of HL and aNHL. The NCCN recommends PET for staging in iNHL as optional but potentially useful in iNHL that appears to be localized and if concern exists about histological transformation. The NCCN guidelines recommend PET for evaluation of residual mass after treatment. The NCCN and IHPL (Juweid, 2007) guidelines recommend use of PET after treatment to determine prognosis. The IHPL guideline states that PET should only be performed in mid-cycle of treatment *if the findings will alter management*. The ACR (2010, 2011) guidelines caution that *changes in treatment based on PET findings should only be performed as part of a clinical trial*. Guidelines from NCCN and ACR recommend against the use of PET for routine surveillance. The ACR guidelines add that PET may be helpful in surveillance patients with clinical findings suspicious for relapse.
  - The evidence based technology assessment report indicated that the guidelines recommend the use of PET for initial staging of HL and aNHL. The routine use of PET to predict subsequent outcome is not recommended by the guidelines. Guidelines recommend against PET in surveillance of asymptomatic patients in remission after primary or secondary treatment. Guidelines are congruent with the evidence gathered for this report.

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 Positron Emission Tomography (PET) scans for Lymphoma demonstrates that there is sufficient evidence to cover with conditions PET scans for Lymphoma. 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 to cover with conditions Positron Emission Tomography (PET) scans for Lymphoma.

Health Technology Clinical Committee Authority

Washington State's legislature believes it is important to use a scientific based, clinician centered approach for difficult and important health care benefit decisions. Pursuant to chapter 70.14 RCW, the legislature has directed the Washington State Health Care Authority, through its Health Technology Assessment program to engage in a process for evaluation process that gathers and assesses the quality of the latest medical evidence using a scientific research company and takes public input at all stages. Pursuant to RCW 70.14.110 a Health Technology Clinical Committee (HTCC) composed of eleven independent health care professionals reviews all the information and renders a decision at an open public meeting. The Washington State Health Technology Clinical Committee (HTCC) determines how selected health technologies are covered by several state agencies (RCW 70.14.080-140). These technologies may include medical or surgical devices and procedures, medical equipment, and diagnostic tests. HTCC bases their decisions on evidence of the technology's safety, efficacy, and cost effectiveness. Participating state agencies are required to comply with the decisions of the HTCC. HTCC decisions may be re-reviewed at the determination of the HCA Administrator.