WASHINGTON STATE HEALTH CARE AUTHORITY

PET for Lymphoma

Health Technology Assessment

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PET for Lymphoma

Comprehensive Report

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Acknowledgements

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This technology assessment report is based on research conducted by a contracted technology assessment center, with updates as contracted by the Washington State Health Care Authority. 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 investigators and authors who are responsible for the content. These findings and conclusions may not necessarily represent the views of the HCA/Agency and thus, no statement in this report shall be construed as an official position or policy of the HCA/Agency.

The information in this assessment is intended to assist health care decision makers, clinicians, patients and policy makers in making sound 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.

Glossary and Abbreviations used in this report:

aNHL = aggressive non-Hodgkin lymphoma

CT = Computed tomography; an imaging test using x-rays and a computer to produce cross sectional images of the body part studied.

^{18}FDG = 2[^{18}F]fluoro-2-deoxy-D-glucose; a glucose analog containing the positron emitting particle Fluorine 18. ^{18}FDG is the radioactive substance used in PET scanning in lymphoma.

^{18} FDG PET = positron emission tomography using ^{18}FDG, one of many positron emitting radionuclides used in various PET scanning applications. In this report, PET always refers to ^{18} FDG PET.

^{67}Gallium scintigraphy = an imaging test using gallium citrate as a radioactive tracer. ^{67}Gallium scans were historically performed to stage lymphomas because of preferential uptake by lymphoma cells.

Hazard ratio = This term is similar to Odds Ratio (OR). The chance of an event occurring in one group compared to the chance of it occurring in another group. The odds ratio (OR) is a measure of effect size and is commonly used to compare results in clinical trials.

HL = Hodgkin lymphoma

iNHL = indolent non-Hodgkin lymphoma

LR (Likelihood ratio) = A measure of the accuracy of a diagnostic test. It is used to determine how likely it is that a person has a specific disease based on test results. When the test result is positive, the likelihood ratio is known as a positive likelihood ratio (LR+). When the test result is negative, the likelihood ratio is known as a negative likelihood ratio (LR-). The likelihood ratio is a way of comparing the probability that the test result would occur in people with the disease as opposed to occurring in people without the disease.

A positive likelihood ratio greater than 10 (>10) or a negative likelihood ratio less than 0.1 (<0.1) would be considered clinically useful in helping guide health care decision making.

MRI = magnetic resonance imaging; an imaging test using radio waves and a computer to produce cross sectional images of the body part being studied.

NHL = Non-Hodgkin lymphoma

NPV (Negative predictive value) = Indicates the likelihood that people with a negative test result would not have a condition. The higher the value of the negative predictive value (for example, 99 percent would usually be considered a high value), the more useful the test is for predicting that people do not have the condition.

PET = positron emission tomography; an imaging test using a positron emitting radionuclide and a computer to produce images of the body part being studied. In this report, PET always refers to 18FDG PET.

PET/CT (PET/CT fusion or fusion PET/CT) = PET is usually performed on a combined PET-CT[1] scanner where both the radioactive PET data and high resolution computed tomography (CT) data are recorded at the same time.

PPV (Positive predictive value) = Indicates the likelihood that a person with a positive test result would actually have the condition for which the test is used. The higher the value of the positive predictive value (for example, 90 percent would be considered a high value), the more useful the test is for predicting that the person has the condition.

Sensitivity = The ability of a test to identify correctly people with a condition. A test with high sensitivity will nearly always be positive for people who have the condition (the test has a low rate of false-negative results). Sensitivity is also known as the true-positive rate.

Specificity = The ability of a test to identify correctly people without a condition. A test with high specificity will rarely be wrong about who does NOT have the condition (the test has a low rate of false-positive results). Specificity is also known as the true-negative rate.

[1] In this report PET will be used to mean both PET alone and PET/CT (PET/CT fusion).

Table of Contents

Executive Summary

Background

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).

This report examines the evidence for PET scans for seven potential indications (screening, diagnosis, staging, re-staging after treatment, estimation of prognosis after treatment, surveillance during remission and monitoring of treatment) for both HL and NHL.

Methods

A full search of the Center for Evidence-based Policy (CEbP) clinical evidence core sources was done to identify systematic reviews (SR), meta-analyses (MA), technology assessments (TA), and clinical practice guidelines (CPG). A MEDLINE search for TAs, MAs, SRs and other study designs was performed for the period 2009 through 2011. Our core source search located seven SRs/TAs, and six CPGs that met inclusion criteria for this report. The MEDLINE search located an additional 18 observational studies that were also used in the report.

Findings

Key Question 1 for this report addresses the comparative diagnostic performance of PET compared to other imaging modalities such as MRI and CT for each of the potential uses of PET noted above. Key Question 2 addresses the additional value of PET in terms of diagnostic thinking, patient management and patient outcomes for HL and NHL. Key Question 3 addresses the issue of subpopulations of patients. Key Question 4 addresses safety of PET, and Key Question 5 addresses costs of PET. In this report, PET will always refer to ^{18}FDG PET. The results of this report are tabulated in the table at the end of the Executive Summary.

There is no evidence for the use of PET for screening for lymphoma or for making the initial diagnosis of lymphoma. In fact, tissue biopsy is required to determine the histological type of

lymphoma which, in turn, is important in determining treatment. The use of PET cannot avoid biopsy.

Both the sensitivity and specificity of PET are high for the staging of HL and NHL. Sensitivity and specificity are higher for HL than NHL and are higher for initial staging than re-staging after treatment. Positron emission tomography appears to have higher sensitivity and specificity than CT, MRI or gallium scanning for staging and re-staging. However, there appears to be little incremental value from adding PET after staging with CT or MRI. Most current PET scanners are fusion PET/CT scanners that provide both PET information and CT synchronously.

Positron emission tomography is sensitive and specific for prediction of subsequent outcomes when performed after the end of treatment for both HL and NHL. Positron emission tomography is more sensitive and specific after primary treatment than after secondary treatment.

Positron emission tomography for surveillance of asymptomatic patients in remission has more false positive than true positive results. The use of PET seems to add radiation dose and financial costs without adding commensurate clinical value.

Monitoring of treatment with PET in mid-cycle of treatment for HL and NHL shows moderate sensitivity and specificity in predicting subsequent outcome. The use of PET for this purpose implies that treatment will be altered in mid-cycle depending on the findings on PET. The most important diagnostic measure for changing treatment would be the positive predictive value (PPV), likelihood ratio of a positive test (LR+), or negative predictive value (NPV) or likelihood ratio of a negative test (LR-). There is only weak evidence for values of PPV or NPV that are sufficiently high to support changing treatment. Values for NPV tend to be significantly higher than values for PPV. However, most current studies are investigating changing patients to secondary treatment if mid-cycle PET scans show “non-response”; this decision would require a high PPV.

There is limited, weak evidence about changes in management with PET but no evidence about other measures of clinical effectiveness. There is no information about subgroups of patients for any of the uses of PET in lymphoma.

Positron emission tomography is safe. The safety profile for PET in lymphoma is no different than for other indications for PET. The evidence for costs is limited. The strongest evidence is that routine PET scanning for surveillance of asymptomatic patients costs $100,000 and 147mSV per lymphoma recurrence detected.

Guidelines make recommendations that are, for the most part, consistent with the evidence identified in this CEbP report.

Limitations of the evidence

The major limitation of the evidence is that the primary studies used in the SRs, MAs, TAs and guidelines are case series; case series provide less rigorous evidence than randomized control trials (RCTs). RCTs are difficult to perform for studies of diagnostic tests. This results in most of

the evidence coming from cases series that are a much weaker form of evidence and contain several methodological flaws. The TAs, SRs, MAs and guidelines used in this report are all well performed. In several indications for PET, meta-analyses of multiple studies show homogeneous results with statistically significant diagnostic parameters; for these the strength of the evidence is moderate. However, for a number of indications, the studies have heterogeneous results or comparators; or there are very few studies and patients. For these, the overall strength of the evidence is low.

Summary Table. Use of PET scanning in HL and NHL

PET indication	Overall Evidence	Strength of Evidence	Guidelines Recommendation	Insurance Coverage
Screening	None	N/A	Against use	No coverage
Diagnosis	Not beneficial. One study of 8 patients.	Low	Against use	No coverage
Original Staging	**For HL and aNHL**, PET sensitivity and specificity 88-100% and 90-100%; Sensitivity and specificity for CT 88% and 80%.	Moderate	For use	All cover
	For iNHL, PET/CT had higher sensitivity (90%) than CT (70%) or PET alone (68%). PET appears to detect additional disease but also miss disease detected by CT.	Low	For use	
Re-staging	**For HL**, PET sensitivity 84% and specificity 90-100%.	Moderate	For use	All cover
	For aNHL, PET sensitivity 72% and specificity 100%.	Moderate		
	For iNHL, no evidence.	No		
Estimation of Prognosis	**For HL and aNHL**, PET sensitivity 81%; specificity 97%; LR+ = 3.6, LR- = 0.4.	Low	For use	All cover
	For iNHL, PET sensitivity 100%; specificity 88%; PPV 62%; NPV 100%.	Low		
Surveillance	**For HL or aNHL,** significant false positive PET scans when used in asymptomatic	Low	Against use	No coverage

PET indication	Overall Evidence	Strength of Evidence	Guidelines Recommendation	Insurance Coverage
	patients in remission.			
	For iNHL, no evidence.	No		
Monitoring of Treatment	**For HL and aNHL**, PET PPV 15-80%; NPV 90-100%.	Moderate	For use if part of a clinical trial. Not for routine use	No coverage
	For iNHL, no evidence.	No		

Background

Hodgkin and non-Hodgkin lymphoma

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, estimation of prognosis after treatment and surveillance for recurrence of cancer.

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.

- Types of NHL involving B cell lymphocytes
  - Indolent
    - Chronic lymphocytic leukemia (CLL)/small cell lymphoma (6%)
    - Follicular lymphoma (22%)
    - Marginal zone lymphoma (5%)
  - Aggressive
    - Diffuse large B-cell lymphoma (31%)
    - Mantle cell lymphoma (6%)
  - Highly aggressive
    - Burkitt lymphoma
    - Lymphoblastic lymphoma
    - AIDS related B-cell lymphoma

- Types of lymphoma involving T cell lymphocytes
  - Peripheral T cell lymphoma (6%)
  - Mycosis fungoides/Sezary syndrome

Clinical Management

Typical clinical management of HL involves initial diagnosis (biopsy is required to characterize the cellular histology), initial staging[2], treatment, restaging after treatment and either surveillance if complete response has been achieved or additional treatment followed by restaging. The need for additional therapy is determined by the response to initial therapy. Response of HL to initial therapy is based on size reduction of enlarged lymph nodes on CT scan, the extent of bone marrow involvement, immunohistochemistry, flow cytometry and findings on PET scans. Clinical response of the lymphoma is described by the following categories: complete response, partial response, stable disease, relapsed disease and progressive disease.

Usual clinical management for NHL depends on the cell type. Aggressive NHL (aNHL)—primarily diffuse large cell lymphoma and mantle cell lymphoma—is managed in a parallel fashion to HL. Management involves diagnosis, staging, treatment, restaging after treatment then follow-up (surveillance) or retreatment. In Key Questions 1 and 2 of this report, HL and aNHL will be grouped together and discussed separately from iNHL.

Indolent NHLs are more variable and many different treatment strategies may be employed. The clinical management is more individualized than for HL because of the variable cell type and the generally more advanced age of NHL patients. Typical management might include diagnosis, staging, treatment or observation followed by restaging for treated patients or observation (surveillance) for those not treated. Another issue for iNHL is late histological transformation from indolent to aggressive NHL. Histological transformation may be detected by change in symptoms, enlargement of tumor mass, change in chemical markers or changes in imaging studies.

The clinical management algorithm adapted from the Australia MSAC Technology Assessment (2010) is included in Appendix A as an example of a framework for identifying potential applications of PET in the clinical management of HL and NHL.

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[2] Staging of HL:
Stage I: Involvement of single lymph node region or localized involvement of single extralymphatic organ or site.
Stage II: Involvement of two or more lymph node regions on the same side of the diaphragm or involvement of single extralymphatic organ or site and its regional lymph nodes with or without involvement of other lymph node regions on the same side of the diaphragm.
Stage III: Involvement of lymph node regions on both sides of the diaphragm which may also be accompanied by localized involvement of an associated extralymphatic organ or site, by involvement of the spleen or by both.
Stage IV: Disseminated multifocal involvement of one or more extralymphatic organs with or without associated lymph node involvement, or isolated extralymphatic organ involvement with distant (nonregional) nodal involvement.
A: No systematic symptoms present
B: Unexplained fevers > 38 C; drenching night sweats; or weight loss > 10% of body weight (NCCN, 2011)
Staging of NHL is more complicated because NHLs are more diverse.

Technology Background

Positron Emission tomography (PET)

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.

Computed Tomography (CT)

Computed tomography (CT) is an imaging test that uses x-rays and a computer to create thin slice digital images of the region of the body studied. Computed tomographic images are always obtained in the axial plane (the plane perpendicular to the long axis of the body). Since the images produced are digital, they may be manipulated on a computer to change brightness and contrast and to subtract one image from another. They may also be combined to create reformatted images in different imaging planes. Computed tomography can be performed from the brain to the extremities and can be performed without or with the administration of intravenous contrast material. Contrast material represents a non-radioactive, iodine containing chemical compound that increases x-ray absorption in the tissues in which it accumulates. Computed tomographic images demonstrate cross sectional anatomy and also demonstrate changes in tissue density. Disease is detected on CT by alterations in the normal anatomy compared either to expected normal patients or to previous studies of the same patient. Other information obtained on CT images that help in detecting disease includes changes in tissue density and level of enhancement from intravenous contrast compared to normal.

Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) is an imaging test that uses radio waves and a computer in the presence of a strong magnetic field to create thin slice digital images of the region of the body studied. Magnetic resonance images can be obtained in any plane (axial, sagittal, coronal or off axis). Like CT, MRI images are digital and can be similarly manipulated on a computer, can be performed from the brain to the extremities and can be performed without or with

intravenous contrast. The contrast agent for MRI is a non-radioactive, gadolinium containing chemical compound that alters the magnetic field of tissues in which it accumulates. Magnetic resonance imaging demonstrates cross sectional anatomy and changes in proton density. Disease detection relies on changes in anatomy, proton density and contrast enhancement.

^{67}Gallium Scintigraphy

^{67}Gallium citrate scintigraphy is a nuclear medicine test. ^{67}Gallium citrate is injected intravenously and accumulates in inflammatory cells and tumor cells. Forty-eight to ninety-six hours after injection of ^{67}gallium citrate, whole body images are obtained. The mechanism for accumulation of ^{67}gallium citrate in tumor or inflammatory cells is unknown, probably related to binding of ^{67}gallium citrate to transferrin and the attachment of this gallium-transferrin complex to transferrin receptor sites on tumor or inflammatory cells. Gallium accumulates only in viable tumor cells and therefore allows the detection of viable tumor within the body. Like PET, ^{67}gallium scintigraphy produces "hot spot" imaging where areas of radioactivity represent abnormality. Gallium scintigraphy is technically limited by slow accumulation of ^{67}gallium citrate in tumors which requires imaging for up to four days after injection. Gallium scintigraphy is also limited by excretion of ^{67}gallium citrate in the bowel with accumulation of ^{67}gallium in the colon; ^{67}gallium accumulation in the colon may mask tumor activity in the abdominal cavity. In 2011, ^{67}gallium scans have been replaced by PET in most practices with access to PET.

The rationale for using PET to replace CT or MRI is that the accumulation of ^{18}FDG is a direct indicator of cell viability. An abnormal mass detected by anatomic imaging methods such as CT and MRI does not indicate cell viability. According to this rationale, cell viability is a more sensitive and specific indicator of the presence of tumor cells such as lymphoma.

The radiation dose from PET, CT or ^{67}gallium scintigraphy is significant. Typical whole body dose ranges are as follows (ACR, 2009):

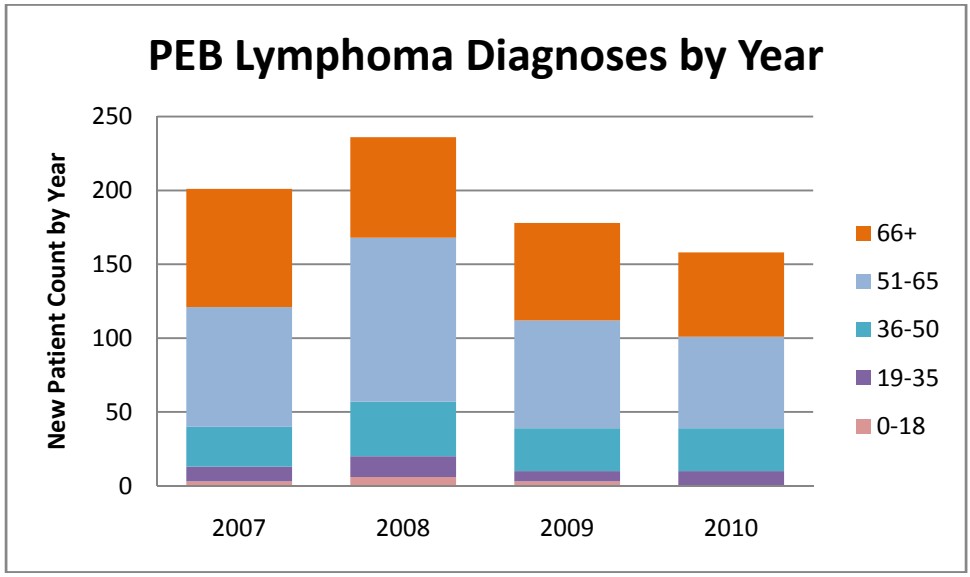
> PET 10-30 mSv (equivalent to approximately 300 PA chest x-rays)
> Whole body CT 10-30 mSv (equivalent to approximately 300 PA chest x-rays)
>
> PET/CT 20-60 mSv (equivalent to approximately 500 PA chest x-rays)
> ^{67}Gallium scintigraphy 10-15 mSv (equivalent to approximately 150 PA chest x-rays)

The Radiological Society of North America and American College of Radiology (2011) Radiologyinfo.org website estimates CT of the abdomen and pelvis with and without contrast to have a radiation dose of 30 mSv; the additional lifetime risk of fatal cancer from this dose is estimated as "moderate" which the ACR defines as a risk of 1 in 1,000 to 1 in 500. Appendix B includes the table from this website.

Policy context

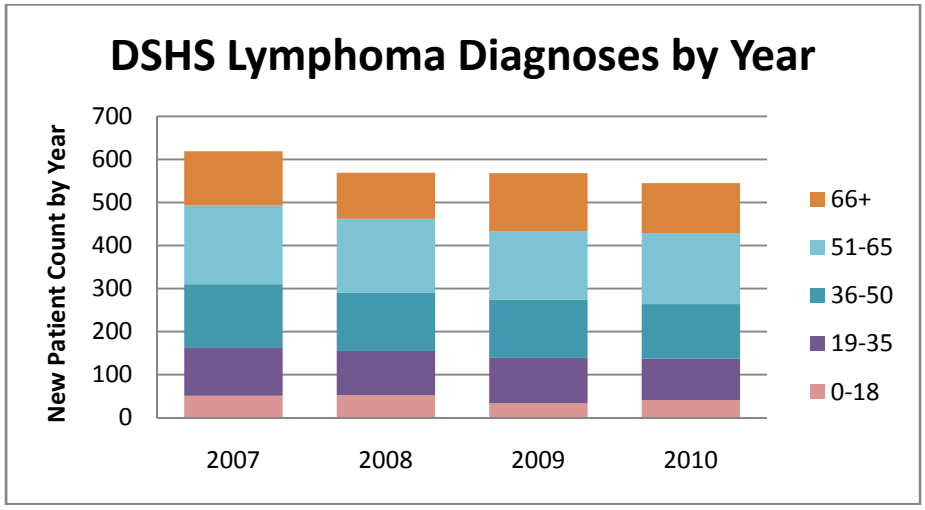
The Washington State utilization data for PEB and DSHS are presented in the following tables.

PEB Lymphoma Diagnoses by Age and Year



Note: May include new members with a pre-existing condition.

DSHS Lymphoma Diagnoses by Age and Year



Note: May include new members with a pre-existing condition.

PEB PET Scans, Costs and Counts

PEB PET Scans	2007	2008	2009	2010	Overall
Lymphoma*					
Members w/PET scans per year	140	168	161	148	409
Scans per year	221	263	246	235	965
Average scans per year**	1.58	1.57	1.53	1.59	2.36
Annual Cost	$489,106	$744,611	$605,527	$612,285	$2,451,529

PEB PET Scans	2007	2008	2009	2010	Overall
Average overall cost	$2,213	$2,831	$2,461	$2,605	$2,540
Average Primary Payer cost	$3,421	$3,876	$3,756	$3,797	$3,735
Non Lymphoma					
Members w/ PET scans per year	550	625	678	684	1910
Scans per year	719	834	894	919	3366
Average scans per year**	1.31	1.33	1.32	1.34	1.76
Annual Cost	$1,545,617	$1,889,568	$2,028,646	$2,089,608	$7,553,439
Average overall cost	$2,150	$2,266	$2,269	$2,274	$2,244
Average Primary Payer cost	$3,203	$3,500	$3,497	$3,518	$3,440
All PET Scans					
Members w/ PET scans per year	690	793	839	832	2319
Scans per year	940	1097	1140	1154	4331
Average scans per year**	1.36	1.38	1.36	1.39	1.87
Annual Cost	$2,034,723	$2,634,179	$2,634,173	$2,701,893	$10,004,968
Average overall cost	$2,165	$2,401	$2,311	$2,341	$2,310
Average Primary Payer cost	$3,252	$3,605	$3,556	$3,579	$3,510

**Patients who were diagnosed with Lymphoma during the 4 year period – includes pre-dx & unrelated tests*
***Average number of scans for all patients who had PET scans during the year*

PEB Lymphoma PET Scans, Hodgkin/Non-Hodgkin Costs and Counts

PEB Lymphoma PET Scans	2007	2008	2009	2010	Overall
Hodgkins Lymphoma					
Scans per year	14	31	24	27	96
Annual Cost	$32,714	$132,410	$64,206	$114,787	$344,117
Average scan cost overall	$2,337	$4,271	$2,675	$4,251	$3,585
Average Primary payer scan cost	$2,683	$4,335	$3,521	$4,251	$3,917
NonHodgkins Lymphoma					
Scans per year	207	232	222	208	869
Annual Cost	$456,392	$612,201	$541,321	$497,498	$2,107,412
Average scan cost overall	$2,205	$2,639	$2,438	$2,392	$2,425
Average Primary payer scan cost	$3,508	$3,778	$3,788	$3,687	$3,702
All Lymphoma PET Scans					
Scans per year	221	263	246	235	965
Annual Cost	$489,106	$744,611	$605,527	$612,285	$2,451,529
Average scan cost overall	$2,213	$2,831	$2,461	$2,605	$2,540
Average Primary payer cost	$3,421	$3,876	$3,756	$3,797	$3,735

DSHS PET Scans, Costs and Counts

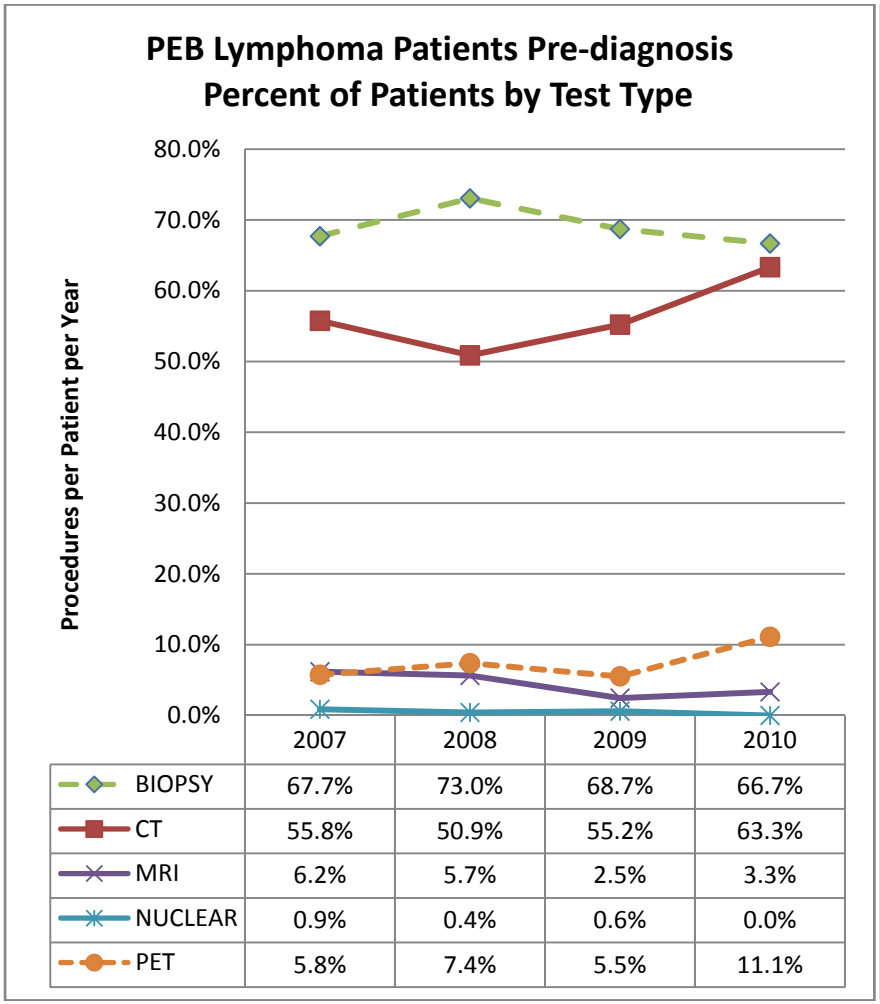
DSHS PET Scans	2007	2008	2009	2010	Overall
Lymphoma					
Members w/ PET scans per year	149	178	192	92	611
Scans per year	198	240	263	113	814
Average scans per year	1.33	1.35	1.37	1.23	1.33
Annual Cost	$151,470	$196,394	$205,563	$87,697	$641,124
Average scan cost	$765	$818	$782	$776	$788
Non Lymphoma					
Members w/ PET scans per year	497	590	525	326	1938
Scans per year	670	799	720	375	2564
Average scans per year	1.35	1.35	1.37	1.15	1.32
Annual Cost	$519,177	$628,434	$575,427	$339,886	$2,062,924
Average scan cost	$775	$787	$799	$906	$805
All PET Scans					
Members w/ PET scans per year	646	768	717	418	2549
Scans per year	868	1039	983	488	3378
Average scans per year	1.34	1.35	1.37	1.17	1.33
Annual Cost	$670,648	$824,827	$780,990	$427,583	$2,704,048
Average scan cost	$773	$794	$794	$876	$800

**Average number of scans for those patients who had PET scans during the year*

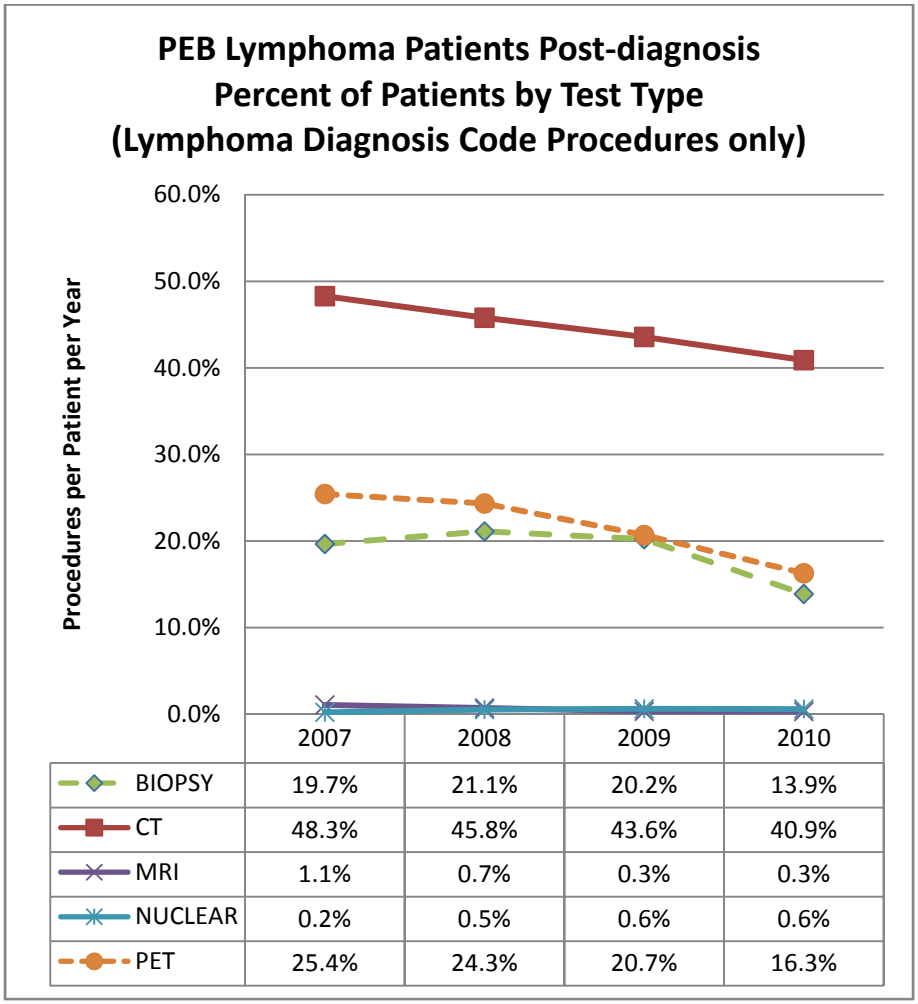
DSHS Lymphoma PET Scans, Hodgkin/Non-Hodgkin Costs and Counts

DSHS Lymphoma PET Scans	2007	2008	2009	2010	Overall
Hodgkins Lymphoma					
Scans per year	41	59	69	32	201
Annual Cost	$25,295	$42,038	$47,237	$24,960	$139,530
Average scan cost	$617	$713	$685	$780	$694
NonHodgkins Lymphoma					
Scans per year	126	134	152	59	471
Annual Cost	$100,514	$115,965	$123,477	$45,772	$385,728
Average scan cost	$798	$865	$812	$776	$819
All PET Scans					
Scans per year	167	193	221	91	672
Annual Cost	$125,810	$158,003	$170,713	$70,732	$525,259
Average scan cost	$753	$819	$772	$777	$782

PEB Lymphoma Test Use Pre and Post Diagnosis



	2007	2008	2009	2010
BIOPSY	67.7%	73.0%	68.7%	66.7%
CT	55.8%	50.9%	55.2%	63.3%
MRI	6.2%	5.7%	2.5%	3.3%
NUCLEAR	0.9%	0.4%	0.6%	0.0%
PET	5.8%	7.4%	5.5%	11.1%



	2007	2008	2009	2010
BIOPSY	19.7%	21.1%	20.2%	13.9%
CT	48.3%	45.8%	43.6%	40.9%
MRI	1.1%	0.7%	0.3%	0.3%
NUCLEAR	0.2%	0.5%	0.6%	0.6%
PET	25.4%	24.3%	20.7%	16.3%

Imaging and biopsy modalities used before and after diagnosis for the same patient group may clarify use for diagnosis versus staging. However, pre-diagnosis tests cannot be verified for relationship to the lymphoma diagnosis. The first appearance of a lymphoma diagnosis in the claims data, starting in 2006, was considered to be the diagnosis date for the purpose of this chart.

For procedures included in each category, see the "Related Medical Codes" section

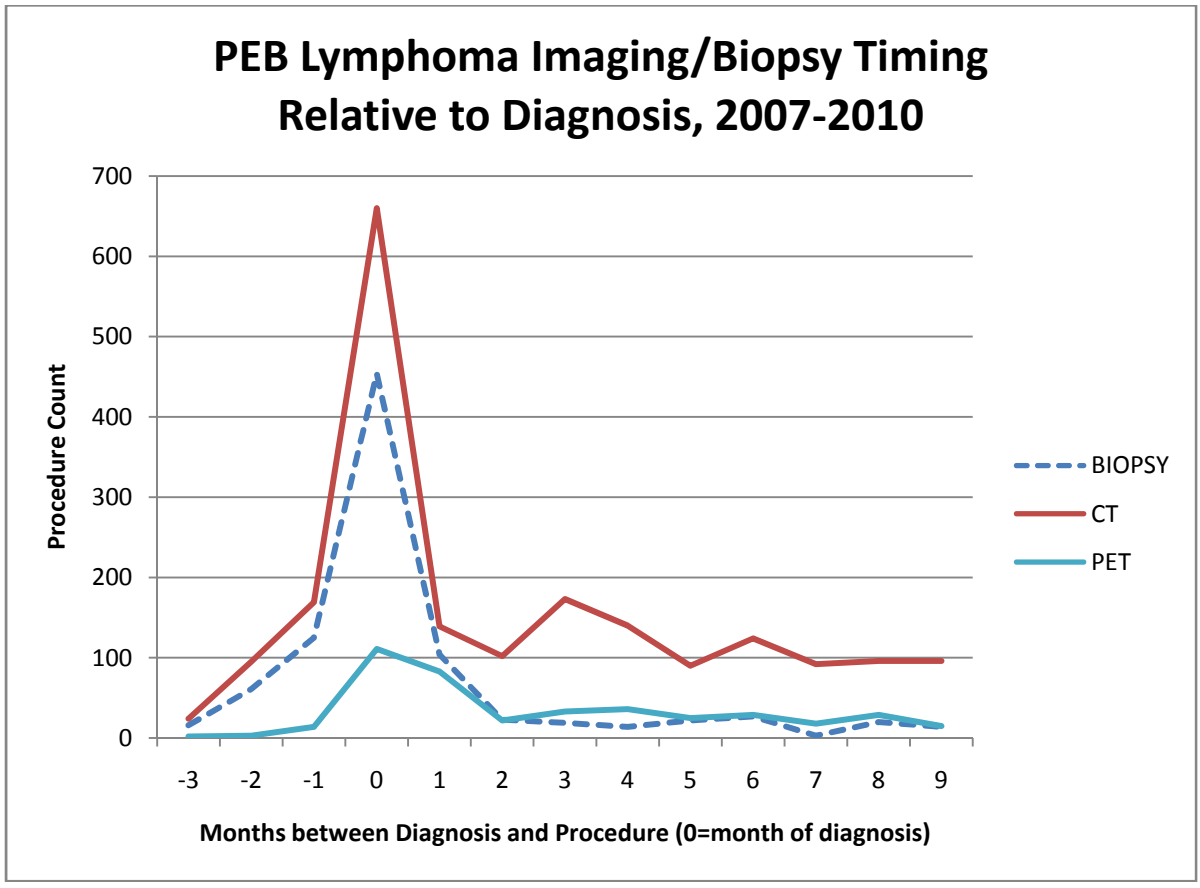
PEB Lymphoma Patient PET Scan Summary Statistics

PEB Lymphoma Diagnosis Code PET Scans, Consolidated 2007-2010

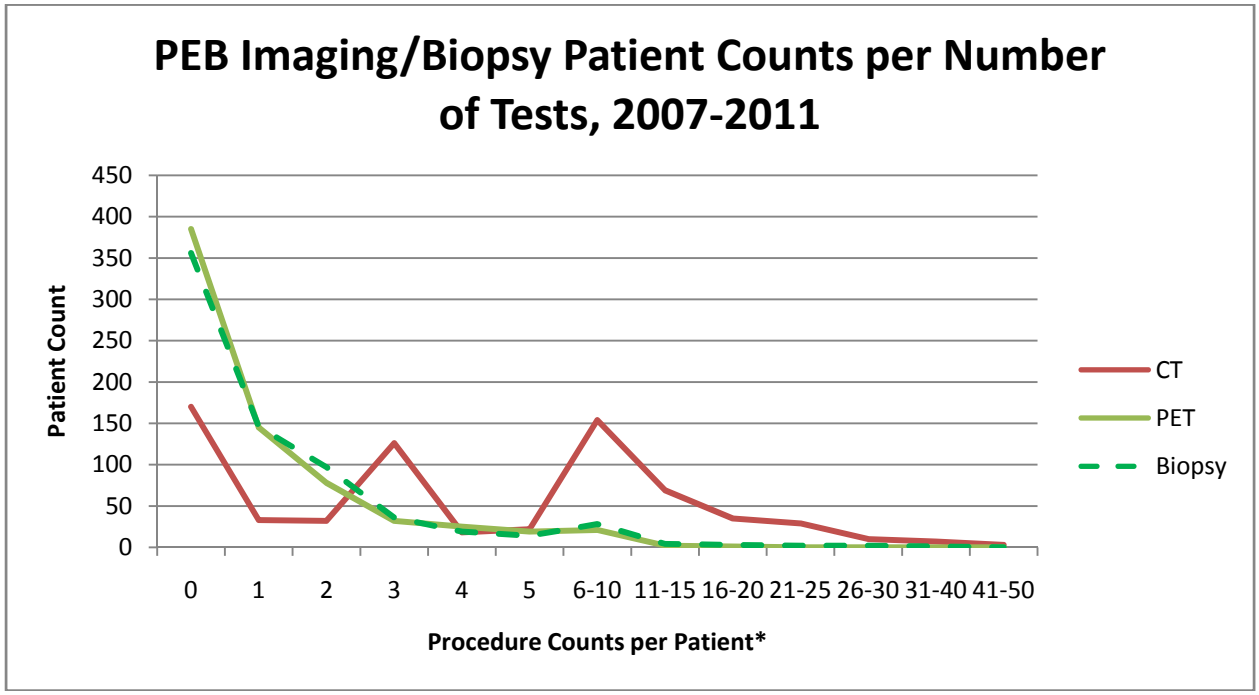
PET Scan in Lymphoma Summary	Hodgkins Lymphoma Patients	Non-Hodgkins Lymphoma Patients	All Lymphoma Patients
PET Scan Count	180	613	793
Patient Count	61	262	323
Average # scans/patient	2.95	2.34	2.46
Median scan count	2	2	2
Maximum scan count	15	19	19
Mode	1	1	1
Std Dev	2.54	2.14	2.23

Note: Table 5a includes PET scans with a Lymphoma diagnosis code only

PEB Lymphoma Visualization Timing Relative to Diagnosis, 2007-2010



PEB Lymphoma Patient Counts by number of Tests, 2007-2011



**Patients with a "0" procedure count on this chart may include patients short term members and members who were at the end of a continuum of treatment in 2006.*

Imaging and Biopsy Categories, PEB Reports

Visualization Category/ Proc Code	Procedure Code Description
BIOPSY	
88305	TISSUE EXAM BY PATHOLOGIST
88307	TISSUE EXAM BY PATHOLOGIST
CT	
71250	CT THORAX W/O DYE
71260	CT THORAX W/DYE
71270	CT THORAX W/O & W/ DYE
72192	CT PELVIS W/O DYE
72193	CT PELVIS W/DYE
72194	CT PELVIS W/O & W/DYE
74150	CT ABDOMEN W/O DYE
74160	CT ABDOMEN W/DYE
74170	CT ABDOMEN W/O &W /DYE
MRI	
71550	MRI CHEST W/O DYE
71552	MRI CHEST W/O & W/DYE
72195	MRI PELVIS W/O DYE
72196	MRI PELVIS W/DYE
72197	MRI PELVIS W/O & W/DYE
74181	MRI ABDOMEN W/O DYE
74183	MRI ABDOMEN W/O & W/DYE
NUCLEAR	
78800	TUMOR IMAGING, LIMITED AREA
78802	TUMOR IMAGING, WHOLE BODY
78803	TUMOR IMAGING (3D)
78804	TUMOR IMAGING, WHOLE BODY
PET	
78812	TUMOR IMAGE (PET)/SKUL-THIGH
78815	TUMORIMAGE PET/CT SKUL-THIGH
78816	TUMOR IMAGE PET/CT FULL BODY

Related Medical Codes			
Code Type	**Codes**	**Short Description**	**Additional Info**
ICD9 Diagnosis			
	200.0 – 202.98	Lymphoma	Diagnosis of interest - Patient selection and comparators
Treatments(CPT)			Select all codes
	78811-78813	PET scans, Diagnostic nuclear medicine	PET Imaging
	78814-78816	PET-CT scan, Diagnostic nuclear medicine	PET Imaging
	38790/92/94	Injection for lymph angiography, identification of sentinel lymph node, Cannulation of thoracic duct	Other Imaging - adjunct code: injection/iv of radiopharmaceuticals
	78102/03/04	Bone marrow imaging for Lymphatic System (includes gallium scintigraphy), limited area, multiple areas, whole body	Other imaging - Comparator procedure
	78800/01/02	Radiopharmaceutical imaging, limited area, multiple areas, whole body	Other imaging - Comparator procedure
	78803	Radiopharmaceutical imaging, tomographic (SPECT)	Other imaging - Comparator procedure
	78804	Radiopharmaceutical imaging, whole body requiring 2 or more days	Other imaging - Comparator procedure
	78808	Injection of radiopharmaceutical by IV for gamma probe study (new code in 2009)	Other imaging - Comparator procedure
	76376/7	Interpretation of imaging results, should not be reported with 78811-78816 (new code in 2006)	Other Imaging - adjunct code; additional interpretation charge for non PET imaging
	71250/60/70	Computed tomography (CT), thorax; without contrast material/ with contrast material/ with and without contrast	Other imaging - Comparator procedure
	74150/60/70	CT of the Abdomen w/o, w, w/o and w contrast	Other imaging - Comparator procedure

Code Type	Codes	Short Description	Additional Info
Treatments(CPT)			Select all codes
	72192/93/94	CT of the Pelvis w/o,w, w/o and w contrast	Other imaging - Comparator procedure
	74176/77/78	CT of the Abdomen and Pelvis, w/o, w, w/o and w contrast (not yet implemented (2011))	Other imaging - Comparator procedure
	71550/1/2 (chest) 74181/2/3 (abdomen) 72195/6/7 (pelvis)	Magnetic resonance (eg, proton) imaging, chest (eg, for evaluation of hilar and mediastinal lymphadenopathy) without contrast material/ with contrast/ with and without contrast	Other imaging - Comparator procedure
	88305/307	Lymph node biopsy	Biopsy - Comparator procedure

Positron emission tomography has diffused rapidly, following several studies that showed that PET or PET/CT used in HL and aNHL at the end of primary, salvage, or high-dose therapy provided accurate information about remission or recurrence of lymphoma. Positron emission tomography has since diffused to use in other lymphoma types and many stages of lymphoma including diagnosis, treatment, and monitoring. Guidelines for use are primarily based on expert consensus. Evidence about timing of PET/CT, the need for repeated scans and the effect of PET on the subsequent use of invasive tests, therapeutic choices, and health outcomes is needed.

PET scans for cancer are covered by Medicare and many commercial insurance companies. In 2009, CMS issued a national coverage decision for PET for solid tumors (CMS, 2010). For the initial antitumor treatment strategy, CMS has decided that, with several exceptions, PET is useful and is covered without evidence development; this represents a change from its previous policy of coverage with evidence development. For subsequent antitumor treatment strategy, CMS has determined that PET may be covered with evidence development again with several exceptions. Coverage policies, including those of CMS, are discussed in more detail at the end of this report.

Key Questions

The purpose of this report is to evaluate the accuracy and effectiveness of ^{18}FDG PET compared to other tests in the management of lymphoma for the Washington HTA program. The following Key Questions were developed to guide this review.

1. What is the evidence of accuracy of ^{18}FDG PET (alone or combined on one system with CT—PET/CT) imaging for known or suspected lymphoma?
    a. Describe sensitivity, specificity, and other key test characteristics (in screening, staging/re-staging, surveillance)
    b. Include comparators of MRI, CT, Gallium
2. What is the evidence of clinical effectiveness of ^{18}FDG PET imaging in patients with known or suspected lymphoma compared to CT and MRI when used as an adjunct to CT or MRI or Gallium, including:
    a. Reduced need for other tests or less invasive test
    b. Change in patient management (e.g. continuation of chemotherapy)
    c. Improvement in quality of life
    d. Reductions in morbidity and mortality
3. What is the evidence that ^{18}FDG PET imaging in patients with known or suspected lymphoma has differential efficacy or safety issues in subpopulations? Including consideration of:
    a. Patient age, gender, characteristics or evidence based patient selection criteria
    b. Type of scanning machine and software, reader training, and other operational factors
    c. Provider type, setting or other provider characteristics
    d. Health care system type, including worker's compensation, Medicaid, state employees
4. What is the safety profile of ^{18}FDG PET for lymphoma?
    a. Adverse events type and frequency (mortality, major morbidity, other)
5. What is the evidence about the cost impact of ^{18}FDG PET for patients with lymphoma? Including consideration of:
    a. Costs in short term
    b. Costs in long term

Methods

Search strategy

A full search of the CEbP clinical evidence primary sources was done to identify systematic reviews (SR), meta-analyses (MA), technology assessments (TA), and clinical practice guidelines (CPG) using the terms *lymphoma, Hodgkin, positron emission tomography, PET and ^{18}FDG PET*. Searches of core sources were limited to citations which were published after 2000. The core sources searched included: Hayes, Inc., Cochrane Library (Wiley Interscience), UK National Institute for Health and Clinical Excellence (NICE), Blue Cross/Blue Shield Health Technology Assessment (HTA) program, Veterans Administration TA program, BMJ Clinical Evidence, the Canadian Agency for Drugs and Technologies in Health (CADTH), the Institute for Clinical Systems Improvement (ICSI), U.S. Services Preventive Task Force, and the Agency for Health Research and Quality (AHRQ).

A MEDLINE (Ovid) search was conducted to identify SRs and MAs as well as additional studies published for the period 2009 through May 2011 (after the search dates of included SR/TAs) that would have met inclusion criteria for indentified SR/TAs. Please see Appendix C for the full MEDLINE search strategy. The search was limited to publications in English which were not commentaries or editorials.

A search for relevant clinical practice guidelines (CPGs) was also conducted, using the following sources: the National Guidelines Clearinghouse database, the Institute for Clinical Systems Improvement (ICSI), the Scottish Intercollegiate Guidelines Network (SIGN), the National Institute for Health and Clinical Excellence (NICE), the Veterans Administration/Department of Defense (VA/DOD) guidelines, the New Zealand Guidelines Group (NZGG), Australian Government National Health and Medical Research Council, National Comprehensive Cancer Network, and American College of Radiology (ACR). Searches for clinical practice guidelines were limited to the last five years.

Inclusion criteria

Population: Adults and children with Hodgkin lymphoma and non-Hodgkin lymphoma
Intervention: ^{18} FDG PET (PET/CT)
Comparator: MRI, CT, gallium, other imaging methods
Outcomes: Comparative diagnostic performance; effects on clinical decision making; effects on patient outcomes, safety and costs. Outcomes will be examined for the following indications for diagnostic imaging:

1. screening and initial diagnosis,
2. initial staging,
3. restaging after primary treatment,
4. restaging after secondary treatment,
5. estimation of prognosis after primary or secondary treatment,
6. surveillance of patients in remission,
7. monitoring of treatment during treatment

Quality assessment

The methodological quality of the included studies was assessed using standard instruments developed and adapted by CEbP that are modifications of the systems in use by NICE and SIGN (Guyatt, 2008; NICE, 2009; SIGN, 2009). All studies and guidelines were assessed by two independent and experienced raters. In cases where there was not agreement about the quality of the study or guideline the disagreement was resolved by conference or the use of a third rater.

The overall strength of evidence was rated using a modified version of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. Each study was assigned a rating of good, fair, poor, based on its adherence to recommended methods and potential for biases. In brief, good quality systematic reviews included a clearly focused

question, a literature search that was sufficiently rigorous to identify all relevant studies, criteria used to select studies for inclusion (e.g., RCTs) and assess study quality, and assessments of heterogeneity to determine if a meta-analysis would be appropriate. Good quality RCTs clearly described the population, setting, intervention and comparison groups; randomly allocated patients to study groups; concealed allocation; had low dropout rates; and reported intention-to-treat analyses. Good quality systematic reviews and RCTs also had low potential for bias from conflicts of interest and funding source. Fair quality systematic reviews and RCTs had incomplete information about methods that might mask important limitations. Poor quality systematic reviews and RCTs had clear flaws that could introduce significant bias.

A summary judgment for the overall quality of evidence was assigned to each key question and outcome (Guyatt, 2008). The GRADE system defines the quality of a body of evidence for an outcome in the following manner:

- High: Further research is *very unlikely* to change our confidence in the estimate of effect. Typical sets of studies would be large RCTs without serious limitations.
- Moderate: Further research is *likely* to have an important impact on our confidence in the estimate of effect and may change the estimate. Typical sets of studies would be RCTs with some limitations or well-performed observational studies with additional strengths that guard against potential bias and have large estimates of effects.
- Low[3]: Further research is *very likely* to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Typical sets of studies would be RCTs with very serious limitations or observational studies without special strengths.

The methodological quality of the guidelines was assessed using an instrument adapted from the Appraisal of Guidelines Research and Evaluation (AGREE) Collaboration. Each guideline was assigned a rating of good, fair, poor, based on its adherence to recommended methods and potential for biases. A guideline rated as good quality fulfilled all or most of the criteria. A "fair" quality guideline fulfilled some of the criteria and those criteria not fulfilled were not likely to alter the recommendations. If no or few of the criteria were met, the guideline quality was rated as "poor". All guidelines were assessed by two independent and experienced raters. In cases where there was not agreement about the quality of the study or guideline the disagreement was resolved by conference or the use of a third rater.

Findings

The CEbP primary source search located seven systematic reviews and technology assessments, three cost or cost effectiveness study designs, and five clinical practice guidelines relevant to this topic. The MEDLINE search retrieved 354 full citations. After a full review of citations and

[3] CEbP collapses the low and very low GRADE categories because they usually have the same policy implications.

abstracts, we included no additional systematic reviews, no RCTs, 18 observational studies, and no additional clinical practice guidelines. In this report, PET always refers to ^{18}FDG PET. All included studies are summarized in Appendices C and D. The evidence tables are organized by lymphoma type and then by Key Question. Appendix D contains evidence tables for HL and aNHL. Appendix E contains evidence tables for iNHL. Appendix F contains evidence tables for the clinical guidelines.

Hodgkin and Aggressive Non-Hodgkin Lymphoma (aNHL)

Key Question #1: What is the evidence of accuracy of PET (alone or combined on one system with CT) imaging for known or suspected lymphoma?

Since PET (including PET/CT) has been advocated by some clinicians for use in screening, diagnosis, staging, monitoring of treatment response mid cycle during primary treatment, estimation of prognosis after treatment and surveillance, each of these potential applications for PET will be discussed separately.

The evidence given in this section frequently mixes patients with HL and aNHL and patients who are being staged before treatment and after treatment. Since diagnostic efficacy of PET may be different for these separate populations, the diagnostic efficacy figures may not accurately reflect values for a single population.

Screening and Diagnosis

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. Most types of lymphoma have been shown to accumulate ^{18}FDG. A PET scan would not distinguish between the various subtypes of lymphoma, and its use would not obviate the need for biopsy.

Original staging by PET (or PET/CT) compared with conventional staging or as an incremental test to conventional staging

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. Staging is also performed after primary treatment and before secondary treatment. Staging at these times has the same potential consequences of altering treatment as original staging.

Systematic reviews and technology assessments

The Australian MSAC technology assessment *Positron Emission Tomography for Lymphoma* (2010) summarizes 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. In two small case series of 33 and 50 patients who had PET after and in addition to conventional staging for HL and aNHL, PET detected additional sites in 18-60% of patients. This increase in detection represents both true positive and false positive results for lymphoma. The ratio of true positive to false positive sites detected by PET was 3:1. Less frequently, PET indicated absence of disease at sites suspected as positive on conventional imaging. However, a large portion of these incremental negative results were found to be false negatives.

Randomized control trials (RCTs) and other study designs

No RCTs or other study designs were identified for original staging.

Routine staging after primary treatment

Systematic reviews and technology assessments

One scenario for staging after primary treatment is the "routine" evaluation of every patient to evaluate for persistent or non-responsive lymphoma. Three of four systematic reviews summarized by the Australian MSAC technology assessment address the use of PET for "routine" staging after primary treatment. An additional systematic review (Terasawa, 2008) also evaluates staging after primary treatment. Kwee (2008) reports CT sensitivity range of 25-100% and specificity of 42-76% for the detection of residual lymphoma; PET sensitivity range was 71-100% and specificity was 57-100%; PET/CT sensitivity range was 91-100%, and specificity was 90-100%. Kirby (2007) reported sensitivity range of 87-100% compared to sensitivity of conventional imaging range of 20-93% for HL. Terasawa (2008) reported PET sensitivity range of 85-100% and specificity of 57-100% for HL; sensitivity range of 43-100% and specificity of 67-100% were reported for aNHL. A single meta-analysis of PET scanning for staging after primary treatment (Zijlstra, 2006) gave pooled sensitivity of 84% and specificity of 90% for HL and pooled sensitivity of 72% and specificity of 100% for aNHL.

Randomized control trials (RCTs) and other study designs

No RCTs were identified. One small, single center case series reported on PET for staging after primary treatment. Cerci (2010) investigated clinical effectiveness and cost effectiveness of 130 consecutive patients with HL who underwent primary treatment. Of 130 patients entered into the study, 50 had PET scans after completion of treatment and after staging by conventional imaging. The sensitivity of PET for recurrent or persistent disease compared to clinical follow-up was 100%; specificity was 92%, positive predictive value (PPV) of PET for the detection of disease was 92%, and negative predictive value (NPV) was 100%.

Overall summary, quality and limitations of the evidence

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 systematic reviews are all graded as fair and good. However, the underlying studies are all case series, which are considered to have a higher potential for serious bias than other higher validity study designs for answering questions of effectiveness. Systematic review authors performed quality assessment of the underlying studies and found a number of methodological flaws. The overall consistency of the results showing improved sensitivity and specificity of PET over conventional staging makes the overall strength of evidence for this finding moderate in strength.

Evaluation of residual mass after primary treatment

Systematic reviews and technology assessments

A second scenario for staging is the evaluation of a persistent mass after primary therapy. These masses may be persistent viable lymphoma or be non-viable fibrous tissue. Terasawa (2008), Facey (2007) and Kirby (2007) include evaluation of residual mass in their systematic reviews. For the evaluation of residual mass following treatment, Terasawa (2008) reported PET sensitivity of 43-100% and specificity of 67-100% for HL; PET has sensitivity of 33-87% and specificity of 75-100% for aNHL. Facey (2007) stated that PET and CT have similar sensitivity of 75-80%, but PET has superior specificity of 90% compared to CT of 45%. Kirby (2007) reported PET sensitivity of 50-100% and specificity of 78-100% for HL; PET has sensitivity of 60-78% and specificity of 94-100% for aNHL.

Randomized control trials (RCTs) and other study designs

No RCTs or other study designs were identified for evaluation of residual mass after treatment.

Overall summary, quality and limitations of the evidence

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

At the completion of primary treatment, a significant proportion of patients achieve complete remission or partial remission (responders); a smaller proportion of patients have progressive or non-responsive disease (non-responders). Current clinical management involves proceeding directly to secondary treatment in "non-responders"; "responders" will undergo clinical follow-up or "surveillance". Positron emission tomography has been advocated for a more accurate determination of remission or progression than conventional imaging methods.

Systematic reviews and technology assessments

Australia MSAC (2010) reports 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). The sensitivity of PET to predict 2-3 year PFS is 95-100% and the specificity is 78-99%; comparable sensitivity of CT is 70-87% and specificity is 25-91%. For HL, PET "responders" (i.e. those with a negative PET) have a 2-3 year PFS rate of 94-96% while PET "non-responders" (i.e. those with a positive PET) have a 2-3 year PFS rate of 0-33%. A negative CT has a 2-3 year PFS rate of 90% and a positive CT has a 2-3 year PFS rate of 0%. For aNHL, PET "responders" have a 2-3 year PFS rate of 87% while PET "non-responders" have a 2-3 year PFS rate of 7%. A negative CT has a 2-3 year PFS rate of 63%, and a positive CT has a 2-3 year PFS rate of 0%.

Randomized control trials (RCTs) and other study designs

No RCTs or other study designs were identified.

Overall summary, quality and limitations of the evidence

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.

Estimation of prognosis after secondary treatment

Systematic reviews and technology assessments

Two systematic reviews address the ability of PET to predict relapse or recurrence after salvage (secondary) treatment. Terasawa (2010) performed a meta-analysis of 12 case series of diagnostic efficacy of PET in predicting relapse or recurrence. Pooled estimates of sensitivity are 69% (95%CI 56-81%) and specificity are 81% (95%CI 73-87%). The likelihood ratio of a positive PET scan was 3.6 and the likelihood ratio of a negative PET scan was 0.38. Poulou (2010) performed a meta-analysis of 17 case series to determine the diagnostic efficacy of PET in predicting relapse from HL or aNHL. The hazard ratio of positive PET for relapse was 3.23 (95% CI 2.14-4.87).

Randomized control trials (RCTs) and other study designs

No RCTs were identified. Three case series address the ability of PET to predict relapse or recurrence after salvage treatment. Moskowitz (2010) evaluated 153 consecutive patients who had relapse or recurrence of HL who proceeded to salvage therapy and autologous stem cell transplant (ASCT). Each had CT plus PET or CT plus ^{67}gallium scanning after salvage therapy was performed (but before ASCT). Positive emission tomography and ^{67}gallium were compared to subsequent rates of relapse or recurrence. A PET or ^{67}gallium scan that returned to normal after salvage therapy but before ASCT was associated with a higher five year event-free survival of 75% compared with 31% for a persistently positive PET or ^{67}gallium scan ($p < 0.0001$) [calculated sensitivity = 50% and specificity = 84%]. ^{67}Gallium and PET scans were equally accurate in predicting relapse or recurrence.

Dodero (2010) evaluated 80 patients with HL or aNHL from four centers in Italy. These patients had salvage chemotherapy because of recurrence or refractory disease. Patients received PET scans prior to reduced-intensity conditioning and to ASCT. In patients with a negative PET scan (53% of patients), 10/24 (41%) patients had a recurrence of HL or aNHL after ASCT. In patients with a positive PET (47% of patients), 21/36 (60%) patients had recurrence of HL or aNHL ($p= 0.007$) [calculated sensitivity = 68%; calculated specificity = 63%].

Qiao (2011) performed a retrospective review of 31 patients with aNHL from a single center in China. These patients had salvage chemotherapy because of recurrence or refractory disease after primary therapy. Patients received PET scans prior and following ASCT. Both pre-ASCT and post-ASCT PET scans had similar diagnostic efficacy for prediction of relapse or recurrence (sensitivity = 75%, specificity = 87-93%, PPV = 82-86% and NPV = 76-78%).

Overall summary, quality and limitations of the evidence

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.

Surveillance of Asymptomatic Patients after Treatment

Systematic reviews and technology assessments

There are 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.

Randomized control trials (RCTs) and other study designs

No RCTs were identified. Five case series evaluate the value of PET during surveillance of patients with HL and aNHL in remission.

Goldschmidt (2011) performed a retrospective analysis of 125 patients with HL or aNHL who had recurrence or relapse more than one month after completion of primary treatment. The authors evaluated the role of clinical examination, CT and PET in detecting recurrence or relapse. Clinical examination or CT detected 54/79 (68%) of recurrence or relapse. Positron emission tomography detected recurrence or relapse in 25/79 (32%). There was no difference in survival rate between patients with relapse detected by PET or clinical examination.

Lee (2010) performed a retrospective analysis of 192 patients with HL in first remission. These patients received CT and PET/CT during a median of 31 months of follow-up. During the period of follow-up, three patients died, twelve patients had recurrence of HL and four patients had new primary cancers. A total of 474 PET scans were performed; 11/474 (2%) were true positive and 37/474 (7%) were false positive. Of 321 CT scans performed, 4/321 (1%) were true positive and 10/321 (3%) were false positive. The PPV of PET was 23% and of CT, 29%.

Crocchiolo (2009) performed a retrospective review of 27 patients with HL who were in complete remission. These patients had repeated PET scans during follow-up. Of the 27 patients, 15 had repeated negative PET scans and remained in remission. Of the 12 patients (13 PET scans) with a positive PET scan during follow-up, 7/13 (54%) were true positives and 6/13 (46%) were false positives. Positive predictive value of PET for recurrence is 54% and negative predictive value is 100%.

Mocikova (2010) performed a retrospective review of 113 patients with HL who had PET scans at the end of primary treatment and during follow-up. Of 113 patients, 19/113 (17%) had positive PET scans after primary treatment and proceeded to secondary treatment. Of 94 patients with negative PET scans after primary treatment, 67/94 (72%) had PET scans for routine follow-up; 27/94 (28%) had PET scans for clinically suspected relapse. For the 67 patients who had routine PET scans, 49/67 (74%) had persistently negative PET scans. Eighteen of 67 patients had positive PET scans of which 6/18 (33%) were true positives, and 12/18 (67%) were false positives. Positive predictive value of PET scan during routine follow-up was 26%, and NPV of PET scan was 90%.

Petrausch (2010) performed a retrospective review of 134 patients in complete remission for HL. The recurrence rate was higher in symptomatic (63%) than in asymptomatic (12%) patients. A residual mass after primary treatment and advanced stage of HL prior to primary treatment were also associated with a higher recurrence rate. Although PET detected all recurrences with a positive predictive value of 98%, the authors conclude that PET need only be performed on symptomatic patients or patients with a high risk of recurrence.

Overall summary, quality and limitations of the evidence

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 ability of PET to distinguish "responders" from "non-responders" before the end of primary treatment (that is midway through primary treatment) has the potential to alter patient management in two ways. First, a "responder" after two to four cycles might be able to have his treatment regimen shortened by several cycles; the evidence for this shortening of primary treatment has not been developed. Second, "non-responders" after two to four cycles might be transferred to secondary treatment without completing the course of primary treatment, thereby saving the cost and side effects of the remainder of primary treatment. The performance of a PET scan midway through primary treatment would have to be based on the assumption that either a positive or a negative PET scan would potentially alter patient management. If the intended management change was to shorten primary treatment in "responders", the NPV of PET to predict remission should be very high or the likelihood ratio of a negative test (LR-) should be very low. If the intended management change was to stop primary treatment and switch to secondary treatment in "non-responders", the PPV of PET to predict progression of disease should be very high or the likelihood ratio of a positive test (LR+) should be very high.

Systematic reviews and technology assessments

A systematic review by Terasawa (2009) evaluated the ability of PET to predict disease progression or relapse when performed in mid-cycle of primary treatment for HL or aNHL. The reported pooled sensitivity of PET to predict relapse or progression was 81% for HL and 78% for aNHL. Pooled specificity of PET was 97% for HL and 87% for aNHL. The reported pooled positive likelihood ratio for HL was 28.4 and for aNHL was 5.9. Reported pooled negative likelihood ratio for HL was 0.19 and for aNHL was 0.26.

Randomized control trials (RCTs) and other study designs

Three recent case series address the ability of PET to predict relapse or recurrence. Zinzani (2011) performed a retrospective review of 91 patients with aNHL who had PET mid-cycle during primary treatment. Of 91 patients, 56 (62%) had a negative PET at mid-cycle; of these 56 patients, 50 (89%) achieved complete remission and six (11%) had either delayed relapse or disease progression. Of the 35 (38%) patients who had a positive PET, seven (20%) achieved complete remission and 28 (80%) had relapse or progression. Calculated diagnostic efficacy for PET from Zinzani: sensitivity = 82%, specificity = 88%, PPV = 80%, NPV = 89. Duhrsen (2009) reported preliminary results on 128 patients with aNHL from a multi-center RCT designed to evaluate mid-cycle change in chemotherapy if mid-cycle PET indicates "non-response". In this study, if mid-cycle PET was negative, the recurrence rate of aNHL was 3% compared to recurrence rate of 17% for patients with positive PET ($p = 0.036$); sensitivity, specificity, PPV and NPV are not given in this preliminary report. Markova (2009) reported on the ability of mid-cycle PET to predict disease progression or recurrence in a case series of 50 patients with HL. Mid-cycle PET was negative in 36 (72%); these patients had no recurrence. Mid-cycle PET was

positive in 14 (28%); in these patients, two had disease progression. Sensitivity of mid-cycle PET was 100% and specificity was 75%. Positive predictive value for mid cycle PET was 15% and negative predictive value was 100%.

Overall summary, quality and limitations of the evidence

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 following table summarizes the evidence of diagnostic efficacy for use of PET in HL and aNHL.

Table 1. Diagnostic Efficacy of PET for HL and aNHL

Indication	Sensitivity	Specificity	PPV	NPV	Other
Original staging	88-100%	90-100%	NR*	NR*	NR*
Routine staging after primary treatment	HL = 84% (pooled) (95% CI 71-91%) aNHL = 72% (95% CI 61-82%)	HL = 90% (pooled) (95% CI 84-94%) aNHL = 100% (95% CI 97-100%)	NR*	NR*	NR*
Evaluation of residual mass	HL = 43-100 aNHL = 60-78	HL 67-100 aNHL = 94-100	NR*	NR*	NR*
Estimate prognosis after primary treatment	HL = 81% (pooled) aNHL = 78% (pooled)	HL = 97% (pooled) aNHL = 87% (pooled)	0%	63%	NR*
Estimate prognosis after secondary treatment	69% (pooled)	81% (pooled)	NR*	NR*	LR+ = 3.6 LR- = 0.387 Hazard ratio = 3.23
Monitoring of treatment (mid-cycle)	HL = 81% HL (pooled) aNHL = 78% (pooled)	HL= 97% (pooled) aNHL = 87% (pooled)	HL= 15% aNHL= 80%	HL = 100% aNHL= 89%	HL LR+ = 28.4; LR- = 0.19 aNHL
Monitoring of					

Indication	Sensitivity	Specificity	PPV	NPV	Other
treatment (mid-cycle)					LR+ = 5.9; LR- = 0.26

NR = Not reported or calculated*

Key Question #2: What is the evidence of clinical effectiveness of PET imaging in patients with known or suspected lymphoma compared to CT and MRI when used as an adjunct to CT or MRI or Gallium?

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.

Systematic reviews and technology assessments

The Australian MSAC (2010) TA reported no direct evidence for PET changing patient management or improving patient care. This TA noted that staging information changes patient care by altering the stage of the lymphoma. The TA also noted that if mid-cycle PET scan accurately predicted subsequent lymphoma recurrence, patients likely to have recurrence could be spared several cycles of primary chemotherapy before starting salvage or secondary treatment.

RCTs and other study designs

No RCTs were identified. Pommier (2011) reported a case series of 137 patients with stage I-II HL from 11 centers in France. Of the original 137 patients, 124 patients were scheduled for radiotherapy and had PET prior to radiotherapy. Of the 124 patients, 102/124 (82%) had no change in treatment plan, 6/124 (5%) had radiotherapy cancelled, and 16/124 (13%) had an altered radiotherapy plan.

Overall summary, quality and limitations of the evidence

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)

Key Question #1: What is the evidence of accuracy of PET (alone or combined on one system with CT—PET/CT) imaging for known or suspected lymphoma?

<u>Original staging by PET compared with conventional staging and PET as an incremental test in addition to conventional staging</u>

Systematic reviews and technology assessments

The Australia MSAC (2010) technology assessment reports on two case series of 103 and 64 patients. In a study of comparative accuracy, Wohrer (2006) found PET (98%) and CT (94%) to have comparable sensitivity in the staging of 64 patients with iNHL. Karam (2006) reported on incremental accuracy of PET in addition to CT in 103 patients with iNHL. In this series, PET

identified additional positive findings in 13/47 patients (28%). Positive predictive value of PET was 100%.

RCTs and other study designs

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. The CT component, PET component and combined PET/CT scans were independently interpreted and analyzed. Statistics were calculated for individual nodal regions rather than for individual patients. In this study, PET/CT (99%) had higher sensitivity than either CT (70%) ($p < 0.001$) or PET (68%) alone ($p < 0.001$).

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. Positron emission tomography detected additional lymphoma sites in 37/74 (50%) of patients, but PET failed to detect lymphoma sites detected by conventional staging in 33/74 (45%) patients; these 33 patients represent false negative PET scans. Gallium scans identified additional lymphoma sites in 5/16 (30%) of patients. Positron emission tomography identified 55 additional sites compared to 35 additional sites for gallium.

Le Dortz (2010) retrospectively reviewed 45 patients with iNHL who underwent initial staging with CT and PET. In this group, PET detected more nodal and extra-nodal sites than CT; PET resulted in up-staging eight of 45 patients (19%).

Bodet-Milin (2010) retrospectively reviewed 45 patients with mantle cell lymphoma (iNHL) who underwent PET in addition to conventional scanning prior to treatment. Positron emission tomography detected lymphoma sites in all 44 patients (100% sensitivity). An additional 37 lymphoma sites were identified by PET (incremental positives), but eight sites identified by conventional imaging were not seen on PET (false negatives).

Overall summary, quality and limitations of the evidence

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.

Assessment of suspected recurrent iNHL

Systematic reviews and technology assessments

As reported in the Australia MSAC (2010) technology assessment, Karam (2006) reported on incremental use of PET compared to conventional imaging in evaluation of patients with suspected recurrence. In this small study, PET identified 1/30 (3%) additional patients with recurrent iNHL.

Estimation of prognosis during or after treatment

RCTs and other study designs

No RCTs were identified. Le Dortz (2010) reported, in a case series of 45 patients with follicular NHL, that PET findings of nodal involvement of at least six nodal areas, extra-nodal involvement or bone marrow involvement were associated with a statistically significant increased risk of incomplete response to treatment or early relapse in patients with follicular lymphoma.

Bodet-Milin (2010) reported, in a case series of 44 patients with mantle cell NHL, that PET scan findings after completion of primary treatment for patients with mantle cell lymphoma had 100% sensitivity and 88% specificity for predicting relapse within one year of treatment. Positive predictive value of PET = 62%, and NPV = 100% in predicting early relapse.

Overall summary, quality and limitations of the evidence

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.

The following table summarizes the evidence for diagnostic efficacy of PET for iNHL:

Table 2. Diagnostic Efficacy of PET for iNHL

Indication	Sensitivity	Specificity	PPV	NPV	Other
Original staging	99%	NR*	NR*	NR*	NR*
Assessment of suspected recurrent iNHL	NR*	NR*	NR*	NR*	NR*
Estimate prognosis after primary treatment	100%	88%	62%	100%	NR*
Histological transformation of iNHL to aNHL	91-93%	65-87%	NR*	NR*	LR pos. = 2.6-7.2 LR neg = 0.08-0.14

Key Question #2: What is the evidence of clinical effectiveness of PET imaging in patients with known or suspected lymphoma compared to CT and MRI when used as an adjunct to CT or MRI or Gallium?

RCTs and other study designs

No RCTs were identified. Scott (2009) reported on change in management after PET staging in a case series of 74 patients with iNHL. Treating physicians made management plans blinded to PET results and then again after given PET results. They then rated the degree of change in their management plans. Results from PET resulted in no changes in 7%, low changes in 59%, medium changes in 7% and high changes in 27%. Actual management was evaluated compared to original management plans. Treatment was unchanged in 74% and was different in 26%. Of the patients whose treatment was changed, the performed treatment was appropriate given the PET findings.

Overall summary, quality and limitations of the evidence

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.

Hodgkin and Aggressive Non-Hodgkin Lymphoma and Indolent Non-Hodgkin Lymphoma

For the remaining Key Questions, the evidence for HL and NHL will be combined rather than reported separately.

Key Question #3: What is the evidence that PET imaging in patients with known or suspected lymphoma has differential efficacy or safety issues in subpopulations?

There is no evidence on subpopulations.

Key Question #4: What is the evidence of PET for lymphoma safety profile?

Systematic reviews and technology assessments

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.

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. The ACR estimates additional lifetime risk of fatal cancer from radiation doses of 30 mSv to be "moderate" at a risk of 1 in 1,000 to 1 in 500. Lymphoma patients have a potentially lethal malignancy. In addition, NHL affects primarily older adults who have a shorter life span during which to manifest tissue damage from radiation. However, HL patients are often younger patients many of whom will be cured and have a long life span. Although individual patients and their doctors may make different decisions on the relative risks and benefits from the radiation associated with PET/CT, the radiation doses may inform their decisions.

There are no data on the number of incidental findings from PET used for the various indications identified in this report. As is noted, PET scans have a small but real number of false positives in lymphoma patients. This group of false positive PET scans may result in additional biopsies or in mistaken upstaging of HL and NHL patients.

Overall summary, quality and limitations of the evidence

There is limited evidence on safety. Although there is a 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.

Key Question #5: What is the evidence about the cost impact of PET for patients with known or suspected lymphoma?

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.

Systematic reviews and technology assessments

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.

RCTs and other study designs

No RCTs were identified. Cerci (2010) evaluated 130 consecutive patients with HL in Brazil. Patients who were considered in complete remission (58%) on CT were followed clinically, and patients who were considered to have progressive disease on CT (1%) proceeded to secondary therapy. Fifty patients (31%) who had unconfirmed complete or partial remission had PET. Of the 50 patients who received PET, 23/50 (46%) had negative PET and 27/50 (54%) had positive PET—25 true positives and 2 false positives. Local restaging costs for all 50 patients were US $350,000 without PET and US $283,000 with PET for an average savings of $1340 per patient. The authors estimated that using PET for this group of patients would result in an overall 1% savings for HL patients in Brazil.

Lee (2010) evaluated 192 patients with HL in remission after primary treatment in the US. These patients received both CT and PET follow-up over a median of 31 months. The cost to detect a single recurrence with this follow-up protocol was US $100,000, and the radiation dose was 147 mSv.

Strobel (2007) performed a retrospective analysis of 68 patients with HL and NHL in Switzerland. These patients had PET in mid-cycle and at the end of primary treatment. A total of 196 PET scans were performed including 53 PET scans at the end of treatment on patients who had a negative PET in mid-cycle. The authors believe that these end of treatment PET scans on patients with negative mid-cycle PET scans could be avoided with a 26% overall savings in PET scanning costs. The study did not consider the alternative strategy of omitting the mid-cycle PET.

Overall summary, quality and limitations of the evidence

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.

Guidelines

Summary of Guidelines and Quality Assessment

A total of nine guidelines were identified 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. Summary tables of the guidelines and their quality assessment ratings are included in Appendix F, and the guideline quality assessment tool is included in Appendix G.

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 following table summarizes the reported guidelines:

Table 3. Guideline Recommendations

Guideline	NCCN HL	NCCN NHL	Juweid (IHPL)	ACR HL F/U	ACR HL Stage I-II
Diagnosis	NA*	NA*	NA*	NA*	NA*
Primary Staging	Recommend	Optional	Recommend	NA*	
Secondary Staging	Recommend	Not recommend	Recommend	NA*	
Estimate Prognosis	Recommend	Not recommend	Recommend if results will alter management	NA*	Only as part of a clinical trial
Surveillance	Not recommend	Not recommend	NA*	Not recommend	NA*

NA = not addressed*

Comparison of guidelines and evidence summary

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.

Policy Considerations

As part of the Washington HTA report on PET scanning in lymphoma, coverage policies for Medicare, Blue Cross Blue Shield, Aetna, and GroupHealth were reviewed. The following section provides summaries of these coverage policies. Details of the policies are provided in Appendix H.

Medicare National Coverage Decision

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.

Private Payers

Aetna

Aetna's Clinical Policy Bulletin *Positron Emission Tomography (PET)* (2010) considers PET as **medically necessary** for lymphoma when the following general and disease-specific criteria for diagnosis, staging, restaging and monitoring are met:

1. **Diagnosis:** The PET results may assist in avoiding an invasive diagnostic procedure, or the PET results may assist in determining the optimal anatomic location to perform an invasive diagnostic procedure.

2. **Staging:** PET is considered medically necessary in situations in which either the stage of lymphoma remains in doubt after completion of conventional imaging or the use of PET would potentially replace one or more conventional imaging studies.

3. **Restaging:** PET is considered medically necessary for restaging after completion of treatment for the purpose of detecting residual disease, for detecting suspected recurrence in persons with signs or symptoms of recurrence, or to determine the extent of recurrence. PET for post-treatment surveillance is considered experimental and investigational in asymptomatic patients.

4. **Monitoring:** PET for monitoring tumor response during the planned course of therapy is not considered medically necessary. Restaging occurs only after a course of treatment is completed (Aetna, 2010).

Blue Cross Blue Shield (BCBS)

No national coverage policies were identified. Coverage determinations are made on a per-state basis. No policies specific to Washington State were identified; however, Regence BlueShield of Washington (2011) requires prior authorization under the Radiology Quality Initiative in partnership with American Imaging Management.

1. **Initial treatment strategy**: one PET scan is medically necessary to identify an optimal site for biopsy or to stage a patient to determine the anatomic extent of malignancy when recommended therapy reasonably depends upon the extent of malignancy.

2. **Subsequent treatment strategy**: PET is medically necessary to assist the physician in the determination of optimal subsequent anti-tumor treatment strategies.

3. **Surveillance**: PET is not medically necessary.

4. **Screening**: PET is not covered as a screening test.

BCBS of Minnesota (2010) outlines specific criteria in their policy for PET for oncologic applications which follow the CMS Initial Treatment Strategy and Subsequent Anti-tumor Treatment Strategy framework. In addition BCBS of Minnesota considers PET for early treatment response assessment and surveillance to be INVESTIGATIVE.

GroupHealth

GroupHealth (2010) follows CMS National Coverage Determination for Medicare members. For non-Medicare members, GroupHealth covers PET for lymphoma for:

1. **Diagnosis:** PET results may assist in determining the optimal location to perform an invasive diagnostic procedure. It is not covered for other diagnostic uses or screening (testing patients without symptoms).

2. **Staging and re-staging:** PET is covered when staging remains in doubt after conventional staging and when clinical management of the patient would differ depending on the stage of lymphoma. Re-staging includes re-staging in the setting of recurrence and restaging following completion of a treatment regimen.

3. **Monitoring of therapy:** PET is NOT covered.

The following table summarizes coverage policies for Medicare and four private insurers:

Table 4. Payment by Payer and PET Indication

Indication	CMS	Aetna	Blue Cross	GroupHealth
Diagnosis	Cover to determine optimal location for biopsy	Cover to determine optimal location for biopsy	Cover to determine optimal location for biopsy	Cover to determine optimal location for biopsy
Staging and restaging	Cover	Cover	Cover	Cover
Monitoring of therapy	Cover if necessary to determine optimal treatment strategies	Not cover	Cover if necessary to determine optimal treatment strategies	Not cover
Surveillance	Not address	Not cover	Not cover	Not address
Screening	Not cover	Not address	Not cover	Not address

Summary

General conclusions

Lymphoma is a heterogeneous group of lympho-proliferative malignancies involving lymph nodes, bone marrow, the spleen and other extra-lymphatic organs. Lymphomas are classified as HL and NHL, and NHL are further classified as aNHL and iNHL. Positron emission tomography is an imaging test using a radioactive glucose analog ^{18}FDG to locate areas of tumor. Positron emission tomography has been used for staging of lymphoma before and after treatment, estimation of prognosis during and after treatment, evaluation of potential recurrence and follow-up during remission.

There is no evidence for the use of PET for screening patients for lymphoma or for use of PET in making a diagnosis of lymphoma. Guidelines recommend against the use of PET in making a diagnosis as biopsy is always required to make a histological diagnosis.

Positron emission tomography appears to be sensitive and specific in the staging of lymphoma. Sensitivity and specificity appear to be higher for HL and aNHL than for iNHL and higher for initial staging than for staging after primary or secondary treatment. Positron emission tomography appears to be better than CT or gallium for initial and subsequent staging when the modalities are compared against one another. Positron emission tomography appears to have little incremental benefit when added to conventional staging. Since most PET scanning is now performed as PET/CT which gives PET and CT information from the same study, there seems to be little benefit to performing the two examinations separately. Guidelines recommend the use of PET (PET/CT) for staging of HL and aNHL. The NCCN guideline considers PET to be optional for staging of iNHL.

Positron emission tomography is sensitive and specific in predicting subsequent outcomes for HL and aNHL. Positron emission tomography is more sensitive and specific after primary treatment than secondary treatment and is more sensitive and specific for HL and aNHL than for iNHL. The diagnostic efficacy of PET for predicting subsequent outcomes is not sufficiently high for current guidelines to recommend its use except in the setting of clinical trials.

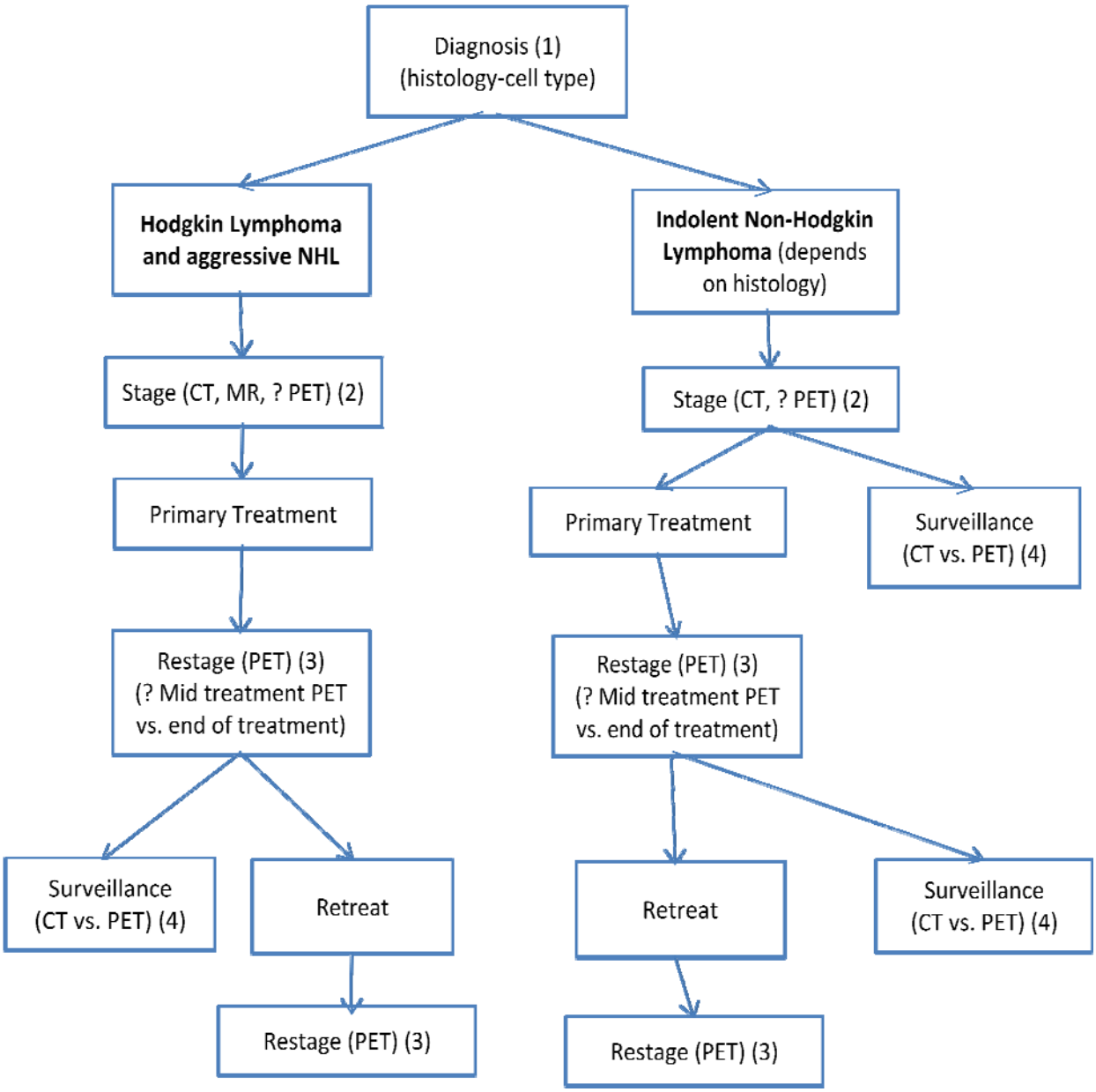
Surveillance PET on asymptomatic patients in remission has more false positive results than true positive results. The use of PET for surveillance adds radiation dose and financial costs without proven clinical value. Guidelines recommend against the use of PET for surveillance.

Monitoring of treatment with mid-cycle PET scans for both HL and aNHL shows moderate sensitivity and specificity of PET to predict subsequent outcome. The most important figures for altering management are NPV or LR (to potentially reduce the number of cycles in "responders") and PPV or LR+
(to potentially switch from primary treatment to secondary treatment in mid-cycle in "non-responders"). Positive predictive values are 96% for HL and 86% for aNHL; NPVs are 84% for HL and 80% for aNHL. It is uncertain if these values justify making management changes in mid-treatment.

Limitations of the evidence

The major limitation of the evidence is that the primary studies used in the SRs, MAs, TAs and guidelines are case series; case series provide less rigorous evidence than randomized control trials (RCTs). RCTs are difficult to perform for studies of diagnostic tests. This results in most of the evidence coming from cases series that are a much weaker form of evidence and contain several methodological flaws. The TAs, SRs, MAs and guidelines used in this report are all well performed. In several indications for PET, meta-analyses of multiple studies show homogeneous results with statistically significant diagnostic parameters; for these the strength of the evidence is moderate. However, for a number of indications, the studies have heterogeneous results or comparators; or there are very few studies and patients. For these, the overall strength of the evidence is low.

Appendix A. Clinical Management Algorithm



(1) No evidence to support PET for screening or diagnosis. Diagnosis will always require histology in order to classify lymphoma type.

(2) Most guidelines now advocate PET for initial staging.

(3) Most guidelines advocate PET as better than CT or gallium for predicting if primary treatment will result in remission.

(4) Most guidelines advocate that surveillance be performed with either plain x-rays or CT and not with PET.

Appendix B. Radiation Dose from Common X-ray and CT Examinations

This comes from a Patient Safety publication for clinicians and patients from the Radiologic Society of North America and the American College of Radiology. The following table is excerpted from this publication which can be accessed in full at http://www.radiologyinfo.org/en/safety/index.cfm?pg=sfty_xray&bhcp=1.

The table gives a comparison of medical radiation dose and background radiation exposure for several radiological procedures. It gives an estimate of the additional lifetime risk of developing a fatal cancer from medical radiation. The additional risk is rated on a scale ranging from negligible to moderate. The quantification of these terms is listed at the end of the table.

For this procedure:	* Your approximate effective radiation dose is:	Comparable to natural background radiation for:	** Additional lifetime risk of fatal cancer from examination:
ABDOMINAL REGION:			
Computed Tomography (CT)-Abdomen and Pelvis	15 mSv	5 years	Low
Computed Tomography (CT)-Abdomen and Pelvis, repeated with and without contrast material	30 mSv	10 years	Moderate
Computed Tomography (CT)-Colonography	10 mSv	3 years	Low
Intravenous Pyelogram (IVP)	3 mSv	1 year	Low
Radiography (X-ray)-Lower GI Tract	8 mSv	3 years	Low
Radiography (X-ray)-Upper GI Tract	6 mSv	2 years	Low
BONE:			
Radiography (X-ray)-Spine	1.5 mSv	6 months	Very Low
Radiography (X-ray)-Extremity	0.001 mSv	3 hours	Negligible
CENTRAL NERVOUS SYSTEM:			
Computed Tomography (CT)-Head	2 mSv	8 months	Very Low

For this procedure:	* Your approximate effective radiation dose is:	Comparable to natural background radiation for:	** Additional lifetime risk of fatal cancer from examination:
Computed Tomography (CT)-Head, repeated with and without contrast material	4 mSv	16 months	Low
Computed Tomography (CT)-Spine	6 mSv	2 years	Low
CHEST:			
Computed Tomography (CT)-Chest	7 mSv	2 years	Low
Computed Tomography (CT)-Chest Low Dose	1.5 mSv	6 months	Very Low
Radiography-Chest	0.1 mSv	10 days	Minimal
DENTAL:			
Intraoral X-ray	0.005 mSv	1 day	Negligible
HEART:			
Coronary Computed Tomography Angiography (CTA)	16 mSv	5 years	Low
Cardiac CT for Calcium Scoring	3 mSv	1 year	Low
MEN'S IMAGING:			
Bone Densitometry (DEXA)	0.001 mSv	3 hours	Negligible
WOMEN'S IMAGING:			
Bone Densitometry (DEXA)	0.001 mSv	3 hours	Negligible
Mammography	0.4 mSv	7 weeks	Very Low

Note for pediatric patients: Pediatric patients vary in size. Doses given to pediatric patients will vary significantly from those given to adults.

* The effective doses are typical values for an average-sized adult. The actual dose can vary substantially, depending on a person's size as well as on differences in imaging practices.

**** Legend:**

Risk Level	Approximate additional risk of fatal cancer for an adult from examination:
Negligible:	less than 1 in 1,000,000
Minimal:	1 in 1,000,000 to 1 in 100,000
Very Low:	1 in 100,000 to 1 in 10,000
Low:	1 in 10,000 to 1 in 1000
Moderate:	1 in 1000 to 1 in 500
Note: These risk levels represent very small additions to the 1 in 5 chance we all have of dying from cancer.	

Appendix C. Updated Search Strategy

1. exp Lymphoma/di, pa, ra, ri, us
2. exp Positron-Emission Tomography/
3. 1 and 2
4. limit 3 to english language
5. limit 4 to yr="2009 -Current"

Appendix D. Summary of Findings for Hodgkin Lymphoma and Aggressive Non-Hodgkin Lymphoma

Key Question 1: Diagnostic Accuracy of PET for screening, diagnosis, staging and surveillance.

Reference Study Design and number of studies	Intervention/ Comparators/ Reference Standard	Outcomes Evaluated and Main Findings	Quality Rating and Comments
Screening No evidence was found for screening for lymphoma with PET **Diagnosis** No evidence was found for diagnosis of lymphoma with PET			
Original staging by PET (or PET/CT) compared with conventional staging			
Kwee (2008) SR of 17 case series on PET; 4 case series on PET/CT and 3 case series on CT. (Included in Australia MSAC 2010)	Intervention: PET or PET/CT Comparator: CT, Reference standard: Histology or clinical follow-up	**Sensitivity and Specificity of PET, CT to detect lymphoma sites:** **Patients with HL and aNHL (populations mixed in summary figures).** PET sensitivity = 88%; specificity = 100%; PET/CT sensitivity = 97-100%; specificity = 100% (one study only) CT sensitivity = 88% specificity = 86%	Good quality SR. Authors' quality assessment of individual studies was moderate quality.
Facey (2007) TA of one SR and 7 case series. (Included in Australia MSAC 2010)	Intervention: PET or PET/CT Comparator: CT or ^{67} Gallium Reference standard: concordance with conventional work-up	**Sensitivity and Specificity of PET, CT to detect lymphoma sites:** **Patients with HL and aNHL (populations mixed in summary figures).** PET sensitivity = 79-100%; specificity ≥ 90%; PET sensitivity greater than ^{67} Gallium citrate; PET better than or equal to CT for pooled HL and NHL patients	Good quality SR. Authors' quality assessment of individual studies was moderate quality.

Reference Study Design and number of studies	Intervention/ Comparators/ Reference Standard	Outcomes Evaluated and Main Findings	Quality Rating and Comments
Kirby (2007) SR of 4 case series. (Included in Australia MSAC 2010)	Intervention: PET Comparator: CT or ^{67} Gallium Reference standard: concordance of results with CT findings and clinical follow-up	**Sensitivity and Specificity of PET, gallium to detect lymphoma sites:** **Patients with HL and aNHL (populations mixed in summary figures).** PET sensitivity = 87-100%; specificity not calculated for HL Sensitivity for CT or Gallium = 20-93%	Poor quality SR. Individual studies not quality rated by authors.
Pakos (2005) MA of 13 case series. (Included in Australia MSAC 2010)	Intervention: PET Comparator: none Reference standard: bone marrow biopsy	**Sensitivity and Specificity of PET to detect lymphoma sites in bone marrow:** **Patients with HL and aNHL (populations mixed in summary figures).** PET sensitivity for bone marrow infiltration = 51%; specificity = 91%	Fair quality SR. Individual studies not quality rated by authors.
Van Ufford (2011) Case series of 22 patients with lymphoma in single center in The Netherlands	Intervention: MRI whole body Comparator: PET/CT Reference standard: PET/CT	**Sensitivity and Specificity of PET, CT and MRI to detect lymphoma sites**: **Patients with HL and aNHL (populations mixed in summary figures).** MRI and PET/CT concordant in staging = 17/22 (77%) MRI under-stages compared to PET/CT = 0/22 (0%) MRI over-stages compared to PET/CT = 5/22 (23%)	Poor quality study of 22 patients with HL or aNHL. PET/CT is the reference standard.
PET as an incremental test in addition to conventional staging			

Reference Study Design and number of studies	Intervention/ Comparators/ Reference Standard	Outcomes Evaluated and Main Findings	Quality Rating and Comments
Australia MSAC (2010) SR of three case series (33, 46 and 22 patients)	Intervention: PET plus CT Comparator: CT Reference standard: concordance with CT	**Sensitivity and Specificity of PET, CT to detect lymphoma sites:** **Patients with HL and aNHL (populations mixed in summary figures).** PET detected additional sites in 18-60% of patients. These incremental sites were both true positive and false positive for lymphoma. The ratio of true positive to true negative sites detected by PET was 3:1. Less frequently, PET indicated absence of disease at sites suspected as positive on conventional imaging; however, a large portion of these incremental negative results were found to be false negative.	Good quality SR. Quality of underlying studies rated as fair to poor by TA authors.
Restaging after primary treatment			
Australia MSAC (2010) SR of two case series of 26 and 45 patients	Intervention: PET or PET/CT Comparator: CT Reference standard: clinical follow-up	**Sensitivity and Specificity of PET, CT to detect lymphoma sites:** **Patients with HL and aNHL (populations mixed in summary figures).** PET sensitivity = 96-100%;specificity = 70-99% CT sensitivity = 70-87%; specificity = 26-91%.	Good quality SR. Only two small studies.
Terasawa (2008) SR of 16 case series. (Included in Australia MSAC 2010)	Intervention: PET Comparator: CT or MRI Reference standard: clinical follow-up with or without histology	**Sensitivity and Specificity of PET to detect lymphoma sites:** **Patients with HL and aNHL (populations mixed in summary figures).** PET sensitivity 85-100%; specificity = 57-100% for HL PET sensitivity 43-100%; specificity = 67-100% for NHL	Good quality SR. Authors' assessment of primary studies noted limited quality with bias and variation validity.

Reference Study Design and number of studies	Intervention/ Comparators/ Reference Standard	Outcomes Evaluated and Main Findings	Quality Rating and Comments
Kwee (2008) SR of 17 case series on PET; 4 case series on PET/CT and 3 case series on CT. (Included in Australia MSAC 2010)	Intervention: PET or PET/CT Comparator: CT Reference standard: clinical follow-up or histology	**Sensitivity and Specificity of PET, CT to detect lymphoma sites:** **Patients with HL and aNHL (populations mixed in summary figures).** CT sensitivity = 25-100%; specificity = 42-76% PET sensitivity =71-100%; specificity = 57-100% PET/CT sensitivity = 91-100; specificity = 90-100%	Good quality SR. Authors' quality assessment of individual studies was moderate quality.
Kirby (2007) SR of 27 case series. (Included in Australia MSAC 2010)	Intervention: PET or PET/CT Comparator: conventional imaging Reference standard: concordance of results with CT findings and clinical follow-up	**Sensitivity and Specificity of PET to detect lymphoma sites:** **Patients with HL and aNHL (populations mixed in summary figures).** HL: Sensitivity of PET for disease recurrence = 87-100% compared to sensitivity of conventional imaging = 20-93%. Specificity not reported.	Poor Quality SR. Individual studies not quality rated by authors.
Zijlstra (2006) SR and MA of 15 case series	Intervention: PET Comparator: none Reference standard: clinical follow-up	**Sensitivity and Specificity of PET to detect lymphoma sites:** **Patients with HL and aNHL (populations mixed in summary figures).** For HL, pooled sensitivity = 84% (95% CI 71-91%); pooled specificity = 90% (95% CI 84-94%) For aNHL, pooled sensitivity = 72% (95% CI 61-82%); pooled specificity = 100% (95% CI 97-100%)	Good quality SR. Authors assess quality of primary studies as fair.

Reference Study Design and number of studies	Intervention/ Comparators/ Reference Standard	Outcomes Evaluated and Main Findings	Quality Rating and Comments
Cerci (2010) Single center prospective case series of 130 consecutive patients with HL in Brazil	Intervention: PET Comparator: none Reference standard: clinical follow-up	**Sensitivity and Specificity of PET to detect lymphoma sites.** **127 (of original 130) consecutive patients with HL were staged with CT following completion of primary treatment.** Of 127 staged with CT, 74 (58%) were considered in complete remission and were followed clinically. 3 were considered to have progressive disease and were biopsy proven. These proceeded directly to secondary treatment. 50 (39%) were considered unconfirmed complete or partial remission and underwent PET. Of the 50 patients with unconfirmed complete or partial remission on PET: 23/50 (46%) had negative PET; on clinical follow-up, no disease was found in any of the patients. 27/50 (54%) had positive PET; on clinical follow-up, 25 had confirmation of HL on biopsy and 2 had only inflammatory disease on biopsy. PET sensitivity = 100%; specificity = 92%; PPV = 92%; NPV = 100%	Good quality study.
Evaluation of residual mass after primary treatment			
Terasawa (2008) SR of 14 case series. (Included in Australia MSAC 2010)	Intervention: PET Comparator: none Reference standard: clinical follow-up with or without histology	**Sensitivity and Specificity of PET to detect lymphoma in patients with a residual mass:** Patients with HL and aNHL (populations mixed in summary figures). PET sensitivity = 43-100%; specificity = 67-100% for HL PET sensitivity = 33-87%; specificity = 75-100% for HL	Good quality SR. Authors assess individual studies for quality. Bias and variation limit the internal and external validity of the test results.
Facey (2007) SR of one HTA and three case	Intervention: PET Comparator: CT	**Sensitivity and Specificity of PET to detect lymphoma sites:** Patients with HL and aNHL (populations mixed in summary figures). PET and CT had similar sensitivity for detection of residual disease = 75-80%.	Good quality SR.

Reference Study Design and number of studies	Intervention/ Comparators/ Reference Standard	Outcomes Evaluated and Main Findings	Quality Rating and Comments
series. (Included in Australia MSAC 2010)	Reference standard: clinical follow-up	PET had superior specificity = 90% compared to 45% on CT	Authors do not assess individual studies for quality.
Kirby (2007) SR of 9 case series. (Included in Australia MSAC 2010)	Intervention: PET and PET/CT Comparator: conventional imaging Reference standard: concordance of results with CT findings and clinical follow-up	**Sensitivity and Specificity of PET to detect lymphoma sites:** Patients with HL and aNHL (populations mixed in summary figures). For HL, sensitivity of PET = 50-100%; specificity = 78-100% For aNHL. Sensitivity of PET = 60-78%; specificity = 94-100%.	Poor quality SR. Individual studies not quality rated by authors.
Estimation of prognosis during or after primary treatment			
Australia MSAC (2010) SR of two case series of 99 and 127 patients	Intervention: PET Comparator: CT Reference standard: progression-free survival by clinical follow-up	**Diagnostic efficacy of PET, CT to predict relapse or recurrence.** **Patients with HL or aNHL had PET or CT either mid-cycle or at the end of primary treatment. Results of PET or CT compared with two to three year progression-free survival (PFS):** For **HL**, PET "non-responders" (PET positive for tumor viability) had 2-3 year PFS = 19-33%; PET "responders" (PET negative for tumor viability) had 2-3 year PFS= 94-96% For **HL**, CT shows response had 2-3 year PFS = 90%, CT stable disease PFS = 79% and CT progressive disease had 2-3 year PFS = 0% For **aNHL**, PET "non-responders" had 2-3 year PFS = 7%; PET "responders" had 2-3 year PFS = 87% For **aNHL**, CT shows response had 2-3 year PFS = 63%, CT stable disease had 2-3 year PFS = 58% and CT progressive disease PFS = 0%.	Good quality SR. These results are based on two case series of 99 and 127 patients.

Reference Study Design and number of studies	Intervention/ Comparators/ Reference Standard	Outcomes Evaluated and Main Findings	Quality Rating and Comments
Monitoring of treatment in mid-cycle of primary treatment			
Terasawa (2009) SR of 13 case series	Intervention: PET scan during primary therapy Comparator: treatment failure Reference standard: clinical follow-up	**Diagnostic efficacy of PET, CT to predict relapse or recurrence.** **Patients with advanced-stage HL (360 patients) and diffuse large B-cell lymphoma (DLBCL) (311 patients) had PET scans in mid-cycle of primary treatment and compared with subsequent treatment failure (progression or relapse):** **HL**: PET pooled sensitivity = 81% (95% CI 72-89%); pooled specificity = 97% (95% CI 94-99%; Likelihood ratio (LR) for positive PET = 28 (95% CI 14-57) ; LR for negative PET = 0.19 (95% CI 0.12-0.30) **DLBCL (aNHL**): PET pooled sensitivity = 78% (95% CI 64-87%); pooled specificity = 87% (95% CI 75-93%. LR for positive PET = 5.9 (95% CI 2.8-12.3); LR for negative PET = 0.26 (95% CI 0.15-0.46)	Good quality SR. Authors' assessment of quality of primary studies shows fair quality. Treatment failure not defined in SR or in primary studies.
Zinzani (2011) Retrospective case series of 91 patients with NHL in Italy	Intervention: PET scan midway through treatment Comparator: none Reference standard: clinical follow-up	**Diagnostic efficacy of PET to predict relapse or recurrence.** **91 patients being treated for aggressive aNHL who had PET scan midway (6 weeks) through a 12 week course of chemotherapy. PET scan results are compared with progression or relapse of aNHL:** 91 patients experienced: 56 persistent complete remission, 11 delayed recurrence, 11 partial remission, 13 progression during therapy. PET scans at mid treatment: 56/91(62%) were negative; 35 (38%) were positive. Negative PET scan: 50/56 (89%) remained in complete remission; 4/56 (7%) had a delayed recurrence; 2/56 (4%) showed progression of disease. Positive PET scan: 6/35 (17%) remained in complete remission; 7/35 (20%) had delayed recurrence; 11/35 (315) had partial remission; 11/35 (35%) had progressive disease. (p = 0.001) [Calculated sensitivity = 82% calculated specificity = 89%; calculated PPV = 82%; calculated NPV = 89%]	Good quality study.
Duhrsen (2009) Multi-center prospective	Intervention: PET after two cycles (out of	**Diagnostic efficacy of PET to predict relapse or recurrence.** **175 patients enrolled in prospective RCT of altered mid-cycle chemotherapy if mid-cycle PET scan was positive:**	Good quality study.

Reference Study Design and number of studies	Intervention/ Comparators/ Reference Standard	Outcomes Evaluated and Main Findings	Quality Rating and Comments
case series of 128 patients with NHL in Germany	six) of chemotherapy Comparator: none Reference standard: clinical follow-up	128/175 patients reached stage of interim PET scanning If mid-cycle PET is positive, recurrence rate = 17% If mid-cycle PET is negative, recurrence rate = 3%	Preliminary results; main purpose of RCT is to evaluate the effect of change in treatment if PET scan is positive.
Markova (2009) Single center prospective case series of 50 patients with HL in Czech Republic	Intervention: PET after 4 cycles (of 6 or 8 cycles) of chemotherapy Comparator: none Reference standard: clinical follow-up	**Diagnostic efficacy of PET to predict relapse or recurrence.** **50 patients enrolled in prospective RCT of three drug regimens had PET in mid cycle of chemotherapy:** PET scan positive 14/50; PET scan negative 36/50. If PET positive in mid-cycle: 2/14 patients had progressed or relapsed. If PET negative at mid-cycle: 0/36 patients had progressed or relapsed. [Calculated sensitivity = 75% specificity = 100%] PPV = 2/14 (15%); NPV = 36/36 (100%)	Good quality study. Small study with low progression or relapse rate which may over-estimate the NPV.
Prognosis after secondary treatment			
Terasawa (2010) SR of 12 case series	Intervention: PET Comparator: none Reference standard: progression-free survival	**Diagnostic efficacy of PET to predict relapse or recurrence.** **PET scan after salvage chemotherapy before high-dose chemotherapy in patients with relapsed or refractory HL or aggressive NHL.** For detection of relapse or recurrence, PET pooled sensitivity = 69% ((95% CI 56-81%); pooled specificity = 81% (95% CI 73-87%). LR positive PET = 3.6 LR negative PET 0.38	Good quality SR. Authors report methodological flaws in all studies.

Reference Study Design and number of studies	Intervention/ Comparators/ Reference Standard	Outcomes Evaluated and Main Findings	Quality Rating and Comments
Poulou (2009) SR and MA of 16 case series	Intervention: PET Comparator: none Reference standard: progression-free survival	**Diagnostic efficacy of PET to predict relapse or recurrence.** **PET scan after salvage chemotherapy before high-dose chemotherapy in patients with relapsed or refractory HL or aggressive NHL.** Pooled hazard ratio for positive PET prior to ASCT = 3.23 (95% CI 2.14-4.87).	Fair quality SR and MA. Authors did not quality rate studies included in MA.
Moskowitz (2010) Single center prospective case series of 153 patients in USA	Intervention: CT and PET Comparator: CT and Gallium Reference standard: event free survival (EFS) and overall survival (OS)	**Diagnostic efficacy of PET to predict relapse or recurrence.** **153 patients with HL either relapsed after primary treatment or refractory to primary treatment were evaluated with CT and PET or CT and gallium before salvage treatment and autologous stem cell transplant (ASCT) and after ASCT:** Normalization (conversion to negative) of CT and PET or CT and gallium before ASCT was the only factor associated with improved EFS and overall survival OS. 5 year-EFS for negative PET or gallium = 75% 5 year-EFS for positive PET = 31% [calculated sensitivity = 50% and specificity = 84%] Difference between PET negative and PET positive is statistically significant ($p<0.001$) Hazard risk for normalization of PET or gallium = 3.4 for EFS and 3.7 for OS. No significant difference between normalization of PET or gallium.	Good quality study.
Dodero (2010) Four center retrospective case series of 80 patients in Italy	Intervention: PET Comparator: none Reference standard: progression free survival (PFS)	**Diagnostic efficacy of PET to predict relapse or recurrence.** **80 patients with HL or NHL who showed either complete remission or partial remission to salvage chemotherapy had PET before reduced-intensity conditioning and allogentic stem cell transplant:** PET negative 42/80 (53%); in PET negative 10/42 (24%) patients had recurrent lymphoma PET positive 38/80 (47%); if PET positive, 21/38 (60%) patients had recurrent lymphoma. Difference between PET negative and PET positive is statistically significant (p=0.007) [calculated sensitivity = 68%; calculated specificity = 63%]	Fair quality study.

Reference Study Design and number of studies	Intervention/ Comparators/ Reference Standard	Outcomes Evaluated and Main Findings	Quality Rating and Comments
Qiao (2010) Single center retrospective case series of 31 patients in China	Intervention: PET Comparator: none Reference standard: PFS and OS	**Diagnostic efficacy of PET to predict relapse or recurrence.** **31 patients with NHL scheduled for salvage chemotherapy and ASCT had PET after salvage chemotherapy and prior to and after ASCT.** **Diagnostic efficacy of PET to predict recurrence or relapse :** **Test** — **Sensitivity** — **Specificity** — **PPV** — **NPV** — **Accuracy** PET before ASCT — 75% — 87% — 86% — 76% — 81% PET after ASCT — 75% — 93% — 82% — 78% — 84%	Fair quality study.
Surveillance of asymptomatic patients to detect lymphoma recurrence or relapse			
Goldschmidt (2011) Case series of 125 patients at single center in Israel	Intervention: PET/CT Comparator: clinical evaluation, CT	**Diagnostic efficacy of PET to detect relapse or recurrence of lymphoma. 125 patients with relapse of HL or NHL ≥ 1 months after completion of primary therapy:** **Mode of detection of relapse:** Clinical exam or CT = 54/79 (68%) total; for HL, 14/26 (54%); for NHL, 40/53 (75%) PET/CT 25/79 (32%) total; for HL, 12/26 (46%); for NHL, 13/53 (25%) **Survival after relapse:** No difference in survival rate between relapse detected by clinical exam, CT or PET.	Poor quality study. Small single center study with only 125 patients out of 1992 total lymphoma population qualifying for analysis (selection bias). Potential lead time bias. Potential of false positive PET noted by authors.

Reference Study Design and number of studies	Intervention/ Comparators/ Reference Standard	Outcomes Evaluated and Main Findings	Quality Rating and Comments
Petrausch (2010) Retrospective case series of 134 at single center in Switzerland	Intervention: PET Comparator: none Reference standard: recurrence verified by histology vs. no recurrence verified by clinical follow-up	**Diagnostic efficacy of PET to detect relapse or recurrence of lymphoma. 134 patients in complete remission after primary therapy for HL:** **Recurrence of HL during follow-up after primary treatment:** Asymptomatic patients: 10/83 (12%) Symptomatic patients: 32/51 (63%) **Performance of PET in detection of recurrence:** PET detected all recurrences None of patients with a negative PET scan after primary therapy had a relapse PPV of PET for recurrence = 98%. **Risk factors for recurrence:** Morphological residual mass after primary treatment: Hazard ratio (HR) = 7.6 Symptomatic: HR 14.6 Advanced stage prior to primary therapy: HR = 3.6	Poor quality study. Retrospective, small study. Higher prevalence of recurrence than other studies which may indicate selection bias (suspected recurrence leads to referral for PET).
Crocchiolo (2009) Retrospective case series of 27 patients with HL in Italy	Intervention: PET Comparator: none Reference standard: biopsy or clinical follow-up	**Diagnostic efficacy of PET to detect relapse or recurrence of lymphoma:** **27 patients with HL in relapse after primary or secondary treatment had 165 PET scans during follow-up (median 5 scans per patient):** 15/27 (55%) had repeated negative PET scans and remained in clinical remission 12/27 (45%) had positive PET scans (13 PET scans total); of these 7/13 (54%) were true positives and confirmed recurrence; 6/13 (46%) were false positives. Sensitivity of PET for recurrence = 100%; Specificity for recurrence = 70% PPV of PET for recurrence = 54%; NPV for recurrence = 100%	Fair quality study. Small retrospective study; methods for selecting this group of patients not mentioned; probable selection bias.
Mocikova	Intervention:	**Diagnostic efficacy of PET to detect relapse or recurrence of lymphoma:**	Poor quality

Reference Study Design and number of studies	Intervention/ Comparators/ Reference Standard	Outcomes Evaluated and Main Findings	Quality Rating and Comments
(2010) Retrospective case series of 113 patients at single center in Czech Republic	PET Comparator: none Reference standard: clinical follow-up	**113 patients with HL had PET scans at completion of primary treatment and during follow-up:** 94/113 (83%) of patients had negative PET scans at end of primary treatment; 19/113 (17%) had positive PET scans. Of 94 negative PET scan patients, 67/94 ((72%) had routine follow-up PET scans; 27/94 (28%) had follow-up PET scans for clinically suspected relapse. Routine PET follow-up: 49/67 (74%) had continued negative PET scans; 18/67 (26%) had subsequent positive PET scans; of 18 positive PET scans, 6/18 (33%) were true positives and 12/18 (67%) were false positives. Of PET scans for suspected recurrence, 16/27 (60%) of PET scans were negative; 11/27 (40%) were positive; of 11 positive PET scans 5/11 (45%) were true positives and 6/11 (55%) were false positives. After primary treatment, NPV of PET for recurrence = 90% After primary treatment PPV of PET for recurrence = 26%.	retrospective study.
Lee (2010) Single center retrospective case series of 192 patients in USA	Intervention: PET Comparator: CT Reference standard: RFS and costs.	**Diagnostic efficacy of PET to detect relapse or recurrence of lymphoma:** **192 adult patients with HL in remission after primary treatment. These patients were followed up with 474 PET/CT and 321 CT scans during a median follow-up of 31 months.** Of 192 patients, 3/192 (2%) died for an overall survival rate of 98%. Of 192 patients, 12 cases of recurrent HL and 4 cases of new primary cancers = 16/192 (8%) for an EFS of 92%. PET scans: 11/474 were true positives; 37/474 were false positive. PPV of positive PET = 23% CT scans: 4/321 were true positive; 10/321 were false positive. PPV of positive CT = 29%.	Fair quality study from US.

Key Question 2: Effectiveness of PET in reducing other tests, changing patient management, improving quality of life, increasing survival or reducing morbidity.

Reference Study Design and number of studies	Intervention/ Comparators/ Reference Standard	Outcomes Evaluated and Main Findings	Quality Rating and Comments
Australia MSAC (2010)	Intervention: PET Comparator: none Reference standard: none	**Change in management from PET.** Australia MSAC reports no direct evidence for PET changing patient management or improving patient outcomes. This TA points out that PET scans performed in mid-cycle primary treatment or in secondary (salvage) treatment have the potential to stop further treatment when PET predicts non-response of treatment. No studies investigating changing treatment on the basis of PET scans in mid-cycle were reported by this TA. One study (Duhrsen 2009 above) reports PET accuracy results from a study designed to investigate the results of changing treatment in mid-cycle if PET scan predicts non-response.	Good quality SR. No evidence
Pommier (2011) Prospective case series of 137 patients at 11 centers in France	Intervention: PET Comparator: none Reference standard: self reported change in management after getting PET results	**Change in management from PET.** **124 patients (out or original 137) with stage I-II HL had PET immediately before undergoing radiotherapy for HL; 123/124 had chemotherapy before radiotherapy.** Pre-treatment PET resulted in: No change in treatment plan in 102/124 (82%) Cancelled radiotherapy in 6/124 (5%) Altered radiotherapy plan in 16/124 (13%)	Fair quality study. Prospective, multi-center case series with well defined reference standard. Fair quality.

Appendix E. Summary of Findings for Indolent Non-Hodgkin Lymphoma

Key Question 1: Diagnostic Accuracy of PET for screening, diagnosis, staging and surveillance.

Reference Study Design and number of studies	Intervention/ Comparators/ Reference Standard	Outcomes Evaluated and Main Findings	Quality Rating and Comments
Original staging by PET (or PET/CT) compared with conventional staging			
Australia MSAC (2010) SR of two case series of 103 and 64 patients	Intervention: CT and PET Comparator: CT only Reference standard: re-biopsy or clinical follow-up	**Sensitivity and Specificity of PET, CT to detect lymphoma sites.** **Incremental accuracy of PET in addition to CT compared with CT alone:** Patients with HL and aNHL (populations mixed in summary figures). Karam (2006) reported additional positive findings on PET in 13/47 (28%). PPV of PET = 13/13 (100%) **Comparative accuracy of PET and CT:** Wohrer (2006) reported comparative accuracy of PET and CT: Sensitivity PET = 98%; Sensitivity CT = 94%	Good quality SR. MSAC rates the studies as fair quality.
Fueger (2009) Single center retrospective case series of 45 patients in USA	Intervention PET/CT Comparator: CT and PET Reference standard: clinical follow-up (including additional imaging and biopsy	**Sensitivity and Specificity of PET, CT to detect lymphoma sites:** **45 patients with indolent NHL had PET/CT. Scans were independently analyzed for separate CT, PET and combined PET/CT results. Statistics were determined on a nodal region rather than patient basis.** 33/45 patients had evidence of active disease; 117/585 nodal areas were involved with active NHL (by clinical follow-up). **Test** — **Sensitivity** — **Specificity** — **Accuracy** PET — 68% — 98% — 92% CT — 70% — 100% — 95% PET/CT — 99% — 100% — 99.8% P value PET/CT — p<0.001 (vs. CT or PET) — p<0.001 (vs. PET only) — p<0.001	Poor quality study. Small, heterogeneous population. Analysis on basis of nodal areas rather than individual populations.

Scott (2009) Prospective case series of 74 patients from six centers in Australia	Intervention: PET Comparator: Gallium Reference standard: concordant findings and clinical follow-up	**Sensitivity and Specificity of PET, CT, gallium, US to detect lymphoma sites** **74 patients with indolent NHL received PET at time of staging; 16 of these same patients also received gallium scans. All patients had conventional staging with CT, ultrasound, fine needle aspiration, biopsy or clinical examination before PET or gallium:** In 74 patients who had PET after conventional staging: 37/74 (50%) had additional NHL sites identified incremental positive PET); 33/74 (45%) had sites on conventional imaging not identified on PET (false negative PET). PET resulted in up-staging in 21/74; down-staging in 3/74. In 16 patients who had gallium scans after conventional imaging: Gallium identified additional NHL sites in 5/16 (30%) of patients. Gallium resulted in up-staging in 4/16 patients and down-staging in 1/16. Comparison of gallium and PET: PET identified 55 disease sites and gallium identified 35 sites in the same patients. PET resulted in upstaging of 7/16; gallium resulted in upstaging in 4/16.	Good quality study.
Le Dortz (2010) Retrospective case series of 45 patients from France	Intervention: PET Comparator: CT Reference standard: unclear	**Sensitivity and Specificity of PET, CT to detect lymphoma sites** **45 patients with follicular NHL who underwent primary treatment (note, patients who were followed rather than treated were not included in this series). All patients had CT and PET/CT:** PET detected 87 more abnormal nodal areas than CT (258 vs. 171 = 51% more). PET detected 16 additional extranodal sites than CT (34 vs. 18 = 89% more). PET resulted in upstaging of 8/45 (20%) of patients.	Poor quality study. Reference standard unclear; selection bias.
Feeney (2010) Retrospective case series of 135 patients from single center in USA	Intervention: PET Comparator: none Reference standard: unclear	**Sensitivity and Specificity of PET to detect lymphoma sites** **135 patients with T-cell NHL who underwent PET during initial staging or when recurrence was suspected were analyzed:** 122/135 (90%) patients had abnormal PET uptake. 55/122 (45%) had cutaneous involvement on PET. 95/122(78%) had lymph node involvement on PET. 54/122 (44%) had extranodal involvement (other than cutaneous) on PET.	Poor quality study. Retrospective descriptive article. Reference standard is not stated.

Bodet-Milin (2010) Multi-center retrospective case series of 44 from France	Intervention: PET Comparator: conventional staging Reference standard: biopsy	**Sensitivity and Specificity of PET to detect lymphoma sites.** **44 patients with mantle cell NHL had PET scanning in addition to conventional staging prior to treatment.** 44/44 (100%) had positive PET uptake. 37 sites were positive on PET and not on conventional imaging (incremental positive PET). 8 sites were positive on conventional imaging but not on PET (false negative PET).	Poor quality study. Some of data relates to patients and some relates to lymphoma sites.
Assessment of suspected recurrent disease			
Australia MSAC (2010) SR of one case series of 103 patients	Intervention: CT and PET Comparator: CT only Reference standard: re-biopsy or clinical follow-up	**Sensitivity and Specificity of PET, CT to detect lymphoma sites.** **Incremental accuracy of PET in addition to CT compared with CT alone in patients with confirmed recurrence of indolent NHL:** Patients with HL and aNHL (populations mixed in summary figures). Karam (2006) reported additional finding on PET scanning after CT in 1/30 patients for an incremental yield of 3%.	Good quality SR. MSAC rates the study as fair quality.
Estimation of prognosis during or after primary treatment			
Le Dortz (2010) Retrospective case series of 45 patients from France	Intervention: PET Comparator: none Reference standard: clinical follow-up	**Diagnostic efficacy of PET to predict relapse or recurrence.** **74 patients with follicular NHL who underwent primary treatment were evaluated with PET/CT before and after treatment:** PET/CT results were correlated with incomplete therapeutic response or early relapse. PET findings of at least 6 nodal areas involved, extranodal involvement or bone marrow involvement correlated with incomplete response or early relapse with a p value < 0.05.	Poor quality study. Selection bias.

Bodet-Milin (2010) Multi-center retrospective case series of 44 from France	Intervention: PET Comparator: conventional imaging: Reference standard: clinical follow-up	**Diagnostic efficacy of PET to predict relapse or recurrence.** **44 patients with mantle cell NHL had PET scanning in addition to conventional staging prior to treatment and 36 patients also had PET and conventional staging at the end of treatment. Findings on PET were correlated with relapse rates within one year.** Positive PET findings at initial staging had a sensitivity of 100% and specificity of 88% for predicting relapse at year 1. PPV for PET = 62% and NPV = 100%.	Poor quality study.
Histological transformation of indolent to aggressive NHL			
Australia MSAC (2010) SR of two case series of 38 and 37 patients	Intervention: PET Comparator: none Reference standard: biopsy or clinical follow-up	**Diagnostic efficacy of PET to detect histological transformation of iNHL to aNHL.** **Accuracy of PET in detecting histological transformation of indolent NHL to aggressive NHL** **Bodet-Milan (2008):** All patients had suspected histological transformation on basis of development of Stage B symptoms or enlargement of tumor mass. Sensitivity of PET = 14/15 (93%) (95% CI 66-99%); specificity of PET = 20/23 (87%) (95% CI 65-97%); LR for negative PET = 0.08; LR for positive PET = 7.2 **Bruzzi (2008):** Only 17/37 patients had suspected histological transformation. PET sensitivity = 10/11 (91%) (95% CI 57-99%); specificity of PET = 65-80% (95% CI 44-82%); LR negative PET = 0.11-0.14; LR positive PET = 2.6-4.6.	Good quality SR. Small series. MSAC identifies methodological deficiencies in Bruzzi. MSAC rates the studies as high and fair quality.

Key Question 2: Effectiveness of PET in reducing other tests, changing patient management, improving quality of life, increasing survival or reducing morbidity.

Reference Study Design and number of studies	Intervention/ Comparators/ Reference Standard	Outcomes Evaluated and Main Findings	Quality Rating and Comments
Scott (2009) Prospective case series of 74 patients from six centers in Australia	Intervention: management plans before PET Comparator: Management plans after PET Reference standard: self analysis of change in management decision	**Change in management from PET.** **Clinicians rated the change in management plan on a scale of none, low, medium or high:** Impact on management plans: none = 5 (7%); low = 44 (59%); medium = 5 (7%) and high = 20 (27%). **Actual management compared to post PET management plan:** 55/74 (74%) of treatment was the same as in the management plan. 19/74 (26%) of treatment was different than that in the management plan. Of the 19 patients whose treatment was altered, 17/19 had treatment that was appropriate to the PET findings.	Good quality study.

Key Question 4: Safety profile of PET for HL and NHL.

Reference Study Design and number of studies	Intervention/ Comparators/ Reference Standard	Outcomes Evaluated and Main Findings	Quality Rating and Comments
Australia MSAC (2010)	Safety of PET	This TA identifies no direct evidence on the safety of PET. It concludes that PET is safe based on assessments of PET for other indications.	Good quality SR. No evidence

Key Question 5: Costs of PET for HL and NHL.

Reference Study Design and number of studies	Intervention/ Comparators/ Reference Standard	Outcomes Evaluated and Main Findings	Quality Rating and Comments
Australia MSAC (2010)	Costs of PET	The Australia MSAC HTA identifies no published studies that it considers relevant or of sufficient quality to include in its SR.	Good quality SR. No evidence
Cerci (2010) Single center prospective case series of 130 consecutive patients with HL in Brazil	Intervention: PET Comparator: none Reference standard: cost effectiveness	**Total costs:** **127 (of original 130) consecutive patients with HL were staged with CT following completion of primary treatment.** Of 127 staged with CT, 74 (58%) were considered in complete remission and were followed clinically. 3 were considered to have progressive disease and were biopsy proven. These proceeded directly to secondary treatment. 50 (39%) were considered unconfirmed complete or partial remission and underwent PET. Of the 50 patients with unconfirmed complete or partial remission on PET: 23/50 (46%) had negative PET; on clinical follow-up, no disease was found in any of the patients. 27/50 (54%) had positive PET; on clinical follow-up, 25 had confirmation of HL on biopsy and 2 had only inflammatory disease on biopsy. Local restaging costs without using PET = $350,000; local restaging costs with PET = $283,000. Incremental cost effectiveness ratio for using PET for staging is $3268 to detect one true case. Applying these savings to all patients with HL in Brazil would result in a 1% cost savings by using PET to restage after primary treatment (in place of CT).	Good quality study. Moderate quality cost effectiveness study from Brazil.

Lee (2010) Single center retrospective case series of 192 patients with HL in USA	Intervention: PET Comparator: CT Reference standard: RFS and costs	**Total costs:** **192 adult patients with HL in remission after primary treatment. These patients were followed up with 474 PET/CT and 321 CT scans during a median follow-up of 31 months.** Of 192 patients, 3/192 (2%) died for an overall survival rate of 98%. Of 192 patients, 12 cases of recurrent HL and 4 cases of new primary cancers = 16/192 (8%) for an EFS of 92%. PET scans 11/474 were true positives; 37/474 were false positive. PPV of positive PET = 23% CT scans 4/321 were true positive; 10/321 were false positive. PPV of positive CT = 29%. Cost to detect a single recurrence or new primary cancer was $100,000. Radiation exposure to detect a single recurrence or new primary cancer was 147 mSv.	Fair quality cost effectiveness study from US.
Strobel (2007) Single center retrospective case series of 68 patients from Switzerland	Intervention: PET Comparator: none Reference standard: clinical follow-up	**Total costs:** **68 patients with HL or NHL had PET scan in mid-cycle and again at completion of primary treatment:** For HL, 22/30 (73%) had negative PET in mid cycle; 7/30 (24%) had partial remission in mid cycle and 1/30 (3%) had stable disease in mid cycle. If mid cycle PET was negative, 22/22 (100%) had complete remission on PET at the end of primary treatment. If mid cycle PET showed only partial remission or stable disease, PET at end of treatment showed complete remission in 6/8 (75%) and 2/8 (25%) had progressive disease. A total of 196 PET scans were carried out at mid-cycle and at the end of primary treatment at a cost of $1,900 (US) per scan. A total of 53 end treatment PET scans were performed on patients with mid-cycle PET scans that were negative. If PET was not performed at the end of treatment on patients with negative mid-cycle PET scans, there would be a 27% reduction in PET imaging costs.	Poor quality cost effectiveness study from Switzerland.

Appendix F. Summary of Guidelines

Recommending Body, Year Published	Guideline(s)	Evidence Base	Overall Quality
National Comprehensive Cancer Network (NCCN), 2011 (Hodgkin Lymphoma)	1. PET recommended for initial staging of HL and for evaluation of residual masses after treatment. 2. PET recommended after completion of treatment to determine prognosis. Use of PET has eliminated the "unproven complete remission" category. 3. PET scans not recommended for routine surveillance.	Literature review and expert consensus	Fair
National Comprehensive Cancer Network (NCCN), 2011 (Non-Hodgkin lymphoma)	1. PET scanning is recommended for aNHL for staging of aNHL but is considered optional for other NHLs. 2. NHLs are mostly avid for ^{18}FDG except for extra-nodal Mantle cell lymphomas. 3. In iNHL, PET not usually performed for staging. In iNHL which appears to be localized a PET scan may help identify occult sites of disease or be useful if concern exists about histologic transformation.	Literature review and expert consensus	Fair
Juweid (International Harmonization Project in Lymphoma), 2007 Recommendations apply to HL	1. PET is recommended for assessment of response to primary or salvage treatment. 2. PET is not required prior to treatment but its performance then improves interpretation of post-treatment PET scans. 3. After-treatment PET should not be performed before 3 weeks after chemotherapy and 8-12 weeks after radiation therapy. 4. PET during treatment of HL and aNHL is justified if findings will alter management.	Expert consensus	Poor

Recommending Body, Year Published	Guideline(s)	Evidence Base	Overall Quality
American College of Radiology (ACR) 2010. Follow-up of Hodgkin Lymphoma	Regular follow-up with PET scans in PET-negative patients at the end of therapy is not indicated. However, in patients with clinical findings suspicious for relapse, PET scan may be of value.	Literature review and expert consensus	Fair
American College of Radiology (ACR) 2011. Hodgkin Lymphoma: Favorable prognosis stage I-II	Trials will further clarify whether PET response can be used to guide treatment for Hodgkin's lymphoma. However, changes in therapy (either changing chemotherapy or omitting RT) based on PET response for early-stage patients are not supported by currently available data and should only be performed as part of a clinical trial	Literature review and expert consensus	Fair

Quality of Guidelines

Key Recommendations	Guidelines			
	NCCN NHL, 2011	**NCCN HL, 2011**	**Juweid, 2007**	**ACR, 2010, 2011**
Ending date of literature search	2010	2010	2006	2009
Section 1: Primary Criteria				
Rigor of Development: Evidence	fair	fair	poor	fair
Rigor of Development: Recommendations	fair	fair	fair	fair
Editorial Independence	poor	poor	poor	fair
Section 2: Secondary Criteria				
Scope and Purpose	good	good	good	good
Stakeholder Involvement	unclear	unclear	unclear	unclear
Clarity and Presentation	good	good	good	good
Applicability	good	good	good	good
Section 3: Overall Assessment of the Guideline				
How well done is this guideline?	fair	fair	poor	fair
Other Comments:	Comprehensive but PET use is not a central focus of guideline	Comprehensive but PET use is not a central focus of guideline	No methods section; several panel members have associations with manufacturers	PET use is not a central focus of these guidelines

Appendix G. Guideline Quality Assessment Tool

[This tool is adapted from the Appraisal of Guidelines Research & Evaluation (AGREE) II tool. The full AGREE II tool is available from http://www.agreetrust.org/resource-centre/agree-ii/]

MED PROJECT	Methodology Checklist: Guidelines		
Guideline citation *(Include name of organization, title, year of publication, journal title, pages)*			
MED Topic:		Key Question No.(s), if applicable:	
Checklist completed by:			Date:

SECTION 1: PRIMARY CRITERIA				
To what extent is there		***Assessment/Comments:***		
1.1	**RIGOR OF DEVELOPMENT: Evidence** • Systematic literature search • Study selection criteria clearly described • Quality of individual studies and overall strength of the evidence assessed • Explicit link between evidence & recommendations *(If any of the above are missing, rate as poor)*	GOOD	FAIR	POOR
1.2	**RIGOR OF DEVELOPMENT: Recommendations** • Methods for developing recommendations clearly described • Strengths and limitations of evidence clearly described • Benefits/side effects/risks considered • External review	GOOD	FAIR	POOR
1.3	**EDITORIAL INDEPENDENCE**[4] • Views of funding body have not influenced the content of the guideline • Competing interests of members have been recorded and addressed	GOOD	FAIR	POOR
If any of three primary criteria are rated poor, the entire guideline should be rated poor.				
SECTION 2: SECONDARY CRITERIA				
2.1	**SCOPE AND PURPOSE** • Objectives described	GOOD	FAIR	POOR

4 Editorial Independence is a critical domain. However, it is often very poorly reported in guidelines. The assessor should not rate the domain, but write "unable to assess" in the comment section. If the editorial independence is rated as "poor", indicating a high likelihood of bias, the entire guideline should be assessed as poor.

	• Health question(s) specifically described • Population (patients, public, etc.) specified			
SECTION 2: SECONDARY CRITERIA, CONT.				
2.2	**STAKEHOLDER INVOLVEMENT** • Relevant professional groups represented • Views and preferences of target population sought • Target users defined	GOOD	FAIR	POOR
2.3	**CLARITY AND PRESENTATION** • Recommendations specific, unambiguous • Management options clearly presented • Key recommendations identifiable • Application tools available • Updating procedure specified	GOOD	FAIR	POOR
2.4	**APPLICABILITY** • Provides advice and/or tools on how the recommendation(s) can be put into practice • Description of facilitators and barriers to its application • Potential resource implications considered • Monitoring/audit/review criteria presented	GOOD	FAIR	POOR
SECTION 3: OVERALL ASSESSMENT OF THE GUIDELINE				
3.1	How well done is this guideline?	GOOD	FAIR	POOR
3.2	Other reviewer comments:			

Description of Ratings: Methodology Checklist for Guidelines

The checklist for rating guidelines is organized to emphasize the use of evidence in developing guidelines and the philosophy that "evidence is global, guidelines are local." This philosophy recognizes the unique situations (e.g., differences in resources, populations) that different organizations may face in developing guidelines for their constituents. The second area of emphasis is transparency. Guideline developers should be clear about how they arrived at a recommendation and to what extent there was potential for bias in their recommendations. For these reasons, rating descriptions are only provided for the primary criteria in section one. There may be variation in how individuals might apply the good, fair, and poor ratings in section two based on their needs, resources, organizations, etc.

Section 1. Primary Criteria (rigor of development and editorial independence) ratings:

Good: All items listed are present, well described, and well executed (e.g., key research references are included for each recommendation).
Fair: All items are present, but may not be well described or well executed.
Poor: One or more items are absent or are poorly conducted

Appendix H. Payer Policy Comparison Table

Payer	Coverage Summary
Medicare Effective: 8/4/2010	**Medicare National Coverage Determinations Manual Chapter 1, Part 4** ***220.6.17 - Positron Emission Tomography (PET) (FDG) for Oncologic Conditions - (Various Effective Dates)*** *(Rev. 124, Issued: 09-24-2010, Effective: 08-04-2010, Implementation: 10-25-2010)* *FDG PET for Lymphoma covered for **Initial Treatment Strategy** and **Subsequent Treatment Strategy** as outlined below.* **Initial Anti-tumor Treatment Strategy** Effective for claims with dates of service on and after April 3, 2009, CMS has determined that the evidence is adequate to determine that the results of FDG PET imaging are useful in determining the appropriate initial treatment strategy for beneficiaries with suspected solid tumors and myeloma and improve health outcomes and thus are reasonable and necessary under §1862(a)(1)(A) of the Social Security Act (the Act). Therefore, effective for claims with dates of service on and after August 4, 2010, CMS will continue to nationally cover one FDG PET study for beneficiaries who have solid tumors that are biopsy proven or strongly suspected based on other diagnostic testing when the beneficiary's treating physician determines that the FDG PET study is needed to determine the location and/or extent of the tumor for the following therapeutic purposes related to the initial treatment strategy: • To determine whether or not the beneficiary is an appropriate candidate for an invasive diagnostic or therapeutic procedure; or • To determine the optimal anatomic location for an invasive procedure; or • To determine the anatomic extent of tumor when the recommended anti-tumor treatment reasonably depends on the extent of the tumor. In addition, effective for claims with dates of service on and after August 4, 2010, CMS believes that an NCD is not appropriate for addressing coverage for additional FDG PET scans for the therapeutic purposes related to the initial treatment strategy. Therefore, local Medicare contractors will have discretion to cover (or not cover) within their jurisdictions any additional PET scan for the therapeutic purposes related to the initial treatment strategy as described above. **Subsequent Anti-tumor Treatment Strategy** Lymphoma covered without exception.
Aetna Last review: 5/6/2011	**Aetna Clinical Policy Bulletin Number 0071: Positron Emission Tomography (PET)** PET and PET-CT Fusion are considered medically necessary for lymphoma, when the following general and disease-specific criteria for diagnosis, staging, restaging and monitoring are met:

Payer	Coverage Summary

A. General Criteria

4. **Diagnosis:** The PET results may assist in avoiding an invasive diagnostic procedure, or the PET results may assist in determining the optimal anatomic location to perform an invasive diagnostic procedure. In general, for most solid tumors, a tissue diagnosis is made prior to the performance of PET scanning. PET scans following a tissue diagnosis are performed for the purpose of staging, not diagnosis. Therefore, the use of PET in the diagnosis of lymphoma, is rarely considered medically necessary.
5. **Staging:** PET is considered medically necessary in situations in which clinical management of the member would differ depending on the stage of the cancer identified and *either*:
    a. the stage of the cancer remains in doubt after completion of a standard diagnostic workup, including conventional imaging (computed tomography, magnetic resonance imaging, or ultrasound); *or*
    b. the use of PET would potentially replace one or more conventional imaging studies when it is expected that conventional study information is insufficient for the clinical management of the member.
6. **Restaging:** PET is considered medically necessary for restaging after completion of treatment for the purpose of detecting residual disease, for detecting suspected recurrence in persons with signs or symptoms of recurrence, or to determine the extent of recurrence. Use of PET is also considered medically necessary if it could potentially replace one or more conventional imaging studies when it is expected that conventional study information is insufficient for the clinical management of the member. PET for post-treatment surveillance is considered experimental and investigational, where surveillance is defined as use of PET beyond the completion of treatment, in the absence of signs or symptoms of cancer recurrence or progression, for the purpose of detecting recurrence or progression or predicting outcome.
7. **Monitoring:** PET for monitoring tumor response during the planned course of therapy is not considered medically necessary. Restaging occurs only after a course of treatment is completed.

B. Disease-Specific Criteria

Lymphoma: FDG-PET scans are considered medically necessary for the diagnosis*, staging and restaging of lymphoma when the general medical necessity criteria for oncologic indications (A. listed above) are met.

*Note: A diagnostic tissue sample is usually obtainable without PET localization. Therefore, PET for diagnosis of lymphoma is rarely considered medically necessary.

Payer	Coverage Summary
Regence Blue Shield – Washington (2011)	*No medical necessity criteria identified. Prior authorization required under Radiology Quality Initiative (see below).* **Radiology Quality Initiative** Designed to promote the use of advanced diagnostic imaging services based on widely accepted clinical judgment. Regence has partnered with American Imaging Management (AIM) to administer the program for our Regence members. **Requirements for Positron emission tomography (PET) studies** • Order numbers must be obtained by ordering or referring non-radiological physicians or other health care professionals before scheduling elective outpatient diagnostic imaging services for Regence members. • Radiology providers and free-standing imaging centers should confirm that an order number has been obtained prior to service delivery **Order numbers are not required for:** • 23-hour observation • Emergency room (ER) visits • Inpatient hospitalization • Contracted urgent care centers • Outpatient surgeries (hospital or freestanding surgery centers) **Order numbers for urgent care services:** • If the patient is referred by an urgent care provider to the ER for advanced diagnostic imaging services, an order number from AIM is NOT needed. • If a patient is referred by an urgent care provider to a free-standing imaging center for advanced diagnostic imaging services, an order number from AIM IS needed.
Blue Cross Blue Shield – Minnesota Effective Date: 12/20/2010	**Medical and Behavioral Health Policy Manual** **Section: Radiology; Policy Number: V-03** **POSITRON EMISSION TOMOGRAPHY (PET): ONCOLOGIC APPLICATIONS** **Initial Treatment Strategy** Positron emission tomography (PET) or positron emission tomography/computed tomography (PET/CT) may be considered MEDICALLY NECESSARY as an Initial Treatment Strategy (Diagnosis and Staging) for known or suspected malignancy when the following criteria are met: • One (1) PET or PET/CT for myeloma, solitary pulmonary nodule, and all solid tumors when the test is needed to determine the location and/or extent of the suspected or proven malignancy in order to make at least one of the

Payer	Coverage Summary

following determinations:

- Whether or not the patient is an appropriate candidate for an invasive diagnostic or therapeutic procedure; or
- The optimal anatomic location for an invasive procedure; or
- The anatomic extent of malignancy, when recommended therapy reasonably depends on the extent of malignancy.

AND

- Other standard imaging modalities (e.g., CT, MRI, or ultrasound) are either not indicated or unable to conclusively provide the required information.

Subsequent Treatment Strategy

Positron emission tomography (PET) or positron emission tomography/computed tomography (PET/CT) may be considered
MEDICALLY NECESSARY as a Subsequent Treatment Strategy (Restaging and Monitoring) for known or suspected malignancy
when the following criteria are met:

- PET or PET/CT for myeloma and all solid tumors when the test is performed after completion of initial therapy for malignancy and the imaging results are required to assess therapeutic success, in order to establish the need for any subsequent therapy, by determining at least one of the following:
  - Presence or extent of residual disease; or
  - Presence or extent of recurrent disease; or
  - Presence or extent of metastasis; or
  - Other assessment of tumor response

  AND
- Other standard imaging modalities (e.g., CT, MRI, or ultrasound) are either not indicated or unable to conclusively provide the required information. PET or PET/CT is considered INVESTIGATIVE when used as a Subsequent Treatment Strategy (Restaging and Monitoring) for all other tumor types (solid and non-solid), including, but not limited to: Small cell lung, Pancreas, Kidney, Solitary pulmonary nodule, Prostate, Basal and squamous cell skin cancer, and Bladder.

Early Treatment Response Assessment

PET or PET/CT for early treatment response assessment, also referred to as Interim PET, (i.e., involving comparison of PET images before treatment and at some interval during the initial course of treatment) is considered INVESTIGATIVE due to a lack of evidence demonstrating an impact on improved health outcomes.

Surveillance

Positron emission tomography (PET) or PET/CT as a surveillance tool for patients with

Payer	Coverage Summary
	cancer or with a history of cancer when there are no new or worsening symptoms, physical findings, lab tests, or other imaging tests suggesting recurrence or progression of malignancy is considered INVESTIGATIVE due to a lack of evidence demonstrating an impact on improved health outcomes. **Coverage:** Prior authorization: No. However, services with specific coverage criteria may be reviewed retrospectively to determine if criteria are being met. Retrospective denial may result if criteria are not met.
Group Health Last review: 12/7/2010	**Clinical Review Criteria For Non-Medicare Members:** PET Scan using FDG for **diagnosis, staging and re-staging** of lymphoma is covered when one of the following is true: a) For the **diagnosis** of lymphoma, the PET results may assist in determining the optimal location to perform an invasive diagnostic procedure. It is not covered for other diagnostic uses or screening (testing patients without symptoms). b) For **staging and re-staging** lymphoma both are true: i. The stage of the cancer remains in doubt after completion of a standard diagnostic work-up, including conventional imaging unless PET could potentially replace one or more conventional imaging studies. ii. Clinical management of the patient would differ depending on the stage of the cancer identified. c) **Re-staging** includes: i. Re-staging in the setting of recurrence and ii. Re-staging following completion of a therapeutic regimen or to assess whether complete response has been achieved. Monitoring of tumor response during the planned course of therapy (when no change in therapy is being contemplated) is not covered. The efficacy of this scan is still being evaluated. Because medical staff members have asked to have this study covered for cancer detection, a criteria set for medical necessity has been developed which involves review by the Medical Director of the radiology department and maintenance of a request log with determination outcomes. **For Medicare members, the policy refers to the Medicare National Coverage Determination manual.**

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