

**Health Technology Clinical Committee**

**Date: September 16<sup>th</sup>, 2011**

**Time: 8:00 am – 3:30 pm**

**Location: SeaTac Airport Conference Center – Central Auditorium**

**Adopted: November 18<sup>th</sup>, 2011**

**HTCC MINUTES**

**Members Present:** Dr. Carson Odegard; Dr. Richard Phillips; Dr. Craig Blackmore; Dr. Marie-Annette Brown; Dr. Kevin Walsh; Dr. Christopher Standaert; Dr. Michelle Simon; Dr. Joann Elmore; Dr. Michael Souter; Dr. Seth Schwartz and Dr. David McCulloch.

**HTCC FORMAL ACTION**

1. **Call to Order:** Dr. Blackmore, Chair, called the meeting to order. Sufficient members were present to constitute a quorum.
2. **June 17<sup>th</sup>, 2011 Meeting Minutes:** Chair referred members to the draft minutes; motion to approve and second, and adopted by the committee.
  - *Action: Eight committee members approved the June 17<sup>th</sup>, 2011 meeting minutes. Three committee members abstained from voting.*
3. **Applied Behavioral Analysis (ABA or ABA Therapy) based Behavioral Interventions for the Treatment of Autism Spectrum Disorder draft Findings & Decision:** Chair referred members to the draft findings and decision and called for further discussion or objection. The ABA findings & decision was approved and adopted by the committee.
  - *Action: Ten committee members approved the ABA Therapy findings & decision document. One committee members abstained from voting.*
4. **Positron Emission Tomography (PET) Scans for Lymphoma:** The HTCC reviewed and considered the PET technology assessment report; information provided by the Administrator; state agencies; public members; and heard comments from the evidence reviewer, HTA program, an invited clinical expert, the public and agency medical directors. The committee considered all the evidence and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

<b>HTCC COMMITTEE COVERAGE DETERMINATION VOTE</b>			
	<b>Not covered</b>	<b>Covered Unconditionally</b>	<b>Covered Under Certain Conditions</b>
Positron Emission Tomography (PET) Scans for Lymphoma	0	1	10

- ✓ *Discussion:* The Chair called for discussion on conditions related to PET due to the majority voting for coverage. The following conditions were discussed and approved by a majority:
  - *Limitations of Coverage:* Positron Emission Tomography (PET) scans for Lymphoma is a covered benefit when the following conditions are met:
    1. One scan for initial treatment planning;

2. Additional scans for restaging with clinical suspicion of disease progression or treatment failure subject to agency approval;
3. No coverage for routine surveillance

✓ *Action:* The committee chair directed HTA staff to prepare a Findings and Decision document on PET reflective of the majority vote.

- 5. Hip Surgery for Femoroacetabular Impingement Syndrome (FAI):** The HTCC reviewed and considered the FAI technology assessment report; information provided by the Administrator; state agencies; public members; and heard comments from the evidence reviewer, HTA program, an invited clinical expert, the public and agency medical directors. The committee considered all the evidence and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

HTCC COMMITTEE COVERAGE DETERMINATION VOTE			
	Not covered	Covered Unconditionally	Covered Under Certain Conditions
Hip Surgery for Femoroacetabular Impingement Syndrome (FAI)	9	0	2

✓ *Action:* The committee chair directed HTA staff to prepare a Findings and Decision document on FAI reflective of the majority vote.



**SUMMARY OF HTCC MEETING TOPICS, PRESENTATION, AND DISCUSSION**

**Agenda Item: Welcome & Introductions**

- ✓ The Health Technology Clinical Committee (HTCC) met on September 16<sup>th</sup>, 2011

**Agenda Item: Meeting Open and HTA Program Update**

Dr. Craig Blackmore, HTCC Chair, opened the public meeting.

- ✓ New committee member, Dr. David McCulloch, was introduced
- ✓ Leah Hole-Curry, HTA Program Director, provided an overview of the agenda, meeting guide and purpose, room logistics and introductions.
  - Newly hired HTA Program Director, Josh Morse, was introduced. Josh Morse will start officially at HCA-HTA on October 1<sup>st</sup>, 2011.

**Agenda Item: Previous Meeting Business**

June 17<sup>th</sup>, 2011 Meeting Minutes: Chair referred members to the draft minutes and called for a motion and discussion. Minutes were circulated prior to the meeting and posted.

- *Action: Eight committee members approved the June 17<sup>th</sup>, 2011 meeting minutes. Three committee members abstained from voting.*

Applied Behavioral Analysis (ABA or ABA Therapy) based Behavioral Interventions for the Treatment of Autism Spectrum Disorder draft Findings & Decision: Chair referred members to the draft findings and decision and called for further discussion. The draft findings and decision document was circulated prior to the meeting and posted to the website for a two week comment period. Five public comments were received, included in the meeting materials, and were reviewed and discussed.

- *Action: Ten committee members approved the ABA Therapy findings & decision document. One committee members abstained from voting.*

**Agenda Item: HTA Program Review**

- Leah Hole-Curry, HTA Program Director, provided the HTA context for the meeting and an update on program activities including:
  - State purchasing context and budget reductions and reform efforts, medical technology is driver of increased medical costs and has quality gaps
  - HTA is designed to use reliable science and independent committee to get best information on what works, what is safe and what provides value
  - HTA outcomes include transparency; reports and articles reviewed; and coverage decisions made
  - Comparison with private industry and Medicare decisions completed
  - Program has received recent recognition from public media, clinical press, and various medical and health policy groups with either story highlights or invited presentations

**Agenda Item: Positron Emission Tomography (PET) Scans for Lymphoma Topic Review**

Leah Hole-Curry, HTA Program Director, introduced the technology topic up for discussion:

- ✓ Staff provided an overview of the timeline and referred HTCC members to the included key questions and population of interest for PET review.
- ✓ Staff welcomed, per HTCC request, an invited clinical expert; Dr. Janet Eary is a Professor of Radiology, working in Nuclear Medicine and Molecular Imaging. Dr. Eary completed a conflict of interest and indicated no conflicts.

**Agenda Item: Public Comments**

The Chair called for public comments.

- ✓ Scheduled Public Comments: No stakeholders scheduled time for public comments.
- ✓ Open Public Comments: No individuals provided comments during the open portion.

**Agenda Item: PET Topic – Agency Comments**

Dr. Jeff Thompson, Medical Director, Health Care Authority, presented the agency utilization and outcomes for PET to the committee, full presentation published with meeting materials.

- ✓ PET Background:
  - Positron emission tomography (PET) is a diagnostic imaging test using a positron emitting radioactive particle.
  - In using PET for cancer, the radioactive particle is usually 18fluorine (18F) which is incorporated into a glucose molecule. 18FDG preferentially accumulates in areas of high glucose metabolism such as areas of active cancer. 18FDG 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 (anatomical vs. biologic)
- ✓ Agency Concerns:
  - Technology is not new, but the application is changing. Routine use of PET is not authorized due lack of literature on outcomes.
  - A PET Scan policy was brought forward to the Advanced Imaging Management (AIM) work group for Medicaid
  - PET is authorized for diagnosis for Lung and GI cancers to abate risky biopsies
  - PET is authorized when conventional scanning (CT, MRI, plain films) are non-diagnostic
  - PET is authorized if lab test and conventional scanning is not congruent (normal scan with increasing CA125 ovarian cancer)
  - Key concerns:
    - Will this additional method increase benefits when lesser cost screening has known outcomes?



- More expensive/additional test increases costs – what about outcomes?
- Is the measure of a new test only SN/SP – what about PPV?
- Is it appropriate to measure PET against CT scan – anatomic vs. biologic?
- Are there better outcomes or reduced costs for the extra radiation dose?

✓ Current State Agencies Policies:

- DSHS allows PET when: there is a Non-diagnostic conventional scan for diagnosis, biopsies, staging/restaging or surveillance
- UMP allows PET in lymphoma:
  - SURVEILLANCE OF ASYMPTOMATIC PATIENTS AFTER THERAPY FOR MALIGNANCY PET or PET/CT is considered not medically necessary for patients who have completed therapy twelve (12) or more months ago for lymphoma or six (6) or more months ago for all other malignancies unless the patient demonstrates signs, symptoms, laboratory or other objective findings suggestive of recurrence or spread of the original malignancy
  - SCREENING: PET or PET/CT IS NOT COVERED AS A SCREENING TEST (I.E., FOR EVALUATION OF PATIENTS WITHOUT SPECIFIC SIGNS AND SYMPTOMS OF DISEASE).

✓ State Agencies Questions:

- Safety: Benefit vs. Harms issues?
  - Do less expensive diagnostics have less risk for radiation exposure?
  - Does the identification of non-specific findings (false positives) lead to unnecessary interventions?
  - Is that a Red Flag for over use of PET?
  - Mode was 1, the mean was 2, and the max per case 19 PET ( > 40 CT scans) in 5 year period
- Effectiveness:
  - Is the evidence of sensitivity, specificity, and reliability enough to make a benefit decision?
  - Can we define when an MRI/CT/Gallium scan vs. PET is needed in a diagnosis, staging/restaging, surveillance?
- Cost
  - Does routine PET lead to higher cost for unproven outcomes?
  - What is the impact of differential activity in the community (multiple PET and CT Scans per case)?

✓ Cost and Utilization for PET and CT/PET by Year:

*PEB PET Scans, Costs and Counts for patients diagnosed with Lymphoma 2007-2010*

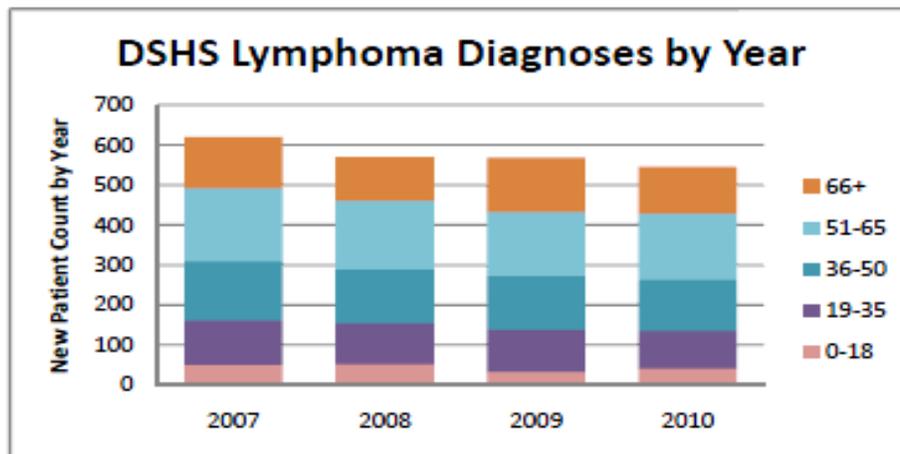
<b>PEB PET Scans</b>	<b>2007</b>	<b>2008</b>	<b>2009</b>	<b>2010</b>	<b>Overall</b>
Members w/PET scans per year	140	168	161	148	409
Scans per year	221	263	246	235	965
Average scans per year**	1.58	1.57	1.53	1.59	2.36
Annual Cost	\$489,106	\$744,611	\$605,527	\$612,285	\$2,451,529
Average overall cost	\$2,213	\$2,831	\$2,461	\$2,605	\$2,540

PEB PET Scans	2007	2008	2009	2010	Overall
Average Primary Payer cost	\$3,421	\$3,876	\$3,756	\$3,797	\$3,735

*DSHS PET Scans, Costs and Counts for patients diagnosed with Lymphoma 2007 -2010*

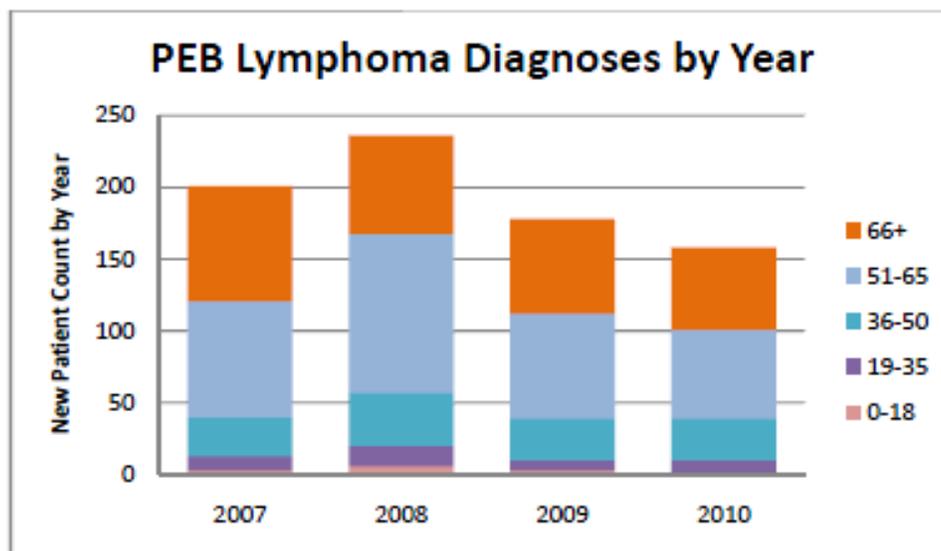
DSHS PET Scans	2007	2008	2009	2010	Overall
Members w/ PET scans per year	149	178	192	92	611
Scans per year	198	240	263	113	814
Average scans per year	1.33	1.35	1.37	1.23	1.33
Annual Cost	\$151,470	\$196,394	\$205,563	\$87,697	\$641,124
Average scan cost	\$765	\$818	\$782	\$776	\$788

**DSHS Lymphoma Diagnoses by Age and Year**



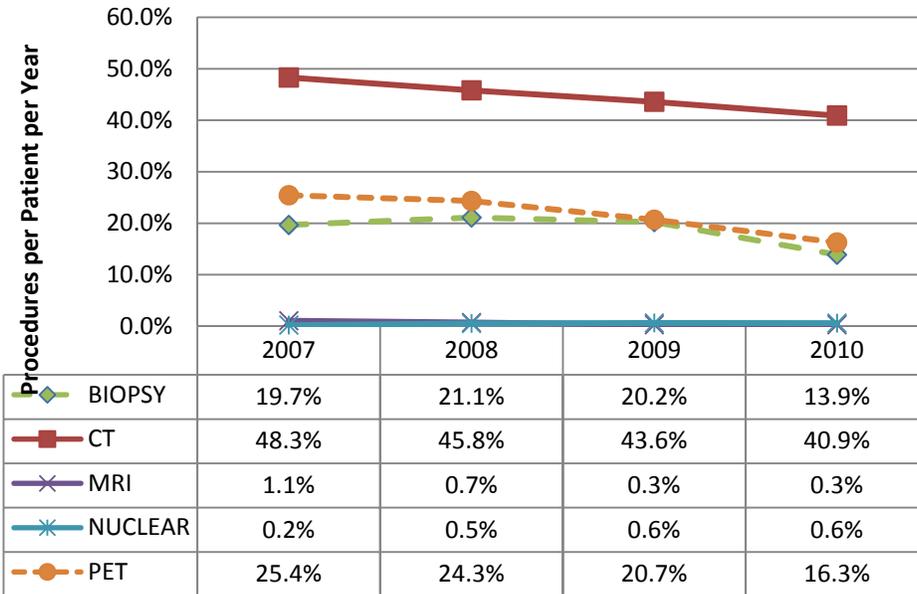
*Note: May include new members with a pre-existing condition.*

**PEB Lymphoma Diagnoses by Age and Year**

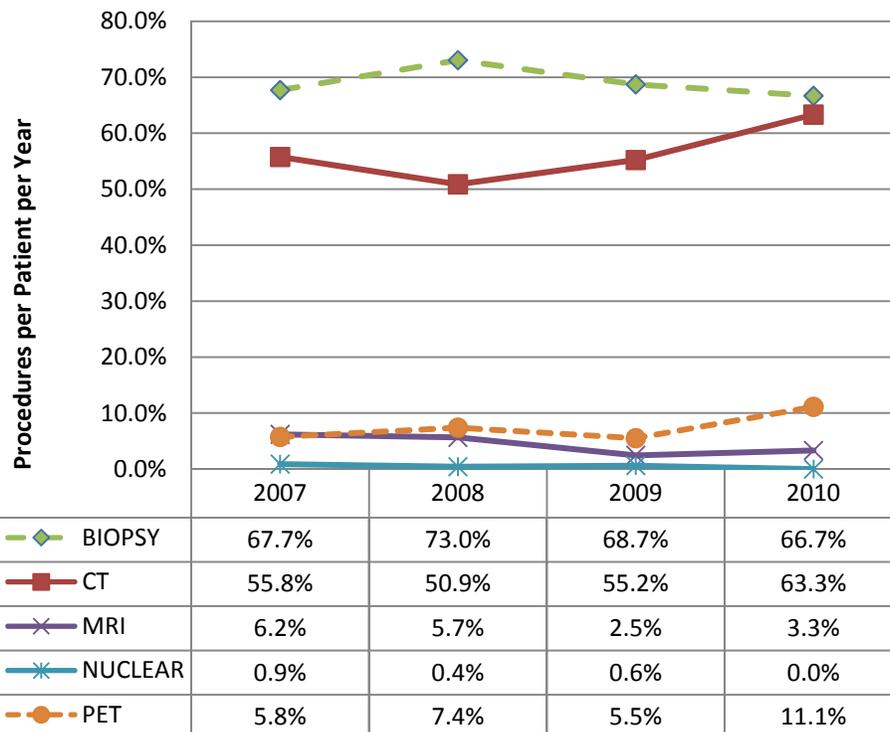


*Note: May include new members with a pre-existing condition.*

**PEB Lymphoma Patients Post-diagnosis  
Percent of Patients by Test Type  
(Lymphoma Diagnosis Code Procedures only)**



**PEB Lymphoma Patients Pre-diagnosis  
Percent of Patients by Test Type**

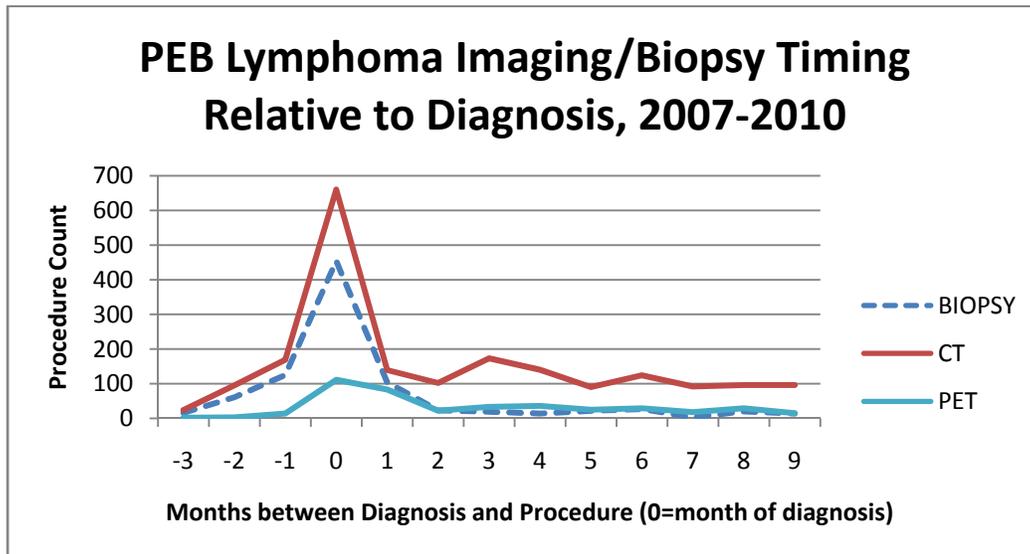


PEB Lymphoma Patient PET Scans Summary Statistics

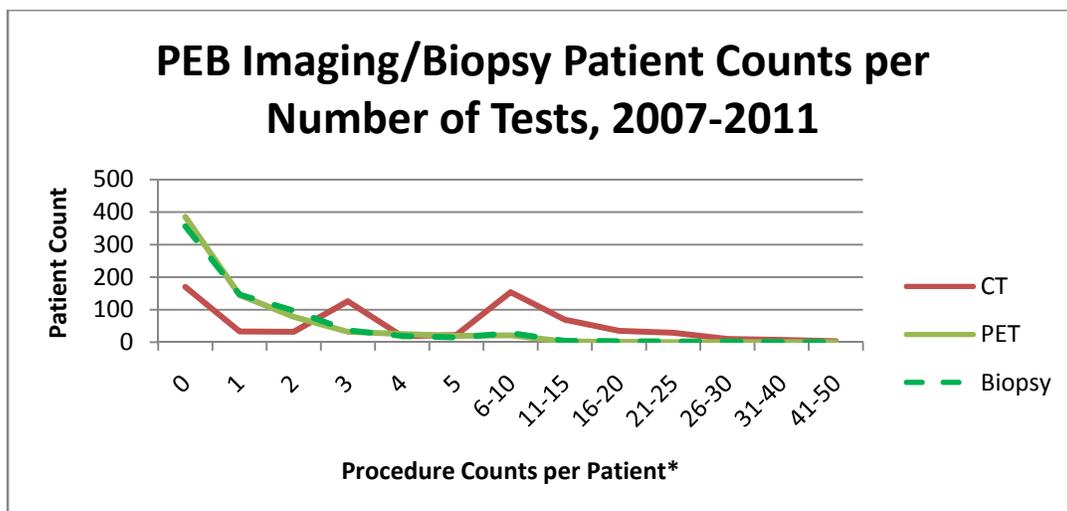
PEB Lymphoma Diagnosis Code PET Scans, Consolidated 2007-2010

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

✓ PEB Lymphoma Visualization Timing Relative to Diagnosis, 2007-2010



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



✓ Hayes Inc. (07)

- Hodgkin's lymphoma (primary staging)
    - **B** and in patients with biopsy-proven recurrent Hodgkin's disease or non-Hodgkin's lymphoma (restaging):
    - **B** - for FDG PET as an adjunct to standard staging techniques, including laparotomy, CT, x-ray, MRI, US, and bone scan, when used as **an alternative to gallium scanning**;
    - **B** - for FDG PET when used as a guide to limited or directed biopsy, imaging, or visualization for evaluation of a particular lesion, when used as an **alternative to gallium scanning**;
    - **C** - for standard staging techniques or a guide to limited or directed staging methods for evaluation of a particular lesion. For PET when used as an early method for monitoring the effects of therapy and altering treatment accordingly:
    - **C** - for patients with Hodgkin's disease or non-Hodgkin's lymphoma when used as a method for tumor grading when the presence of primary or recurrent tumor is known:
  - **C for FDG PET non-Hodgkin's disease.**
  - **C.** for FDG PET with any image analysis method for differentiating lymphomatous from nonmalignant CNS lesions in patients with HIV infection or AIDS:
  - **D** for all other applications
- ✓ Centers for Medicare & Medicaid Services (CMS):
- CMS issued a decision not to make a national coverage decision (NCD) for PET scanning in malignancies. This leaves ultimate coverage decisions on 18FDG 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.(CMS, 2010).
  - 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 without exception.
- ✓ Group Health (Other Centers, Agencies and HTAs)
- 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).
  - 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.
  - Monitoring of therapy: PET is NOT covered.



✓ Pet and Lymphoma: Risks and Benefits

**TABLE 2: Radiation Doses From Common Imaging Studies**

Test	Dose (mSv)	Equivalent Period of Background Radiation	Reference
Chest x-ray (standard two views)	0.06–0.1	8–12 days	13, 14
Mammography	0.13–0.7	16–88 days	13, 14
Abdomen x-ray	0.5–0.7	62–88 days	14
Lumbar spine x-rays	1.8	7 months	14
Head CT	2.0	8 months	13
Chest CT	8.0	3 years	13
Abdomen and pelvis CT	10.0	3 years	13
Virtual colonoscopy	10.2	3 years	15
Whole-body PET/low dose CT	8.5–10.3	3 years	16
Whole-body PET/full dose CT	23.7–26.4	8–9 years	16
Prospective ECG-gated coronary CT angiography	3.0	1 year	17
Retrospective ECG-gated coronary CT angiography	11.7–13.0	4 years	17
Coronary angiography (diagnostic)	4.6–15.8	2–5 years	14
Coronary angiography (with intervention)	7.5–57.0	2–19 years	14

✓ State Agencies Summary View:

- PET in Lymphoma:
  - Improved Sen/SpE but not related to PPV
  - No better than convention Gallium
  - State policy allows PET after conventional scanning is shown non-diagnostic
- Safety Issues not resolved
  - Increased amounts of radiology for questionable outcomes
- Costs Issues
  - Added cost but no outcome data
  - Costs Effectiveness studies – none available
- Non cover for routine diagnostic
  - Cover for biopsies when conventional not adequate
  - For all other reasons (i.e. staging, restaging, surveillance) cover only when conventional scans are non-diagnostic
- Limit the number of scans to no more than 1 per year unless medically justified



**Agenda Item: Evidence Review Presentation**

Oregon Health & Science University (OHSU) presented an overview of their evidence report on PET scans, full presentation in meeting materials.

- ✓ Background: Lymphoma
  - Heterogeneous group of malignancies involving lymph nodes, bone marrow, spleen and other extra-lymphatic organs. Approximately 74,000 cases in US annually.
    - Hodgkin lymphoma (HL) ~ 13%
    - Non-Hodgkin lymphomas (NHL) ~ 87%
    - HL = classic (95%) and nodular lymphocyte predominant (5%)
    - NHL = B-cell (80%) and T-cell (20%) lymphomas
    - NHL = aggressive (aNHL), indolent (iNHL) and highly aggressive
  - Treatment: Chemotherapy, radiation therapy or combination chemo-radiation. Treatment dependent on cell type and on stage of lymphoma. Primary treatment may result in remission; if lymphoma progresses or recurs, secondary treatment is undertaken.
- ✓ Background: PET
  - Nuclear Medicine test using a positron emitting radionuclide fluorine 18 (<sup>18</sup>F)
    - Positrons annihilate with electrons resulting in two gamma photons detected by the scanner
  - <sup>18</sup>F incorporated into a glucose analog (<sup>18</sup>FDG) and injected intravenously
  - <sup>18</sup>FDG accumulates in areas of high glucose metabolism
  - PET results in “hot spots” where glucose metabolism is high– e.g. cancer, infection
  - PET uses abnormal glucose metabolism rather than changes in normal anatomy and tissue characteristics (e.g. CT and MRI) to detect cancer
  - **Claim:** PET more sensitive and specific than CT or MRI for detecting viable cancer
    - E.g. residual mass in mediastinum after primary treatment for HL; is it residual fibrous tissue or viable HL?
  - PET images have low spatial resolution
  - PET usually performed with CT in a fusion PET/CT scanner that gives metabolic and high spatial anatomic information synchronously
  - In this report PET and PET/CT are considered as one test
  - Older literature is PET alone; newer literature is PET/CT
- ✓ Background: Washington Experience
  - Lymphoma incidence
    - PEB: 150-230 cases per year
    - DHHS: 530-610 cases per year
  - PET utilization
    - PEB: 220-263 PET scans per year
    - DHHS: 113-263 PET scans per year
  - PET costs
    - PEB: \$2,213-\$2,831 per scan
    - DHHS: \$765-\$818 per scan
- ✓ PICO:
  - **Population:** Adults and children with Hodgkin lymphoma and non-Hodgkin lymphoma.
  - **Intervention:** 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.
    - screening and initial diagnosis,
    - initial staging,
    - restaging after primary treatment,
    - detection of recurrence,
    - predicting patient outcomes after primary or secondary treatment,
    - monitoring of response to treatment, and
    - surveillance of patients in remission
- ✓ Methods:



- For the WA HTA program, MED core sources searched for SRs, MAs, TAs from 2000 to 2011. MEDLINE search for 2009-2011 included SRs, MAs, TAs and case reports. Search terms *positron emission tomography, PET, lymphoma, Hodgkin disease.*
- Search for relevant clinical practice guidelines using MED core sources and Guidelines.gov databases
- Quality of included systematic review and guidelines rated with standard MED instruments
- State, private payers, and policy websites searched to identify insurance coverage policies
- ✓ Search Results:
  - Core source search yielded 7 SRs and TAs, 3 cost or cost-effectiveness study designs and 6 clinical practice guidelines
  - MEDLINE search yielded 354 citations from which 18 observational studies were included in this report
- ✓ Findings: Evidence presented by Lymphoma Type
  - Hodgkin disease (HL) and aggressive non-Hodgkin disease (aNHL) are combined
  - Indolent non-Hodgkin disease (iNHL) is considered separately
  - Highly aggressive non-Hodgkin disease – no evidence identified
- ✓ Findings: Overview
  - Primary evidence comes from case series
    - Case series considered to be lower strength of evidence than RCTs or cohort studies
  - SOE for most KQs is low to moderate even when SRs are of high quality
  - More evidence for diagnostic accuracy than for clinical effectiveness, safety, cost
  - More evidence for HL and aNHL than for iNHL
- ✓ Accuracy of PET: Screening and Initial Diagnosis
  - No evidence on use of PET for screening or initial diagnosis
  - Diagnosis requires histology; PET cannot eliminate biopsy
  - No guidelines support PET for these indications
- ✓ Initial Staging:
  - Australian MSAC TA (4 SRs)
  - As a separate test, PET has higher combined sensitivity and specificity than CT or gallium

Test	Sensitivity	Specificity
PET	88-100%	90-100%
CT	88%	80%
Gallium	29-93%	n/a

- As an incremental test (added to CT), two small series of 33 and 50 patients (from Australian MSAC):
  - PET increased the number of true and false positives (ratio of TP: FP = 3:1).
  - PET occasionally was negative at sites positive on CT; large portion of these negative PET scans were false negatives.
- ✓ Staging after Primary Treatment
  - Routine (Four SRs): Evidence is heterogeneous, mixing HL and aNHL, initial and post-treatment staging CT. PET has higher sensitivity and specificity for detection of HL and aNHL than CT.

Modality	Sensitivity	Specificity
CT (Kwee) (mixed HL and aNHL)	25-100%	42-67%
PET (Kwee)	71-100%	57-100%
PET/CT (Kwee)	91-100%	87-100%
PET meta-analysis (Terasawa)	84% (HL) 72% (aNHL)	90% (HL) 100% (aNHL)

- Evaluation of residual mass (3 SRs): Sensitivity and Specificity for PET ranges 40-100%. Both sensitivity and specificity important in clinical decision making about a residual mass. Sensitivities and specificities of 40% may not be sufficiently high for clinical decision making
- ✓ Estimation of Prognosis after Treatment:
  - After primary or secondary treatment responders (PET negative) proceed to surveillance and non-responders (PET positive) proceed to additional treatment



- After **primary** treatment, 2 small case series (99 and 127 patients): PET performed and compared with 2-3 year progression free survival (PFS)

Modality	2-3 year PFS if study negative (responder)	2-3 year PFS if study positive (non-responder)
PET (HL)	94-96	19-33
CT (HL)	90	0%
PET (aNHL)	87	7%
CT (aNHL)	63%	0%

- ✓ Estimation of Prognosis after Secondary Treatment:
  - Two SRs and three case series
  - PET done prior to salvage chemotherapy and stem cell transplant

Study	Population	Sensitivity	Specificity	Other
Terasawa (SR/MA)	HL and aNHL	69%	81%	LR + 3.6 LR - 0.38
Poulou (SR/MA)	HL and aNHL			HR + 3.23
Moscowitz (153 pts)	HL	50%	84%	HR + 3.4
Dodero (80 pts)	HL and aNHL	68%	63%	
Qaio (34 pts)	aNHL	75%	87%	PPV 86% NPV 76%

- ✓ Surveillance of Asymptomatic Patients:
  - Surveillance = routine study of patients without symptoms
  - Not the same as re-evaluation of patients with clinical evidence of progression such as progressive symptoms, new or increasing lymphadenopathy or other masses
  - No SRs or RCTs; 5 case series
  - Studies consistently show a high false positive rate for PET scans performed on asymptomatic patients
  - PPVs 23-54%; NPVs 90-100%
  - Clinical symptoms were effective in predicting relapse

- ✓ Monitoring of Treatment during Treatment:
  - PET advocated in mid-cycle of treatment (e.g. after 4 of 8 cycles of chemotherapy)
    - Rationale # 1: if PET can predict non-response in mid-cycle, initial treatment could be terminated and secondary treatment begun, saving the expense and side effects of additional cycles of primary treatment. **Need high PPV or LR + for PET**
    - Rationale # 2: if PET showed response in mid-cycle, *perhaps* no additional treatment needed; *perhaps* stop at 4 cycles. **Need high NPV or low LR - for PET**
      - No evidence to support this rationale
  - One SR/MA and 3 case series

Study	Population	Sensitivity	Specificity	Other
Terasawa (SR/MA)	HL (360 pts) NHL (311 pts)	81% 78%	97% 87%	LR+ 28 LR- 0.19 LR+ 5.9 LR- 0.26
Zinzani (91 pts)	aNHL	82%	89%	PPV 82% NPV 89%
Markova (50 pts)	HL	75%	100%	PPV 75% NPV 100%
Duhrsen (128 pts)	aNHL	n/a	n/a	PET +, recurrence rate 17% PET -, recurrence rate 3%

- Studies consistently show higher specificity (87-97%) than sensitivity (78-81%)
- NPVs are higher than PPVs
- LR - are stronger than LR +
- PPV, NPV, LR + and LR - may not be strong enough to change clinical decision making
- ✓ KQ2: Clinical Effectiveness for HL and aNHL



- No evidence on the effect of PET on
  - Reduction of use of other tests
  - Patient survival
  - Quality of life
- Limited evidence of effect of PET on
  - Changes in management
- Changes in clinical management:
- Australian MSAC TA
  - No direct evidence
  - Staging alters clinical decisions
  - Monitoring could alter clinical decisions
- Pommier (case series of 137 patients)
  - 137 HL patients; 124 patients scheduled for radiotherapy had PET:
    - 102 (82%) had no change in plan; 6 (5%) had radiotherapy cancelled; 16 (13%) had radiotherapy plan altered
- ✓ KQ1: Accuracy of PET in Indolent NHL (iNHL)
  - Evidence on iNHL is very heterogeneous— different studies report on different iNHLs which do not necessarily behave similarly; individual case series for each iNHL; no MAs or RCTs; reference standard in these studies often not stated; analyses mix patients and lymphoma sites. Strength of evidence is LOW.
- ✓ Original Diagnosis and Staging:
  - No evidence on diagnosis
  - PET appears to detect additional sites of disease not detected on CT but PET also misses disease sites identified on CT
  - One study (Fueger) reported that PET/CT had higher sensitivity (99%) than the individual components PET (68%) and CT (70%) for detection of lymphoma sites
- ✓ Estimation of Prognosis after Treatment:
  - No SRs, MAs; 2 small case series of 45 and 44 patients
    - PET evidence of nodal activity after treatment correlated with subsequent relapse  $p < 0.05$
    - PET had a sensitivity of 100% and specificity of 88% for predicting relapse at one year. PPV = 62%; NPV = 100%
- ✓ KQ2: Changes in Management
  - One case series (74 patients with mantle cell lymphoma)
    - Treating physicians asked for management plan blinded to PET results
    - Management plans before and after PET results
      - No change 7%; small change 59%; medium change 7% and large change 27%
- ✓ KQ3: Differences in sub-populations
  - No evidence for any differences in sub-populations
    - Patient age, gender, patient selection criteria
    - Type of scanning machine, software, training
    - Provider type, setting
    - Health care system type
- ✓ KQ4: Safety of PET in Patients with Lymphoma
  - Australia MSAC considers PET to be safe and not different for lymphoma than for other indications for PET
    - This is an editorial opinion
    - No direct evidence
  - Potential safety issues:
    - Contrast reaction to  $^{18}\text{F}$ FDG
      - Glucose analog; no reactions reported
    - Radiation dose significant but patients have a potentially fatal disease
      - Radiation dose considerations more important in HL (mostly younger patients) and in surveillance (multiple PETs in potentially cured patients)
    - Incidental findings: no evidence on rate of incidental findings but a number of false positive PETs reported
- ✓ Radiation Dose
  - PET: 10-30 mSv (~300 CXRs)



- Standard CT: 10-30 mSv (~300 CXRs)
- Low dose CT: 2-10 mSv (~100 CXRs)
- PET/CT: 12-60 mSv (potentially 600 CXRs)
- ACR estimates the additional lifetime risk of fatal cancer from 30 mSv to be “moderate” (risk = 1/1,000 to 1/ 500)
- ✓ KQ5: Costs of PET
  - Evidence is weak
    - Different health delivery systems and costs
    - Australian MSAC (2010). Economic model using PET for staging estimated savings of A \$150-210 per patient with PET
    - 130 HL in Brazil, PET used for staging if CT inconclusive; savings of 1% overall for HL
    - 192 HL in US; PET and CT used for surveillance; US \$100,000 and 147 mSV per recurrence detected
    - 68 HL and aNHL in Switzerland with PET at mid-treatment and again at end of therapy; if PET at mid-treatment was negative, could avoid PET at end of treatment with a savings of 26% on PET costs
- ✓ Guidelines: Six guidelines included in report: CADTH (2010); IHPL(2007); NCCN (2011 and 2011); and ACR (2010 and 2011)
  - Guidelines quality rated as poor (IHPL) to fair (NCCN, ACR) to good (CADTH) based primarily on systematic literature review and author independence

Guideline	CADTH	NCCN HL	NCCN NHL	Juweid (IHPL)	ACR HL F/U	ACR HL Stage I-II
Diagnosis	Not addressed	Not addressed	Not addressed	Not addressed	Not addressed	Not addressed
Primary staging	Recommend	Recommend	Optional	Recommend	N/A	N/A
Secondary staging	Recommend	Recommend	Not recommend	Recommend	N/A	N/A
Estimate prognosis	Some reports suggest value	Recommend	Not recommend	Recommend if results will alter management	N/A	N/A
Monitor treatment	Not addressed	Not addressed	Not addressed	Not addressed	Not addressed	Not addressed
Surveillance	Not recommend	Not recommend	Not recommend	Not recommend	Not recommend	Not recommend

- ✓ Policy Considerations:
  - Coverage policies for Medicare, Regence Blue Cross, Aetna and Group Health
  - CMS Decision Memo (2010): CMS did NOT issue a national coverage decision
  - CMS (2010) has a new PET framework:
    - Initial treatment strategy: NCD of one PET
    - Subsequent anti-tumor treatment strategy: left to local regional carriers to decide
    - Exception for lymphoma– cover all PET
- ✓ Policy Considerations – Insurance Coverage

Indication	CMS	Aetna	Blue Cross	GroupHealth
<b>Diagnosis</b>	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
<b>Staging and re-staging</b>	Cover one PET for initial staging; subsequent staging unlimited (NCD)	Cover	Cover	Cover
<b>Monitoring of treatment</b>	Cover if necessary to determine optimal treatment strategies (NCD)	Not covered	Cover if necessary to determine optimal treatment strategies	Not covered
<b>Surveillance</b>	Not addressed	Not covered	Not covered	Not addressed
<b>Screening</b>	Not covered	Not addressed	Not covered	Not addressed

✓ **Summary:**

- Lymphoma is a heterogeneous group of malignancies with varied treatment dependent on cell histology and stage
- The evidence for this report is based on case series rather than RCTs
- Strength of evidence is low to moderate
- PET is used for a number of indications in the evaluation of lymphoma

✓ **Summary – Strength of Evidence:**

- For KQ1 – diagnostic accuracy, there is a moderate amount of low to moderate strength evidence
- For KQ2 – clinical effectiveness, there is very limited, low strength evidence
- For KQ3 – sub-populations and KQ 4 – safety, there is no evidence
- For KQ5 – costs, there is very limited low strength evidence

PET indication	Overall Evidence	Strength of Evidence	Guidelines Recommendation	Insurance Coverage
<b>Screening</b>	None	N/A	Against use	No coverage
<b>Diagnosis</b>	Not beneficial. One study of 8 patients.	Low	Against use	No coverage
<b>Original Staging</b>	<b>For HL and aNHL</b> , PET sensitivity and specificity 88-100% and 90-100%; Sensitivity and specificity for CT 88% and 80%. <b>For iNHL</b> , 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.	Moderate  Low	For use  For use	All cover