WASHINGTON STATE HEALTH CARE AUTHORITY

# PET for Lymphoma

## Health Technology Assessment

**September 1, 2011**

**Health Technology Assessment Program**

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# Public Comments and Responses

## PET for Lymphoma

## Washington Health Technology Assessment

September 1, 2011

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## RESPONSE TO PUBLIC COMMENTS

*The Center for Evidence-based Policy is an independent vendor contracted to produce evidence assessment reports for the WA HTA program. For transparency, all comments received during the comments process are included in this response document. Comments related to program decisions, process, or other matters not pertaining to the evidence report are acknowledged through inclusion only.*

This document responds to comments from the following parties:

- Medical Imaging and Technology Alliance (MITA)

Specific responses pertaining to each comment are included in Table 1 below. The full version of each public comment received is available in the Public Comments section, beginning on page seven.

## Table 1. Response to Public Comments

| Comment | Disposition |
|---|---|
| **Medical Imaging and Technology Alliance (MITA)** | |
| **PET's role in Staging, Re-Staging, & Estimation of Prognosis**<br>MITA affirms the draft report's determination that PET is effective in staging, restaging, and estimating prognosis in patients diagnosed with lymphoma. | *Thank you for the comment.* |
| **PET's role in Treatment Monitoring**<br>The draft report suggests that PET does not add value in the monitoring of treatment for lymphoma. MITA would like to note that ongoing clinical trials are currently generating clinical evidence to address the lack of extensive, definitive research on this topic. As further research is made public in the arena of PET's role in treatment monitoring, MITA looks forward to working with the authors and the HTA program to ensure Washington State's coverage and reimbursement policies reflect the latest clinical findings. | *Washington HTA process will decide on the timeline for any reexamination of this report topic. If MITA could provide information on these ongoing trials it would be helpful to know if any of them are likely to be able to contribute additional information on this topic and the timeline for their availability.*<br>*See also the response below which includes guideline recommendations from the International Harmonization Project (Juweid 2007) cited in the reference (Delbeke 2009) given by MITA.* |
| **PET's role in the Surveillance of Asymptomatic Patients**<br>MITA requests an examination of the following additional peer-reviewed research in order to better evaluate PET's clinical value in the surveillance of asymptomatic patients: Delbeke (2009), Vicente (2011), and Evans (2011). | *Evans (2011) and Delbeke (2009) have been reviewed. Both are non-systematic reviews that represent the opinions of the authors. Vicente (2011) is in Spanish and thus did not meet inclusion criteria. The Delbeke study references the Guidelines published by the International Harmonization Project (Juweid 2007) which is one of the Guidelines used in the WA HTA report. These guidelines include the following recommendations:*<br>"4. Although numerous studies have shown that PET performed after a few cycles of chemotherapy can predict therapeutic outcome (as discussed later in this article), no definitive proof has yet emerged that |

| Comment | Disposition |
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| | altering treatment based on this information results in superior survival outcomes. Until such data exist, this indication should be restricted to clinical trials evaluating PET in this context.<br>5. Current data are inadequate to recommend routine surveillance PET scans after the restaging study."<br>*Guideline recommendation 5 agrees with the position taken in the WA HTA report. Guideline recommendation 4 agrees with the position taken in the WA HTA report concerning monitoring of treatment.* |
| **Radiation Dose**<br>MITA asserts that PET devices are safe. Radiopharmaceuticals and PET and PET/CT devices have been approved and/or cleared by the US Food and Drug Administration (FDA) as safe and effective. Radiopharmaceuticals and PET/CT devices are tools used by clinicians that when used appropriately deliver the radiation dose necessary to diagnose, plan and monitor treatment for lymphoma and other diseases. As with other imaging equipment, the necessary dose level continues to be reduced as manufacturers develop new, innovative technological enhancements to equipment hardware and software. | *Information in the report on radiation doses and comparative doses was provided. While the report supports the statement that PET is generally safe, the use of PET and PET/CT if not needed or not effective increases total radiation dose to patient and would therefore be harmful.* |
| **Radiation Dose**<br>MITA believes strongly that decisions about the risks and benefits of a PET procedure must be left to a patient and her doctor. MITA strongly urges the HTA to avoid making these deeply personal value judgments for Washington patients by restricting coverage or altering reimbursement based on the radiation dose levels | *Thank you for the comment. The Washington HTA program's purpose as stated publically is as follows:*<br>"The primary purpose of HTA is to ensure medical treatments and services paid for with state health care dollars are safe and proven to work. HTA serves as a resource for state agencies purchasing health care. HTA contracts for scientific, evidence-based reports about whether certain medical devices, procedures, and tests are safe and |

| Comment | Disposition |
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| associated with scans prescribed by a physician for his or her patient. | work as promoted. An independent clinical committee of health care practitioners then uses the reports to determine if programs should pay for the medical device, procedure, or test."<br>*The program's website also discusses the background of the program:*<br>"New innovations in medicine, even in the last ten years, have improved the health and lives of patients, yet they have come at a high cost in terms of health, safety, and affordability. Health care spending and costs are rising dramatically, but patients in the U.S. are not getting healthier nor using health care that is available, recommended, and proven to work. Medical products and treatments are introduced without independent, scientific evidence about whether they are safe, effective, and provide benefits that are better than existing alternatives."<br>*While healthcare decisions do involve personal values and conversations between patients and physicians, the Washington HTA program is also committed to using the best available evidence to inform coverage decisions.*<br>*The Washington HTA report has been modified to include a statement that individual patients and their doctors may make different decisions about the relative benefits and costs of PET and PET/CT.*<br>*In addition, data on radiation doses from CT and x-ray procedures from the Radiological Society of North America (RSNA) and the American College of Radiology (ACR) (http://www.radiologyinfo.org/en/safety/index.cfm?pg=sfty_xray&bhcp=1) have been inserted into the report. The RSNA and ACR consider CT of the abdomen and pelvis to have a radiation dose of 30 mSV and they judge the additional lifetime risk of fatal* |

| Comment | Disposition |
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| | *malignancy from the examination to be "moderate" which they define as risk of 1 in 1,000 to 1 in 500. By extension, PET scan with a dose of 30 mSv would also be judged to have a moderate risk of subsequent cancer.* |
| **Radiation Dose**<br>The draft report alternatively refers to the dose associated with PET and PET/CT as "high", "substantial", and "considerable", all of which are qualitative assessments made without a clarifying definition. Without an accompanying discussion of what dose threshold qualifies as "high", "substantial", or "considerable", the HTA and the public are unable to evaluate this qualitative assessment. In addition, the draft report claims that the "use of PET for surveillance adds radiation dose…without adding commensurate clinical value". This statement implies that the authors have conducted an objective risk-benefit analysis which quantifies the stated risks and weighs them against an identified clinical benefit. Unfortunately, the authors have not published the risk-benefit analysis used to support this claim. As a result, the HTA and the public are unable to accurately evaluate this statement. | *The term "considerable" is used once in the WA HTA report and has been changed to "moderate," in accord with the rating system of the RSNA/ACR. The terms "high" and "substantial" in regards to radiation dose have been removed. The disposition to the above comment adds clarification about risks from radiation associated with CT and PET.*<br>*The statement* "use of PET for surveillance adds radiation dose…without adding commensurate clinical value" *has been modified to read* "use of PET for surveillance adds radiation dose…without proven clinical value." |
| **Radiation Dose**<br>The draft report refers to a radiation dose level of 10-30 mSv per PET scan—a dose level the authors cite as equivalent to 300 chest x-rays. Importantly, the biological impact of medical radiation is determined by numerous factors, including the radiopharmaceutical used, the dose, the type of scan, patient size, etc. all of which can | *See response previously noted above.* |

| Comment | Disposition |
|---|---|
| vary widely. The range provided in the report may, without additional context, mislead patients and could, if interpreted incorrectly, deter patients from seeking out appropriate health care. | |
| **Radiation Dose**<br>The draft report twice refers to "high-dose CT", despite the fact that this term is not accepted in the medical or regulatory communities and is wholly undefined by the authors. | *The term "high dose" CT has been changed to "standard" CT as opposed to "low dose" CT.* |
| **Strength of Evidence**<br>The authors of the draft report note repeatedly that they consider the "overall strength of the evidence" as "low" in most research questions posed by HTA. The medical community's ability to treat lymphoma has greatly improved in recent years despite a relatively small patient population, and most of the treatment innovations for patients with lymphoma have been developed by piecing together insights gained in research with small patient sample sizes and extrapolating from successes in imaging for other clinical conditions. MITA urges HTA to thoughtfully consider even small sample size studies, since large-scale RCTs are impractical in this area of research. | *It is important to use a methodologically defensible standard of evidence across assessments. This report uses a grading system adapted from the GRADE group (see report section on methodology for details). Indirect evidence was not considered to be of sufficient rigor for inclusion in the report. However, information on lower quality small studies can be presented at public hearings. This comment does not offer enough specificity for detailed comment.*<br>*Many of the studies used in the report are case series with limited numbers of subjects. The results are given but note is made of the small sample sizes and the methodological flaws noted by the authors of the articles or the systematic reviews which included the cited articles.* |

PUBLIC COMMENTS

## Medical Imaging and Technology Alliance (MITA):

The Medical Imaging and Technology Alliance (MITA) appreciates this opportunity to comment on the draft evidence report related to the use of PET scans for lymphoma as compiled for the Washington State Health Technology Assessment (HTA) Program by the Center for Evidence-based Policy at Oregon Health & Science University. As the leading trade association representing PET tracer developers, manufacturers, compounders and distributors, we have an in-depth understanding of the significant health benefits that PET technology provides patients diagnosed with lymphoma. MITA looks forward to working with you to continue exploring the effectiveness of this technology as the assessment is finalized.

PET and PET with computed tomography (PET/CT) imaging have become invaluable tools in the detection, staging, and therapy management of patients with cancer and heart disease. PET/CT scans are highly accurate tests that deliver precise results demonstrated to routinely and significantly affect how physicians manage and treat their patients' disease. Most cancers are approved by CMS for coverage, including lymphoma, which is reimbursed for both initial and subsequent treatment strategies.

Our comments address the following aspects of the draft report. First, we express our concurrence with the draft report's findings related to PET effectiveness for staging, re-staging, and predicting subsequent outcomes. Second, we raise the subject of ongoing research in treatment monitoring. Third, we raise our concerns with the draft report's findings regarding the use of PET in the surveillance of asymptomatic patients. Fourth, we discuss the report's references to radiation dose. Fifth, we discuss the report's consideration of the strength of evidence for research related to PET.

**I. PET's role in Staging, Re-Staging, & Estimation of Prognosis**

MITA concurs with the draft report in its determination that "Both the sensitivity and specificity of PET are high for the staging of HL and NHL, and also that PET "is sensitive and specific for prediction of subsequent outcomes when performed after the end of treatment for both HL and NHL." As the report notes, Medicare, private insurance plans, and other payers all cover PET for original staging, re-staging, and estimation of prognosis. In light of these findings and the strong body of evidence in favor of PET for these uses, it is clear HTA should protect patient access to this technology.

**II. PET's role in Treatment Monitoring**

The draft report suggests that PET does not add value in the monitoring of treatment for lymphoma. MITA would like to note that ongoing clinical trials are currently generating clinical evidence to address the lack of extensive, definitive research on this topic. As further research is made public in the arena of PET's role in treatment monitoring, MITA looks forward to

working with the authors and the HTA program to ensure Washington State's coverage and reimbursement policies reflect the latest clinical findings.

**III. PET's role in the Surveillance of Asymptomatic Patients**

The draft report suggests that PET does not add value in the surveillance of asymptomatic patients who have completed treatment for lymphoma. Consequently, the draft report recommends against general coverage for this service. In fact, however, several peer-reviewed studies have demonstrated the benefits of PET for lymphoma in the surveillance of asymptomatic patients, including Delbeke (2009)[1], Vicente (2011)[2], and Evans (2011)[3]. The draft report does not make reference to this research, and MITA requests that the final evidence report include consideration of this research, which adds considerable evidence in favor of covering this service.

**IV. Draft Report's Discussion of Radiation Dose**

In answering the HTA's question on PET's safety profile, the draft report makes several statements regarding the radiation dose associated with a PET scan or a PET/CT scan. To be clear, PET devices are safe. Radiopharmaceuticals and PET and PET/CT devices have been approved and/or cleared by the United States Food and Drug Administration (FDA) as safe and effective. Radiopharmaceuticals and PET/CT devices are tools used by clinicians that when used appropriately deliver the radiation dose necessary to diagnose, plan and monitor treatment for lymphoma and other diseases. As with other imaging equipment, the necessary dose level continues to be reduced as manufacturers develop new, innovative technological enhancements to equipment hardware and software.

Importantly, MITA believes strongly that decisions about the risks and benefits of a PET procedure must be left to a patient and her doctor. This decision differs based on each patient's medical condition and history, and is best left to health care providers. A study published in the academic journal Radiology, described it thus: "…[U]ltimately a risk-benefit decision must be made at the level of the individual patient and should involve balancing the highly-context-dependent benefits of imaging against the patient-specific cumulative risks."[4] This decision is a personal one, and it shouldn't be met with interference from additional levels of government trying to second-guess the FDA or physicians. MITA strongly urges the HTA to avoid making these deeply personal value judgments for Washington patients by restricting coverage or altering reimbursement based on the radiation dose levels associated with scans prescribed by a physician for his or her patient.

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[1] Delbeke D et al. Expert Opinions on Positron Emission Tomography and Computed Tomography Imaging in Lymphoma. *The Oncologist* 2009; 14; 30-40.

[2] Vicente G et al. F-FDG-PET/CT in the surveillance of patients with lymphoma: detection of asymptomatic recurrences. *Revista Espanola de Medicina Nuclear* 2011; July 8.

[3] Evans W, Gilmore D, and English J. The Role of PET and PET/CT in Managing the Care of Lymphoma Patients. *Journal of Nuclear Medicine Technology* 2011. September 1.

[4] Sodickson A, et al. Recurrent CT, Cumulative Radiation Exposure, and Associated Radiation-induced Cancer Risks from CT of Adults. *Radiology* 2009; 251; 175-184.

In discussing radiation dose, the draft report alternatively refers to the dose associated with PET and PET/CT as "high", "substantial", and "considerable", all of which are qualitative assessments made without a clarifying definition. Without an accompanying discussion of what dose threshold qualifies as "high", "substantial", or "considerable", the HTA and the public are unable to evaluate this qualitative assessment. In addition, the draft report claims that the "use of PET for surveillance adds radiation dose…without adding commensurate clinical value".[5] This statement implies that the authors have conducted an objective risk-benefit analysis which quantifies the stated risks and weighs them against an identified clinical benefit. Unfortunately, the authors have not published the risk-benefit analysis used to support this claim. As a result, the HTA and the public are unable to accurately evaluate this statement.

The draft report also refers to a radiation dose level of 10-30 mSv per PET scan—a dose level the authors cite as equivalent to 300 chest x-rays. Importantly, the biological impact of medical radiation is determined by numerous factors, including the radiopharmaceutical used, the dose, the type of scan, patient size, etc. all of which can vary widely. The range provided in the report may, without additional context, mislead patients and could, if interpreted incorrectly, deter patients from seeking out appropriate health care.

Lastly, the draft report twice refers to "high-dose CT", despite the fact that this term is not accepted in the medical or regulatory communities and is wholly undefined by the authors.

**V. Strength of Evidence**

The authors of the draft report note repeatedly that they consider the "overall strength of the evidence" as "low" in most research questions posed by HTA. According to the draft report:

> *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.*

It is important to note that the medical community's ability to treat lymphoma has greatly improved in recent years despite a relatively small patient population. In fact, most of the treatment innovations for patients with lymphoma have been developed by piecing together insights gained in research with small patient sample sizes and extrapolating from successes in imaging for other clinical conditions. As a result, MITA urges HTA to thoughtfully consider even small sample size studies, since large-scale, randomized control clinical trials are impractical in this area of research.

**VI. Conclusion**

In conclusion, in the final evidence report, MITA urges the HTA Program to:

[5] In another section, the draft report uses the term "seems to add" in this context, rather than this more definitive statement.

- Affirm the draft report's determination that PET is effective in staging, restaging, and estimating prognosis in patients diagnosed with lymphoma;
- Examine the additional peer-reviewed research cited above in order to better evaluate PET's clinical value in the surveillance of asymptomatic patients;
- Reconsider unscientific statements related to radiation dose and provide supporting information for currently unsupported dose statements; and
- Add a discussion of the fact that clinical research on low-prevalence diseases, like lymphoma, is inherently different than high-prevalence diseases as well as a discussion of the impact of those differences on determinations of strength of evidence.

MITA appreciates this opportunity to comment on the draft report. We would be pleased to answer any questions you might have about these comments.

Respectfully submitted,
Dave Fisher
Executive Director, MITA
Vice President, NEMA