Washington State Health Care Authority

Health Technology Assessment

Functional Neuroimaging for Primary Degenerative Dementia or Mild Cognitive Impairment

Draft Report: Public Comment & Response

December 5, 2014

Health Technology Assessment Program (HTA)
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RESPONSES TO PUBLIC COMMENTS

Spectrum Research is an independent vendor contracted to produce evidence assessment reports for the Washington HTA program. For transparency, all comments received during the public comment periods 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 clinical and peer reviews from the following parties:

1. Lisa Silbert, MD (peer reviewer)
2. Tina Tailor, MD (peer reviewer)
3. Gary Franklin, MD

Specific responses pertaining to each comment received are included in the table below.

Section of Report	Comment	Response
Lisa Silbert, MD (peer reviewer)		
Introduction (general)	[In response to questions asked on the review form:] Yes, the overview of topic is adequate, the topic of assessment is important to address, and public policy and clinical relevance are well defined.	Thank you.
Introduction (page 23, section 1.1; page 29, section 1.4.1; page 49, section 2.4)	A couple of times in the report it states that patients "undergo an initial evaluation consisting of a thorough history, detailed cognitive testing, and neurological examination". Unfortunately, this is most likely not the case unless patients are referred for neurological or dementia specialty evaluation, and primary care doctors generally are not trained and do not have time for this type of evaluation/assessment. Not sure how this affects interpretation of these findings. I'm guessing only a small percentage of patients are referred for specialty care.	Thank you. We have modified the text to provide clarity. For example, the sentence on page 23 was modified as follows (with new text in italics): "Patients presenting with symptoms or complaints suggestive of dementia *ideally* undergo an initial evaluation consisting of a thorough history, detailed cognitive testing, and neurological examination*; however, the thoroughness of this work-up may be more likely in patients referred to specialty clinics than those seen by primary care physicians*." On page 29 (in the section on key considerations highlighted by clinical experts) we have added additional language to clarify this issue.
Introduction (page 24, section 1.2)	Under contextual questions, says "provide a summary of the sensitivity and sensitivity" – should be specificity. This error is also within the executive summary multiple times.	Thank you- this error has been corrected throughout the report.
Introduction (page 30, section 1.4.3)	Functional neuroimaging IS used for diagnosis of PPA, in that it distinguishes PPA (which is a neurodegenerative disease) from non-cortical speech disorders (which would not be considered to be PPA). It does not distinguish underlying pathology of AD vs FTLD.	Thank you- this text has been removed.
Background (general)	[In response to questions asked on the review form:] The content of literature review/background is sufficient.	Thank you.
Background (page 42, section 2.1, 4th paragraph)	Would say that such and such conditions are "USUALLY" or "COULD BE" reversible once the condition is treated (tumors in particular may not be treatable and may worsen over time – these would still not be considered neurodegenerative, per se).	Thank you- this change has been made.

Section of Report	Comment	Response
Background (page 43, section 2.2.1)	Clarification regarding structural neuroimaging features of AD: Early features: hippocampal and mesial temporal lobe atrophy Later features: global/generalized atrophy	Thank you- the text has been updated to provide clarification as suggested.
Background (page 43, section 2.2.2)	I do not believe that a "core feature" of LBD is memory loss (although it certain can and eventually is affected). Core COGNITIVE features of LBD are: attention, executive function, and visual spatial skill function impairment relatively early on.	Thank you- the text has been updated and clarified as suggested.
Background (page 45 section 2.2.3)	I do not believe that incontinence and low blood pressure are specific signs of FTLD.	Thank you- these have been removed from the text.
Background (page 46 section 2.2.4)	Would not say "missing appointments" as a feature of MCI, as this implies functional impairment (i.e. dementia).	Thank you- "missing appointments" has been removed from the sentence.
Report objectives and Key Questions (general)	[In response to questions asked on the review form:] Yes, the aims/objectives clearly address relevant policy and clinical issue, and the key questions are clearly defined and adequate for achieving these aims.	Thank you.
Methods (general)	[In response to questions asked on the review form:] Yes, the method for identifying relevant studies is adequate; the criteria for the inclusion and exclusion of studies is appropriate, the method for level/class of evidence rating is appropriate and clearly explained, and the data abstraction and analysis/review are adequate.	Thank you.
Methods (page 95, Table 6)	Generally corticobasal degeneration is not considered a sub-heading of FTLD, although it shares features with it. Also, the table says that CBD is EXCLUDED from the literature review. However, **page 99, section 3.1.3** says that CBD was included in the literature review.	Thank you- this error has been corrected.
Results (general)	[In response to questions asked on the review form:] Yes, the amount of detail presented in the results section was appropriate; the Key Questions were answered when able.	Thank you.

Section of Report	Comment	Response
Results (general)	[In response to questions asked on the review form:] Yes, the figures, tables, and appendices were clear and easy to read (although [I'm] not sure how SoE were downgraded).	Thank you. Details on how the SoE were downgraded are available in the methods section "Assessment of the Overall Strength of Evidence" and in Appendix D. For further clarity, an overview on how the Strength of Evidence ratings were downgraded have been added to the evidence summary tables.
Results (general)	[In response to questions asked on the review form:] No, the implications of the major findings were not clearly stated, and the recommendations do not address limitations of the literature.	Thank you. To clarify, the major findings were summarized using strength of evidence (SoE) ratings, and these ratings correspond to our confidence in the overall estimate of effect and the impact that additional findings are expected to have regarding that estimate (please see the Methods section on Assessment of the Overall Strength of Evidence for details). Thus, a SoE of "moderate" indicates that we are moderately confident that effect size estimates lie close to the true effect for this outcome and that there some deficiencies in the body of evidence; we believe the findings are likely to be stable but some doubt remains. A SoE of "low" indicates limited confidence that effect size estimates lie close to the true effect for this outcome due to major or numerous deficiencies in the body of evidence; we believe that additional evidence is needed before concluding that findings are stable or the estimate is close to the true effect. A SoE of "insufficient" indicates either that we are unable to estimate an effect or have no confidence in the effect estimate for this outcome; OR that there is no available evidence or the body of evidence has unacceptable deficiencies precluding judgment.
Results (page 150)	I think it is a little confusing the have DSC-MRI here, as it was not particularly mentioned elsewhere in the report. This is a completely different technology than other fMRI sequences (requires contrast agent, and therefore is NOT non-invasive). This is a different sequence and protocol than resting state fMRI (for default mode network, etc) or ASL (CBF measure). I do not believe that most institutions (or MRI systems) have any kind of standard DSC packages (i.e., I believe this is still research mainly).	Thank you. Because DSC-MRI was not one of the index tests of interest for the report and should not have been included. It has thus been omitted from Key Question 6.
Conclusions	I do not feel particularly qualified to determine whether conclusions reached were valid, in that I'm not sure why some reports were "downgraded" in their final SoE vs. their starting SoE. In particular, it is my experience (both	Thank you for your comments, we appreciate your insight. The issue of downgrading the SoE was discussed in another response above.

Section of Report	Comment	Response
	clinically, and my knowledge of the literature) that FTG-PET is fairly sensitive at detecting neuronal loss in Alzheimers dementia. I'm surprised that the final SoE in this regard is "low". In terms of all of the questions ask, this would be the one that I would assume with have the strongest evidence for, and would be the most clinically useful. Although pathological validity is the gold standard, it may skew the available data in terms of the type of subjects enrolled. (? End stage disease where functional imaging findings are likely to be more global, and hence nonspecific, or those with atypical presentations who agree to brain autopsy for clarification?)	Regarding the SoE of "low" for the diagnostic accuracy of FDG-PET, several things come into play. First, as you pointed out, restricting studies to those that used autopsy as the reference standard may skew results in terms of the types of patients enrolled, however, it is ideal to include studies that compare a diagnostic test to the gold standard (i.e., the truth) when possible, as using something other than the gold standard will impact the results as the reference standard will be imperfect by nature. Further, restriction to this study type will limit the number of studies available, however, it will restrict the results to the studies with the highest quality of evidence available. The diagnostic accuracy of FDG-PET was evaluated in a few different places. In the context key question, two retrospective studies met our inclusion criteria and together reported high sensitivity (93-95%) of FDG-PET for diagnosing Alzheimer's disease. The SoE was not evaluated for any of the context questions. In Key Question 1, the accuracy of FDG-PET to differentiate between two forms of dementia such as Alzheimer's disease and Frontotemporal dementia was evaluated, and three retrospective studies met the inclusion criteria. The studies that evaluated the images visually (rather than using automated methods) did report high sensitivity (94-98%). The overall strength of evidence was low due downgrading for a) the risk of bias that is inherent in the retrospective nature of these studies, and b) the indirect nature of diagnostic accuracy outcomes. That is, these outcomes were not the primary health outcomes of interest, rather, they are surrogate/intermediate outcomes. While there is no consensus for how to deal with grading the overall strength of evidence for indirect outcomes such as diagnostic accuracy, our approach is consistent with that suggested by the Agency for Healthcare Research Quality's Methods Guide for Medical Test Reviews (Chapter 7) (available at http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=558&pageaction=displayproduct).
Overall presentation and relevancy	[In response to questions asked on the review form:] Yes, the review is well structured and organized; the main points are clearly presented; the report is important for public policy/health.	Thank you.
Overall presentation	It's always difficult when the available evidence is limited to just a handful of	Thank you, we appreciate your input.

Section of Report	Comment	Response
and relevancy	studies to know how to relate conclusions into the context of real-world medicine. The question at hand is relevant to clinical medicine. However, the available studies are so limited it seems difficult to answer the question adequately. In addition, results should not necessarily be based on the assumption that everyone with symptoms of dementia initially receives a very thorough history, exam, and work-up, as this is unfortunately not the case.	
Quality of report	[In response to questions asked on the review form:] The overall quality of the report is good.	Thank you.
Tina Tailor, MD (peer reviewer)		
Introduction (general)	[In response to questions asked on the review form:] Yes, the overview of the topic is adequate, the topic of assessment is important to address, and public policy and clinical relevance are well defined.	Thank you.
Introduction (page 2, line 2nd to last sentence under "Diagnosis" subsection and last sentence in this subsection)	Most of the time, findings on structural neuroimaging are nonspecific. In most patients, we see generalized brain atrophy in a nonspecific pattern. Perhaps revise the sentence to read: "Structural neuroimaging may also aid in the differential diagnosis of the specific subtype of dementia based on patterns of atrophy in the brain, but is often inconclusive." Additionally, the second sentence starts with "Most often a diagnosis can be made…" Perhaps it is more reasonable to say "Most often a diagnosis can be suggested…." In general, most patients with dementia are clinically diagnosed as having Alzheimer's (based on its high prevalence), however true diagnosis of dementia type relies on tissue biopsy (as is later discussed).	Thank you- both changes suggested have been made.
Introduction (page 3, 3rd sentence in the paragraph	Consider changing this sentence to: "In PET for dementia diagnosis, the radiopharmaceutical most commonly used is [^{18}F] Fluorodeoxyglucose, which	Thank you- the text has been updated as suggested.

Section of Report	Comment	Response
labeled "PET" and line 2 on page 50)	consists of fluorine-18, a positron-emitting radioactive isotope, incorporated into a glucose molecule." This is just semantics, but a "radiopharmaceutical" is a term referring to a radioactive particle incorporated into a pharmaceutically-active particle.	
Background (general)	[In response to questions asked on the review form:] Yes, the content of literature review/background is sufficient.	Thank you.
Report objectives and Key Questions (general)	[In response to questions asked on the review form:] Yes, the aims/objectives clearly address relevant policy and clinical issue, and the key questions are clearly defined and adequate for achieving these aims.	Thank you.
Methods (general)	[In response to questions asked on the review form:] Yes, the method for identifying relevant studies is adequate; the criteria for the inclusion and exclusion of studies is appropriate (see comment below regarding the adverse effects of FDG), the method for level/class of evidence rating is appropriate and clearly explained, and the data abstraction and analysis/review are adequate.	Thank you.
Methods (page 25)	May be helpful to state how the kappa value is interpreted (i.e., which kappa values indicate poor, good, moderate, etc agreement).	Thank you. We have provided descriptions on the interpretations of kappa in the section "Outcomes Assessed".
Methods (page 54, first paragraph)	When considering the adverse reactions of injecting 18F-FDG, did the conclusions take into account imaging studies outside of neuroimaging? 18F-FDG is used for many other types of PET scans (whole body PET in oncology, cardiac imaging). It is generally very safe to inject.	The general safety of the imaging modalities and their ligands was addressed in the background of the report, however the studies included in the results to address the key questions were limited to those reporting on the population of interest.
Results (general)	[In response to questions asked on the review form:] Yes, the amount of detail presented in the results section was appropriate; the Key Questions were answered, and the implications of the major findings were	Thank you.

Section of Report	Comment	Response
	clearly stated.	
Results (general)	[In response to questions asked on the review form:] Yes, the figures, tables, and appendices were clear and easy to read for the most part – see comment below.	Thank you.
Results (general)	[In response to questions asked on the review form:] Yes, the gaps/limitations in the literature have been dealt with adequately- there is mention of ongoing studies. However, given that autopsy or brain biopsy is the gold standard for diagnosis, there are challenges in doing large-volume, prospective studies on diagnostic accuracy. This limitation is mentioned, but perhaps could be emphasized more.	Thank you for your feedback. We agree, restricting studies to those that used autopsy as the reference standard will limit study size and study numbers. However, use of autopsy as a reference standard should not theoretically limit studies to those that were conducted retrospectively, although studies that use diagnostic test information from databases of patients with autopsy results available are likely to be more common. In addition, limiting studies to those that use the autopsy gold standard will put the focus on those studies with the highest quality of evidence available; studies that do not use the gold standard will not be comparing the diagnostic test to the "truth" but rather to another imperfect test, which will impact the results. As suggested, we added some of the points you made to the background section in which the reference standard was discussed.
Results (page 167 onward, multiple summary tables, last column entitled "Starting SoE")	It's not clear from reading the table alone how the "starting SoE" (last column of multiple summary tables starting on 167) is arrived upon. In reading the methods, it states that that CoE I/II were classified as high and CoE were classified as "low." A description to this effect in a footer under the table may be beneficial.	Thank you. Details on how the SoE were downgraded are available in the methods section "Assessment of the Overall Strength of Evidence" and in Appendix D. For further clarity, an overview on how the Strength of Evidence ratings were downgraded have been added to the evidence summary tables.
Conclusions (general)	[In response to questions asked on the review form:] Yes, the conclusions reached are valid- there are few large, prospective studies pertinent to these topics, which is reflected by many of the SoE being low or insufficient	Thank you.
Overall presentation and relevancy	[In response to questions asked on the review form:] Yes, the review is well structured and organized. Results feel a bit redundant because they are embedded in multiple areas of the report in summarized fashion, however the summarized results in the Executive summary, Results section, and tables at the end of the report are helpful.	Thank you.

Section of Report	Comment	Response
Overall presentation and relevancy	[In response to questions asked on the review form:] Yes, the main points are clearly presented, the report is relevant to clinical medicine and important to public policy/health.	Thank you.
Quality of report	[In response to questions asked on the review form:] The overall quality of the report is good.	Thank you.
Gary Franklin, MD		
Page 16	In several places, inter-rater reliability is rated as good, moderate or excellent. It is not explained in the report how these ratings are related to the kappa value or the degree of agreement. It would be helpful to give some description on inter-rater reliability and intra-rater reliability, and how the kappa value and the degree of agreement are used to measure or rate the reliability.	Thank you. We have provided descriptions on the interpretations of kappa in the section "Outcomes Assessed".
Page 16	What is the modality "11C-DTBZ-PET" used for specifically? Are there any data on the accuracy of the modality? It is not described in the background section together with other modalities, and there seem to be no other information available for the modality in the report.	^{11}C-DTBZ-PET allows visualization of the nigrostriatal dopamine terminal, and outputs include both ligand transport (K_1), which is correlated with regional blood flow, and distribution volume (DV) of ^{11}C-DTBZ (see section 4.1.4). One study was included in this section that evaluated the reliability of distinguishing between AD, FTD, DLB, and normal controls using this modality. Classification of FTD could be made if there were deficits in K_1 in the frontal or temporal cortex greater than those in the posterior cortex. DLB could be distinguished from AD by ^{11}C-DTBZ DV deficits in the striatum. No other studies that addressed the Key Questions and used ^{11}C-DTBZ-PET were identified; this has been clarified in the summaries and summary tables of the report.
Page 18	"Prevalence of AD: 55%". What does it mean here? Is it the fraction of all the subjects enrolled in the study who had AD confirmed by autopsy?	Yes, this is correct. In order to provide clarity, how prevalence was calculated was added to section 1.3 ("Outcomes Assessed").
Page 21	"Patient progression (MCI to AD/dementia conversion)". The indent level needs to be increased a notch to avoid any confusion.	Thank you, we see the potential for confusion here. We have made changes to clearly label outcomes as such- this should help avoid confusion.
Page 21	Under "SPECT (perfusion)" and several levels down, "Prediction of AD or dementia with FDG-PET alone had 36-76% sensitivity and 39-82% specificity".	Yes, thank you- we have corrected this error.

Section of Report	Comment	Response
	Should it be SPECT instead of FDG-PET?	
Page 24	Long term and short harms of FDG-PET or SPECT. The time actor is critical, but the follow-up times of the study described here are not defined in either the text or the table. It would be good to add.	Thank you. We have provided clarification on this issue to the extent possible as information was available from the studies.
Page 24	"DaTscan". It is questionable to attribute the AEs, such as dry mouse, vomiting and headache, to injection only rather than the ligand injected because these are not local reactions.	Thank you- we took a second look at the study (McKeith) and agree with you. The sentence has been updated to indicate that these events were attributed to the ^{123}I-FP-CIT injection.
Page 24	There might be another type of potential harm, which is indirect. If a modality is not accurate, especially when the specificity is low, which would result in a high false positive rate, the psychological harm would be serious. Is there any study out there to address this potential harm of any of the modalities?	Thank you for your comment. As noted in the results for Key Question 4, no studies were identified that reported on the harms or health impacts of missed diagnoses, false negative diagnoses, or false positive diagnoses.
Page 26	Is DSC-MRI a type of fMRI? If it is, it should be described under fMRI. If it is not, it would be helpful to be introduced in the "Index tests" on p14. DSC-MRI appears only in Key Question 6 section (cost-effectiveness) and not in any other sections. Are there any data on reliability, accuracy and safety of DSC-MRI? Not sure why it is included in the report if it is not one of the index tests defined.	Thank you. DSC-MRI and is not a type of fMRI and was not one of the index tests of interest for the report – this modality should not have been included in the write-up. It has thus been omitted from Key Question 6.

Comprehensive Evidence-Based Health Technology Assessment
Peer Review Form

Thank you for your willingness to read and comment on the Comprehensive Evidence-Based Health Technology Assessment Review for hip resurfacing. Your contribution and time are greatly appreciated.

This form can be filled out electronically on your personal computer. Enter your identification information and comments directly into the shaded areas; use the **TAB** key to move from field to field. Please enter the section, page, and line numbers where relevant. The shaded comment field will expand as you type, allowing for unlimited text. You have been provided comment fields in each section. Should you have more comments than this allows for, please continue with a blank page. Additionally, we are very interested in your evaluation of the ease of use of our Peer Review Form. Please use the last field to enter suggestions for improvement.

When the Peer Review form is complete, save it to your hard drive and return as an e-mail attachment to robin@specri.com

If you have questions or concerns please contact Robin Hashimoto, PhD at the email above.

Reviewer Identification Information

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INTRODUCTION Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Overview of topic is adequate? **yes**
- Topic of assessment is important to address? **yes**
- Public policy and clinical relevance are well defined? **yes**

Page 23 section 1.1
AND page 29 section 1.4.1
AND page 49, section 2.4

A couple of times in the report it states that patients “undergo an initial evaluation consisting of a thorough history, detailed cognitive testing, and neurological examination”. Unfortunately, this is most likely not the case unless patients are referred for neurological or dementia specialty evaluation, and primary care doctors generally are not trained and do not have time for this type of evaluation/assessment. Not sure how this affects interpretation of these findings. Im guessing only a small percentage of patients are referred for specialty care.

Page 24	Section 1.2

Under contextual questions, says “provide a summary of the sensitivity and sensitivity” – should be specificity. This error is also within the executive summary multiple times.

Page 30	section 1.4.3

Functional neuroimaging IS used for diagnosis of PPA, in that it distinguishes PPA (which is a neurodegenerative disease) from non-cortical speech disorders (which would not be considered to be PPA). It does not distinguish underlying pathology of AD vs FTLD.

BACKGROUND Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Content of literature review/background is sufficient? **yes**

Page 42	section 2.1, 4th paragraph

Would say that such and such conditions are “USUALLY” or “COULD BE” reversible once the condition is treated (tumors in particular may not be treatable and may worsen over time – these would still not be considered neurodegenerative, per se)

Page 43	section 2.2.1

Clarification regarding structural neuroimaging features of AD:
Early features: hippocampal and mesial temporal lobe atrophy
Later features: global/generalized atrophy

Page 43	section 2.2.2

I do not believe that a “core feature” of LBD is memory loss (although it certain can and eventually is affected). Core COGNITIVE features of LBD are: attention, executive function, and visual spatial skill function impairment relatively early on.

Page 45	section 2.2.3

I do not believe that incontinence and low blood pressure are specific signs of FTLD.

Page 46	section 2.2.4

Would not say “missing appointments” as a feature of MCI, as this implies functional impairment (i.e. dementia)

REPORT OBJECTIVES & KEY QUESTIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Aims/objectives clearly address relevant policy and clinical issue? yes
- Key questions clearly defined and adequate for achieving aims? yes

Page	Line

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METHODS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Method for identifying relevant studies is adequate? **yes**
- Criteria for the inclusion and exclusion of studies is appropriate? **yes**
- Method for Level of Evidence (LoE) rating is appropriate and clearly explained? **yes**
- Data abstraction and analysis/review are adequate? **yes**

Page 95	Table 6

Generally corticobasal degeneration is not considered a sub-heading of FTLD, although it shares features with it. Also, the table says that CBD is EXCLUDED from the literature review. However, **page 99, section 3.1.3** says that CBD was included in the literature review

Page	Line

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RESULTS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Amount of detail presented in the results section appropriate? **yes**
- Key questions are answered? **When able**
- Figures, tables and appendices clear and easy to read? **Yes (although not sure how SoE were downgraded)**
- Implications of the major findings clearly stated? **Implications not clearly stated**
- Have gaps in the literature been dealt with adequately?
- Recommendations address limitations of literature? **I do not think so**

Page 150	Line

I think it is a little confusing the have DSC-MRI here, as it was not particularly mentioned elsewhere in the report. This is a completely different technology than other fMRI sequences (requires contrast agent, and therefore is NOT non-invasive). This is a different sequence and protocol than resting state fMRI (for default mode network, etc) or ASL (CBF measure). I do not believe that most institutions (or MRI systems) have any kind of standard DSC packages (i.e., I believe this is still research mainly)

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CONCLUSIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Are the conclusions reached valid?

Page	Line

I do not feel particularly qualified to determine whether conclusions reached were valid, in that im not sure why some reports were “downgraded” in their final SoE vs. their starting SoE. In particular, it is my experience (both clinically, and my knowledge of the literature) that FTG-PET is fairly sensitive at detecting neuronal loss in Alzheimers dementia. Im surprised that the final SoE in this regard is “low”. In terms of all of the questions ask, this would be the one that I would assume with have the strongest evidence for, and would be the most clinically useful. Although pathological validity is the gold standard, it may skew the available data in terms of the type of subjects enrolled. (? End stage disease where functional imaging findings are likely to be more global, and hence nonspecific, or those with atypical presentations who agree to brain autopsy for clarification?)

Page	Line

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OVERALL PRESENTATION and RELEVANCY Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Is the review well structured and organized?yes
- Are the main points clearly presented?yes
- Is it relevant to clinical medicine?
- Is it important for public policy or public health?yes

Page	Line

Its always difficult when the available evidence is limited to just a handful of studies to know how to relate conclusions into the context of real-world medicine. The question at hand is relevant to clinical medicine. However, the available studies are so limited it seems difficult to answer the question adequately. In addition, results should not necessarily be based on the assumption that everyone with symptoms of dementia initially receives a very thorough history, exam, and work-up, as this is unfortunately not the case.

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QUALITY OF REPORT

Quality Of the Report
(Click in the gray box to make your selection)

Superior ☐
Good ☒
Fair ☐
Poor ☐

Page	Line

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We would appreciate any feedback you have on the usability of this form. Please add comments in the field below.

This form is a little difficult to use. There are no line numbers in the report, so it is not feasible to fill this portion in. Also, the headings of the report do not match up with the headings in the form, also resulting in some wasted time in finding where to put comments, etc.

Comprehensive Evidence-Based Health Technology Assessment
Peer Review Form

Thank you for your willingness to read and comment on the Comprehensive Evidence-Based Health Technology Assessment Review for hip resurfacing. Your contribution and time are greatly appreciated.

This form can be filled out electronically on your personal computer. Enter your identification information and comments directly into the shaded areas; use the **TAB** key to move from field to field. Please enter the section, page, and line numbers where relevant. The shaded comment field will expand as you type, allowing for unlimited text. You have been provided comment fields in each section. Should you have more comments than this allows for, please continue with a blank page. Additionally, we are very interested in your evaluation of the ease of use of our Peer Review Form. Please use the last field to enter suggestions for improvement.

When the Peer Review form is complete, save it to your hard drive and return as an e-mail attachment to robin@specri.com

If you have questions or concerns please contact Robin Hashimoto, PhD at the email above.

Reviewer Identification Information

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E-mail	**tina.tailor@gmail.com**

Change to Appendix: could you please change my area of expertise to “Radiology”, rather than “nuclear medicine.”? As my part of my radiology training, I receive dedicated training in Nuclear Medicine, however this is not my primary area of expertise.

INTRODUCTION Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Overview of topic is adequate? yes
- Topic of assessment is important to address? yes
- Public policy and clinical relevance are well defined? yes

Page 2	**Line 2nd to last sentence under “Diagnosis” subsection and last sentence in this subsection.**

Most of the time, findings on structural neuroimaging are nonspecific. In most patients, we see generalized brain atrophy in a nonspecific pattern. Perhaps revise the sentence to read: “Structural neuroimaging may also aid in the differential diagnosis of the specific subtype of dementia based on patterns of atrophy in the brain, but is often inconclusive.”

Additionally, the second sentence starts with “Most often a diagnosis can be made…” Perhaps it is more reasonable to say “Most often a diagnosis can be suggested….” In general, most patients with dementia are clinically diagnosed as having Alzheimer’s (based on its high prevalence), however true diagnosis of dementia type relies on tissue biopsy (as is later discussed).

Page 3	**Line 3rd sentence in the paragraph labeled “PET” and Line 2 on page 50.**

Consider changing this sentence to: “In PET for dementia diagnosis, the radiopharmaceutical most commonly used is [^{18}F] Fluorodeoxyglucose, which consists of fluorine-18, a positron-emitting radioactive isotope, incorporated into a glucose molecule.”

This is just semantics, but a “radiopharmaceutical” is a term referring to a radioactive particle incorporated into a pharmaceutically-active particle.

Page	**Line**

Enter Comments Here

BACKGROUND Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Content of literature review/background is sufficient? Yes.

Page	**Line**

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REPORT OBJECTIVES & KEY QUESTIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Aims/objectives clearly address relevant policy and clinical issue? yes
- Key questions clearly defined and adequate for achieving aims? yes

Page	Line

Enter Comments Here

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METHODS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Method for identifying relevant studies is adequate? yes
- Criteria for the inclusion and exclusion of studies is appropriate? Yes. See comment below regarding the adverse effects of FDG.
- Method for Level of Evidence (LoE) rating is appropriate and clearly explained? Yes
- Data abstraction and analysis/review are adequate? Yes.

Page 25	Line: Explanation of kappa values

May be helpful to state how the kappa value is interpreted (i.e., which kappa values indicate poor, good, moderate, etc agreement).

Page 54	Line: first paragraph

When considering the adverse reactions of injecting 18F-FDG, did the conclusions take into account imaging studies outside of neuroimaging? 18F-FDG is used for many other types of PET scans (whole body PET in oncology, cardiac imaging). It is generally very safe to inject.

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RESULTS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Amount of detail presented in the results section appropriate? yes
- Key questions are answered? yes
- Figures, tables and appendices clear and easy to read? For the most part – see comment below.
- Implications of the major findings clearly stated? Yes
- Have gaps in the literature been dealt with adequately? Yes- there is mention of ongoing studies. However, given that autopsy or brain biopsy is the gold standard for diagnosis, there are challenges in doing large-volume, prospective studies on diagnostic accuracy. This limitation is mentioned, but perhaps could be emphasized more.
- Recommendations address limitations of literature? See above

Page 167-onward	**Line Multiple summary tables, last column entitled "Starting SoE"**

It's not clear from reading the table alone how the "starting SoE" (last column of multiple summary tables starting on 167) is arrived upon. In reading the methods, it states that that CoE I/II were classified as high and CoE were classified as "low." A description to this effect in a footer under the table may be beneficial.

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CONCLUSIONS Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Are the conclusions reached valid? Yes – there are few large, prospective studies pertinent to these topics, which is reflected by many of the SoE being low or insufficient.

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OVERALL PRESENTATION and RELEVANCY Comments

While reviewing this section please keep the following questions in mind, but please comment on any point:

- Is the review well structured and organized? Yes. Results feel a bit redundant because they are embedded in multiple areas of the report in summarized fashion, however the summarized results in the Executive summary, Results section, and tables at the end of the report are helpful.
- Are the main points clearly presented? yes
- Is it relevant to clinical medicine? yes
- Is it important for public policy or public health? Yes

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QUALITY OF REPORT

Quality Of the Report
(Click in the gray box to make your selection)

Superior ☐
Good ☒
Fair ☐
Poor ☐

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We would appreciate any feedback you have on the usability of this form. Please add comments in the field below.

The form is usable.

Functional Neuroimaging for Primary Degenerative Dementia or Mild Cognitive Impairment

Presented by Dr. Gary Franklin, Chief Medical Officer, WA State Department of Labor and Industries

1. p16. In several places, inter-rater reliability is rated as good, moderate or excellent. It is not explained in the report how these ratings are related to the kappa value or the degree of agreement. It would be helpful to give some description on inter-rater reliability and intra-rater reliability, and how the kappa value and the degree of agreement are used to measure or rate the reliability.
2. p16. What is the modality "11C-DTBZ-PET" used for specifically? Are there any data on the accuracy of the modality? It is not described in the background section together with other modalities, and there seem to be no other information available for the modality in the report.
3. p18. "Automated classification of images had 67% sensitivity and 100% specificity". Is automated classification of images common in practice? In practice, do most clinicians use both visual assessment and automated classification? How often are the images assessed by automatic classification in practice?
4. p18. "Prevalence of AD: 55%". What does it mean here? Is it the fraction of all the subjects enrolled in the study who had AD confirmed by autopsy?
5. p21. "Patient progression (MCI to AD/dementia conversion)". The indent level needs to be increased a notch to avoid any confusion.
6. p21. Under "SPECT (perfusion)" and several levels down, "Prediction of AD or dementia with FDG-PET alone had 36-76% sensitivity and 39-82% specificity". Should it be SPECT instead of FDG-PET?
7. p24. Long term and short harms of FDG-PET or SPECT. The time factor is critical, but the follow-up times of the study described here are not defined in either the text or the table. It would be good to add.
8. p24. "DaTscan". It is questionable to attribute the AEs, such as dry mouth, vomiting and headache, to injection only rather than the ligand injected because these are not local reactions.
9. p24. There might be another type of potential harm, which is indirect. If a modality is not accurate, especially when the specificity is low, which would result in a high false positive rate, the psychological harm would be serious. Is there any study out there to address this potential harm of any of the modalities?
10. p26. Is DSC-MRI a type of fMRI? If it is, it should be described under fMRI. If it is not, it would be helpful to be introduced in the "Index tests" on p14. DSC-MRI appears only in Key Question 6 section (cost-effectiveness) and not in any other sections. Are there any data on reliability, accuracy and safety of DSC-MRI? Not sure why it is included in the report if it is not one of the index tests defined.