Washington State Health Care Authority

Functional Neuroimaging for Primary Degenerative Dementia or Mild Cognitive Impairment

Assessing Signals for Update

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Health Technology Assessment Program (HTA)

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This report is based on research conducted by the RTI–University of North Carolina Evidence-based Practice Center through a contract between RTI International and the State of Washington Health Care Authority (HCA). The findings and conclusions in this document are those of the authors, who are responsible for its contents. The findings and conclusions do not represent the views of the Washington HCA and no statement in this report should be construed as an official position of Washington HCA.

The information in this report is intended to help the State of Washington Health Care Authority make decisions. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information (i.e., in the context of available resources and circumstances presented by individual patients).

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Executive Summary

The State of Washington's Health Technology Assessment Program published a 2014 health technology assessment (HTA) titled "Functional Neuroimaging for Primary Degenerative Dementia or Mild Cognitive Impairment".[1] Based on this HTA, the Health Technology Clinical Committee found sufficient evidence to not cover Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT), Functional Magnetic Resonance Imaging (fMRI) or Arterial Spin Labeling (ASL) MRI for functional neuroimaging for primary degenerative dementia or mild cognitive impairment. We conducted a signal search to determine whether current evidence suggests the need for an update to the published HTA.

We searched MEDLINE® (via PubMed) for relevant English-language studies published between January 1, 2014, and April 5, 2024. We limited the search to systematic reviews that included primary research studies that would meet the 2014 HTA's inclusion and exclusion criteria but expanded the eligible imaging tests to include amyloid PET and tau PET. We abstracted brief information from 19 systematic reviews into a structured form. Using a modified Ottawa approach, we evaluated each review for whether a signal for new evidence suggests a need for an updated HTA and/or coverage decision.

We identified 9 systematic reviews that included FDG-PET. These reviews suggested that FDG-PET is sensitive for diagnosing Alzheimer's Disease (AD) and distinguishing AD from frontotemporal dementia (FTD). Four reviews suggested that FDG-PET had moderate to good accuracy for predicting progression of mild cognitive impairment(MCI) to AD. Review authors noted meaningful limitations within included studies, specifically methodically heterogenous studies, poorly defined reference standards or comparators, and lack of defined thresholds for determining test positivity. We identified 8 relevant systematic reviews that included amyloid PET, which is new to this topic. These reviews reported that amyloid PET was sensitive for diagnosing AD and distinguishing AD and FTD. One review found specificity and sensitivity for predicting progression from MCI to AD ranged widely across 8 studies. Multiple systematic reviews reported changes in diagnosis, clinical management, and a decrease in the use of other diagnostic tests after amyloid PET. We found 7 systematic reviews that included SPECT. Most of these systematic reviews reported that SPECT had limited benefit or was inferior to FDG-PET. We found 3 systematic review that included tau PET, which is new to this topic. These systematic reviews either documented possible benefit or documented a lack of evidence. We found only 1 systematic review of ASL-MRI suggesting it is inferior to FDG-PET and no relevant systematic reviews of fMRI.

Our signal search findings suggest an updated HTA may be needed for FDG-PET, amyloid PET, and tau PET, in part because amyloid PET and tau PET were not within the scope of the previous HTA.

1. Introduction

The State of Washington's Health Technology Assessment (HTA) Program published a health technology assessment (HTA) titled "Functional Neuroimaging for Primary Degenerative Dementia or Mild Cognitive Impairment" on December 5, 2014.[1] The independent Health Technology Clinical Committee (HTCC) evaluated the findings of this HTA and made an initial coverage determination at its January 16, 2015, meeting with final adoption of the determination on March 20, 2015. The Committee's Coverage Decision for functional neuroimaging for dementia is summarized in **Section 1.2** below. At the request of the state's HTA program, we conducted a signal search to determine whether new evidence is available that suggests a need to update the previous HTA. This report summarizes the findings of that signal search.

1.1 Policy Context

In 2015, the HTCC determined that functional neuroimaging for primary degenerative dementia or mild cognitive impairment should not be covered.[2] The committee concluded that there was sufficient evidence at that time to not cover Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT), Functional Magnetic Resonance Imaging (fMRI) or Arterial Spin Labeling (ASL) MRI. The committee did not identify data suggesting changes in clinical outcomes, treatment, or caregiver benefits to support coverage.[2]

We reviewed Centers for Medicare & Medicaid Services (CMS) national coverage determinations (NCDs) to provide general policy context around functional imaging for dementia. There have been no changes to the NCD for F-fluorodeoxyglucose PET (FDG-PET) scans since September 2004. FDG-PET scan is only covered for the differential diagnosis of Frontotemporal dementia (FTD) and Alzheimer's Disease (AD) under specific requirements (patients previously evaluated for specific alternate neurodegenerative disease or causative factors and cause of symptoms remains uncertain) and for use in CMS-approved trials.[3] CMS does not include any form of dementia in the list of conditions for which SPECT is covered.[4] and CMS does not have an NCD for fMRI or MRI with ASL.

In October 2023, CMS ended its previous NCD for beta-amyloid PET, which specified coverage with evidence development but limited coverage to 1 scan per year. Based on the accumulated evidence since 2013, CMS now allows Medicare Administrative Contractors (MACs) to make coverage determinations for functional neuroimaging stating "While there will not be an NCD, the MACs also use an evidence-based process for making coverage determinations. Based on the evidence, we believe there will be consistent coverage across regions for appropriate Medicare patients."[5]

1.2 Functional Neuroimaging for Dementia 2015 Coverage Determination

Functional neuroimaging for primary degenerative dementia or mild cognitive impairment (MCI) is not covered.[6] The rationale for the committee's decision was as follows:

- Based on the deliberations of key health outcomes, the committee decided that it had the most complete information: a comprehensive and current evidence report, public

comments, and state agency utilization information. The committee concluded that the current evidence on PET, SPECT, fMRI or ASL-MRI demonstrates that there is sufficient evidence to not cover.

- The committee considered all the evidence and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable. Based on these findings, the committee voted to not cover PET, SPECT, fMRI or ASL-MRI for functional neuroimaging for primary degenerative dementia or MCI.

- The committee checked for availability of Medicare national coverage decisions (NCDs). At that time, there was an NCD that included coverage for FDG-PET scanning for dementia, MCI and other conditions. The NCD that included coverage for SPECT did not include MCI, dementia, AD, FTD, or DLB in the list of conditions for which SPECT is covered. No NCD for fMRI was identified.

- The committee did not identify data supporting clinical outcomes or changes in treatment or caregiver benefits to support coverage.

1.3 Scope of the Functional Neuroimaging for Dementia 2014 HTA

The key questions (KQ) from the 2014 HTA included the following[6]:

Contextual Questions (CQ): What is the reliability and accuracy of functional neuroimaging (e.g., SPECT, PET, and fMRI) **as used to diagnose** AD, FTD, and Lewy body dementia (including Dementia with Lewy Bodies (DLB) and Parkinson's Disease with dementia (PDD)) in symptomatic dementia patients who have undergone a comprehensive initial diagnostic work-up (that included structural neuroimaging). Specifically:

- Provide a summary of the inter-rater and intra-rater diagnostic reliability (reproducibility).

- Provide a summary of the sensitivity and specificity based on an appropriate gold standard (e.g., autopsy, genetic confirmation).

KQ 1: What is the diagnostic accuracy of functional neuroimaging for **the differential diagnosis** of AD, FTD, and Lewy body dementia (including DLB and PDD) based on an appropriate gold standard (e.g., autopsy, genetic confirmation)?

KQ 2: What is the ability of functional neuroimaging to predict progression and clinical outcomes? Is one functional test better at predicting progression or clinical outcomes versus another?

KQ 3: Do the results of functional neuroimaging impact therapeutic decisions or clinical management compared to those made for patients who did not receive functional neuroimaging?

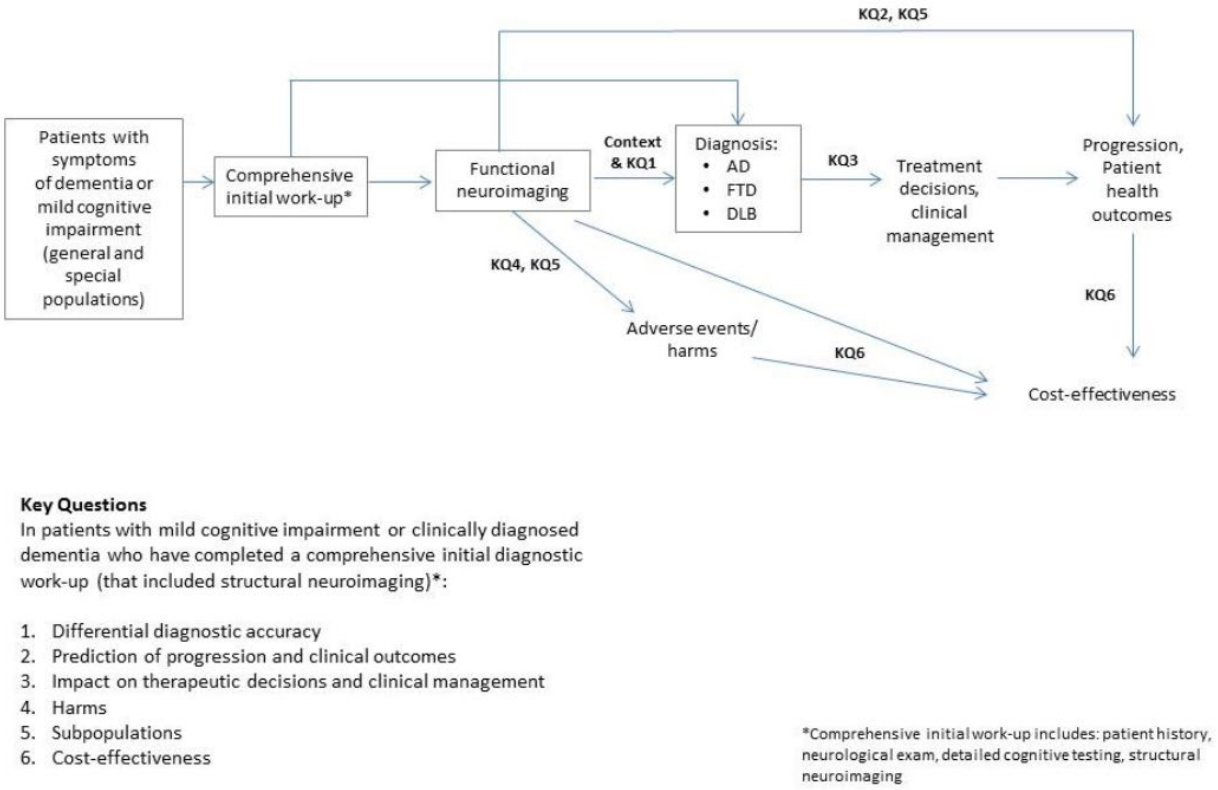
KQ 4: What are the short and long term harms of diagnostic functional neuroimaging?

KQ 5: What is the evidence that functional neuroimaging may perform differently in subpopulations (i.e., younger age, presence of comorbidities, etc.)? Consider the impact on disease progression, clinical outcomes, and harms.

KQ 6: What is the cost-effectiveness of incorporating diagnostic functional neuroimaging into the comprehensive initial diagnostic work-up?

The following analytic framework (***Figure 1***) guided the 2014 HTA:

Figure 1. Analytic framework for functional neuroimaging for dementia 2014 HTA



Abbreviations: AD = Alzheimer's Disease; DLB = Dementia with Lewy Bodies; FTD = Frontotemporal dementia; HTA = health technology assessment; KQ = key question.

Detailed study selection criteria from the 2014 HTA are in ***Appendix A***.[2] In brief, authors of the previous HTA included prospective or retrospective studies. For the accuracy CQ and KQ 1, studies reporting on the diagnostic accuracy of functional neuroimaging were required to use autopsy results as the gold standard; studies that use clinical diagnosis as the reference standard were excluded. For KQ 2, longitudinal studies with at least 1 year follow-up and designed specifically to evaluate progression were considered. The following study types were excluded: case-control studies and studies with less than 10 patients (including case reports). For KQ 3, studies that reported on changes in therapeutic decisions or clinical management following functional neuroimaging compared with to those made for patients who did not receive functional neuroimaging were included. For KQ 4, studies that reported on adverse events/harms

from the neuroimaging procedure in the patient population of interest were sought. For KQ 5, studies that reported on the use of functional neuroimaging to predict progression and/or clinical outcomes (i.e., studies included in KQ 2) and which stratified on patient or other characteristics and formally evaluated effect modification were sought. For KQ 6, full formal economic studies that assessed the impact of incorporating diagnostic functional neuroimaging into the comprehensive initial diagnostic work-up were sought; that is, cost-effectiveness, cost-utility, cost-minimization, and cost-benefit studies.

The 2014 HTA included 34 studies. Fourteen studies provided evidence on the accuracy CQ, 6 studies provided evidence on KQ 1 (differential diagnosis accuracy), 13 studies provided evidence on KQ 2 (disease progression), 2 studies provided evidence on KQ 4 (harms), and 4 studies provided evidence on KQ 6 (cost-effectiveness). No studies were identified for KQ 3 (clinical management) or KQ 5 (subgroups). ***Table 1*** provides a summary of the studies included in the 2014 HTA.[1]

Table 1. Summary of studies included in the 2014 HTA by imaging test

Imaging test	CQ1	KQ1	KQ2	KQ3	KQ4	KQ5	KQ6	Total*
FDG-PET	8	5	10	0	1	0	3	
SPECT	5	1	3	0	1	0	2	
fMRI	0	0	1	0	0	0	0	
ASL	0	0	0	0	0	0	0	
2104 HTA	14	6	13	0	2	0	4	34

*Totals are not mutually exclusive; a study could contribute to more than one key question or test.

1.4 Epidemiology and Burden of Disease

Dementia is characterized by a decline in mental capabilities from a previous level of functioning that interferes with daily functioning in 1 or more cognitive domains: learning and memory, language, executive function, perceptual motor skills, or social cognition.[7,8] The State of Washington's 2014 HTA on this topic[1] evaluated functional neuroimaging for the following specific conditions: AD, DLB including PDD, FTD, and MCI.

1.4.1 Alzheimer's Disease (AD)

AD is the most common form of dementia accounting for 60% to 80% of dementia cases. An estimated 6.9 million Americans aged 65 years and older have AD, including 126,700 adults aged 65 years and older in Washington State.[9,10] Brain changes associated with AD include the accumulation of protein beta-amyloid outside neurons and twisted strands of the protein tau inside neurons. This is accompanied by the death of neurons and damage to brain tissue. Early symptoms include challenges remembering recent conversations or events, communication problems, confusion, poor judgement, and depression.[9]

1.4.2 Dementia with Lewy Bodies (DLB) and Parkinson's Disease with dementia (PDD)

DLB and PDD are caused by abnormal aggregations (or clumps) of the protein alpha-synuclein in neurons in the cortex of the brain or in an area deep in the brain called the substantia nigra.[9] An estimated 5% of older individuals with dementia show evidence of DLB alone, though most patients with DLB also have other brain changes indicative of AD.[11] An estimated 4% of

dementia cases are due to PDD and 25% of people with Parkinson's Disease developed dementia.[12] Symptoms of DLB and PDD include sleep disturbances, visual hallucinations, visuospatial impairment, and problems with movement. For PDD, cognitive symptoms may develop later in the disease, typically years after movement symptoms. [9,12]

1.4.3 Frontotemporal dementia (FTD)

FTD accounts for about 3% of dementia cases in studies that included people 65 years and older and about 10% of dementia cases in studies restricted to those younger than 65 years.[13] An estimated 60% of people with FTD are aged 45 to 60 years.[14] Brain changes that indicate FTD include the shrinking and death of nerve cells in the front and temporal lobes of the brain and evidence of abnormal amounts of tau or transactive response DNA-binding protein (TDP-43).[9] Symptoms include noticeable changes in personality and behavior or difficulty with producing or comprehending language. Memory is typically not impacted in the early stages of disease.[9,14]

1.4.4 Mild cognitive impairment (MCI)

MCI is an intermediate state between normal cognition and dementia characterized by marked cognitive impairments, which may be noticeable to family or friends but not to others, and does not interfere with normal functioning.[9] About 15% of those with MCI develop AD within 2 years[15] and 33% develop AD within five years.[16] However, some with MCI revert to normal cognitive function. A systematic review and meta-analysis of population-based studies found a reversion rate of 26%.[9,17] Estimating the prevalence of MCI and MCI due to AD is challenging. A systematic review of more than 30 studies of all-cause MCI reported that about 17% of people age 65 and older had MCI.[15] The Health and Retirement Study estimated the prevalence of MCI in people age 65 years and older to be 22%.[18] Meanwhile, studies assessing biomarkers for AD with PET scans report that roughly 50% of people with MCI have AD related brain changes.[19,20] Based on this, the Alzheimer's Association estimates that roughly 8% to 11% of the 63 million Americans who are age 65 years and older in 2024, or approximately 5 to 7 million older Americans, may have MCI due to AD.[9]

1.5 Diagnosis

Because dementia conditions have similar clinical presentations, it is difficult to distinguish them in clinical practice. The "gold standard" for definitive diagnosis of a specific type of dementia is histopathologic confirmation; however, this is only available post-mortem so is not helpful in a clinical context.[1] In practice, dementia is generally diagnosed based on a combination of cognitive and neurological exams. An evaluation typically includes an assessment of cognitive function (Mini-Mental State Examination or Montreal Cognitive Assessment), a complete physical exam, screening for depression, and a neurologic examination, which may include laboratory and imaging studies.[9] Structural imaging with MRI or CT scan may be included in a standard medical workup for dementia to rule out other conditions that cause similar symptoms (e.g., subdural hematoma, cancer).[9]

The 2014 HTA found that functional neuroimaging was regarded as an add-on diagnostic test that might be ordered if results from previous clinical evaluations were inconclusive.[1] Functional neuroimaging may aid in the differential diagnosis of AD, DLB, and FTD, and although it is not

typically used to diagnose MCI, it may predict future conversion to AD and would therefore allow patients and their caregivers to know what to expect and to help them prepare for the future.[1]

1.6 Technology

The 2014 HTA[1] evaluated PET to measure glucose metabolism (e.g., FDG-PET), SPECT, fMRI, and ASL-MRI. The 2014 HTA excluded amyloid PET, which was a new technology at the time. Since then, evidence related to this imaging test has accumulated.[5] Additionally, FDA approved a radiopharmaceutical tracer for tau PET imaging in 2020, which could be meaningful to the diagnosis of AD.[21]

1.6.1 FDG- PET

Positron emission tomography (PET) to measure glucose metabolism (e.g., 18F-FDG-PET) is a diagnostic imaging test that uses a positron-emitting radionuclide and a scanner to produce images of the brain or other parts of the body being studied. A radioactive particle, 18F-fluorodeoxyglucose (18F-FDG), is injected into the bloodstream. This particle competes with glucose for absorption and metabolism in a variety of cell types, including neurons, as a result it is a marker for glucose metabolism.[22] FDG-PET scans demonstrating hypometabolism in specific regions can be indicative of specific types of neurodegenerative dementia.

1.6.2 SPECT

Single photon emission computed tomography(SPECT) is used to measure cerebral perfusion (e.g., 99mTC-HMPAO-SPECT) and dopamine transporter uptake (e.g., 123I-ioflupane-SPECT/123I-FP-CIT-SPECT/Dat-SCAN/Dat-SPECT). SPECT is used to investigate changes in the function and molecular composition related to neurodegenerative dementia. A radioactive tracer is injected into the blood stream that allows for the evaluation of cerebral blood flow, which correlates with brain metabolism. As a result, SPECT images provide information about which regions of the brain are impacted by neurodegeneration, aiding with differential diagnosis of forms of dementia. SPECT images are processed in generally the same way as FDG-PET neuroimaging but have a lower spatial resolution.[1,23]

1.6.3 fMRI

Functional MRI (fMRI) measures changes in the concentration of deoxyhemoglobin within active areas of the brain.[24] When used to aid in the diagnosis of dementias, fMRI may be done with or without active stimulation to help determine the cognitive ability of the individual.[25,26] fMRI does not involve radiation and therefore multiple images can be taken over time which may allow for changes within the brain to be tracked over time.[1,26]

1.6.4 MRI with arterial spin labelling (ASL)

MRI with arterial spin labelling (ASL) uses electromagnetically labeled arterial water as a tracer for measuring perfusion within the brain.[27] The magnetized tracer moves to the target area which in turn alters the magnetization of the tissue, generates an MR signal, and an image of brain activation.[1,27] A second control image without the tracer is taken as a comparison using control labeling. These two images are then subtracted from one another to create a map of cerebral

blood flow.[28] There are two types of ASL. Continuous ASL produces a higher perfusion contrast by continuously labeling arterial blood water through a labeling plane allowing the same area to be imaged for several seconds at a time.[28,29] Pulsed ASL sends short and rapid radiofrequency pulses rather than a singular long pulse.[28]

1.6.5 Amyloid PET

Amyloid PET imaging (also known as beta-amyloid PET imaging) is used to detect levels of amyloid in the brain.[30] Accumulation of the protein fragment beta-amyloid into clumps (i.e., beta-amyloid plaques) outside of neurons is one of several brain changes associated with AD. [9] In amyloid PET imaging, a radiopharmaceuticals tracer that binds to amyloid aggregates in the brain is injected and used to estimate the density of beta-amyloid plaque.[31] This class of radiopharmaceutical tracers include Amyvid™ (florbetapir F18), Neuraceq™ (florbetaben F18) and Vizamyl™ (flutemetamol F18), which are all FDA approved.[30] Measurements of cerebral amyloid may be clinically useful in the work up and management of patients with cognitive impairment who are being evaluated for possible AD or other causes of cognitive decline.[30]

1.6.6 Tau PET

Tau PET imaging measures accumulation of an abnormal form of the protein tau (called tau tangles) inside neurons. Tau tangles block the transportation of nutrients and other molecules essential for the normal function and survival of neurons while harming connections between neurons and is associated with AD.[9] Unlike amyloid, tau is intracellular, so it needs to be attached to a molecule (also known as a ligand) that can cross both the blood–brain barrier and the plasma cell membrane of the neuron.[32] In May 2020, FDA approved flortaucipir F18 (Tauvid™) as the first radioactive tracer to help image distinctive characteristics of tau pathology associated with AD.[21] Tauvid is indicated for use in PET imaging to estimate the density and distribution of aggregated tau neurofibrillary tangles, a primary marker of AD. [21]

1.7 Objectives

The primary aim of this signal search is to determine whether there is new evidence that will change the conclusions of the most recent State of Washington HTA on Functional Neuroimaging for Primary Degenerative Dementia or Mild Cognitive Impairment, which was published in January of 2014.[1]

2. Methods

We used a modified Ottawa approach,[33,34] relying primarily on recent systematic reviews (i.e., those published in the last 4 years). Since functional neuroimaging for dementia or MCI is currently not covered, we focused on efficacy outcomes, with particular attention given to outcomes related to changes in clinical management. For this assessment, we abstracted data from relevant systematic reviews until a clear signal for each KQ was achieved. Specifically, we abstracted data for up to 2 systematic reviews for an included imaging test. If we found a consistent signal from the 2 most recent systematic reviews for an included imaging test, we did not abstract data from additional systematic reviews. We abstracted findings from additional

systematic reviews if there were opposing or inconsistent findings or if the reviews differed in scope.

2.1 Literature Search

We searched MEDLINE® (via PubMed) for relevant English-language studies between January 1, 2014, and April 5, 2024, allowing an overlap of 6 months with the previous search. The search strategy is described in detail in ***Appendix B***. We limited the search to systematic reviews using filters. We searched clinicaltrials.gov on June 18, 2024, for trials of FDG-PET, SPECT, fMRI, ASL-MRI, amyloid PET, or tau PET related to AD, DLB, PDD, FTD, or MCI on June 18, 2024.

2.2 Study Selection

We sought to identify systematic reviews that would include primary research studies that meet the HTA's inclusion and exclusion criteria. We included systematic reviews with broader inclusion and exclusion criteria if findings were reported separately for eligible studies. For example, if a review on diagnostic accuracy included both clinical diagnosis and autopsy as an eligible reference standard and reported findings for studies with an autopsy reference standard, we abstracted the findings for studies with the eligible reference standard (autopsy). Likewise, if a review included a mix of eligible and ineligible index tests and reported findings by index test, we abstracted data for the eligible index test.

For this signal search, the only change to the inclusion and exclusion criteria from the 2014 HTA was that we included amyloid PET and tau PET as additional imaging tests based on accumulated evidence and changes in other payer coverage policies since 2014. Detailed inclusion and exclusion criteria are shown in ***Appendix A***.

2.3 Data Abstraction and Signal Assessment

One reviewer evaluated titles and abstracts retrieved by our search; that same reviewer also assessed full text systematic review articles to determine if they met selection criteria and reported relevant findings. Newer systematic reviews were screened and abstracted first to identify the most recent evidence. Note, that when systematic reviews have similar inclusion and exclusion criteria, newer systematic reviews are likely to include the same primary research studies as older systematic reviews, reducing the utility of also abstracting data from the older systematic reviews. Therefore, we stopped abstracting findings from older reviews once we identified a signal for an included index test. We also prioritized abstraction of high impact systematic reviews (e.g., Agency for Healthcare Research and Quality or Cochrane reviews). Because the 2014 HTA did not find evidence leading to coverage, we considered reviews that identified entirely new evidence (i.e., studies of previously unreviewed imaging modalities) or reviews that concluded there was benefit of a given test to be a signal that an updated HTA may be indicated.

3. Results

3.1 Search Yield and Overview of Studies

The PubMed search retrieved a total of 13,235 citations, including 234 systematic reviews. We screened only the systematic reviews for this signal search and excluded 183 systematic reviews after title and abstract review. We reviewed the full text of 51 systematic reviews and found 33 provided evidence related to the previous HTA's inclusion criteria. We excluded 11 systematic reviews because they did not report any eligible outcomes, 6 systematic reviews because they exclusively included studies with ineligible comparator or reference tests, and 1 review that was a full report version of a previously abstracted systematic review. We abstracted summary data from 19 systematic reviews and did not abstract data from 14 additional systematic reviews because findings were redundant to already abstracted reviews.

3.2 Study Characteristics

Among the 19 abstracted systematic reviews, 2 were published in 2024,[35,36] 5 were published in 2023,[37-41] 1 was published in 2022,[42] 3 were published in 2021,[43-45] 2 were published in 2020[46,47] and the remaining 6 were published before 2020.[48-53] Reviews that were included but not abstracted were all published prior to 2020.[54-67] The most recent search date of the included reviews was July 2023.[35]

Nine systematic reviews assessed FDG-PET,[36,39,41,42,44,46,49,50,52], 8 assessed amyloid PET,[36,37,40,43,44,46,48,50] 7 assessed SPECT,[35,36,42,46,47,51,53] 4 assessed tau PET,[36,38,44,45], 1 assessed ASL-MRI[39] and 1 included fMRI but did not report any eligible outcomes for fMRI alone.[41] Note that many systematic reviews included more than 1 imaging test.

The most common use case for imaging that was evaluated was conversion from MCI to AD, which was reported in 8 systematic reviews.[36,40-42,44,49,50,52] Six systematic reviews reported on ability to distinguish AD from non-AD dementia,[37,39,41,45,46,48] 3 reported ability to distinguish AD and FTD,[37,46,53] 2 reported on ability to distinguish DLB from other non-DLB dementias,[47,51] and, finally, 1 focused on the diagnosis of progressive supranuclear palsy.[38]

3.3 Signal Findings

Table 2 provides a summary of the signals identified from systematic reviews; detailed information about these revies is provided in ***Table C-1*** in ***Appendix C***.

Table 2. Summary of evidence from systematic reviews by imaging modality and KQ

Imaging Test	CQ Diagnosis	KQ1 Differential Diagnosis	KQ2 Progression	KQ3 Utility for treatment decisions	KQ4 Harms	KQ5 Sub-popula-tions	KQ6 Cost-effectiveness
FDG-PET	1 review suggesting benefit [46]	*	4 reviews suggesting benefit [36,42,44,50] and 1 review concluding limited benefit [49]	1 review suggesting benefit from a single study [50]	*	*	1 review with mixed signal [50]
SPECT	1 review suggesting benefit [47] and 1 review suggesting inferior to other tests [46]	2 reviews suggesting limited benefit [35,53] and 1 review identifying no eligible studies [51]	2 reviews suggesting limited benefit compared to FDG-PET [36,42]	*	*	*	*
fMRI	*	*	*	*	*	*	*
ASL-MRI	1 review of a single study suggesting ASL-MRI inferior to FDG-PET [39]	*	*	*	*	*	*
Amyloid PET	2 reviews suggesting benefit [37,46]	1 review suggesting benefit [37]	1 review suggesting benefit [36]	2 reviews suggesting benefit [43,48]	1 review suggesting benefit [43] and 1 review with a mixed signal [40]	*	1 review suggesting benefit [43]
Tau PET	1 review suggesting limited benefit [38] and 1 review with unclear inclusion criteria suggesting benefit [45]	1 review that identified no evidence [38]	1 review that included limited evidence [36] and 1 review documenting no evidence [44]	*	*	*	*

Legend:
Green shading indicates new imaging tests not included within the scope of the prior HTA/coverage decision OR a previously included test with new evidence suggesting a change in conclusions from the previous HTA and coverage decision.
Yellow shading indicates mixed evidence, unclear if new evidence is likely to change coverage decision.
No shading indicates new evidence is consistent with previous conclusions.
*No new systematic reviews identified

3.3.1 FDG-PET

We identified 1 systematic review including FDG-PET that reported evidence for the CQ.[46] This review included 2 studies (n = 182 total) that evaluated the accuracy of FDG-PET compared to an autopsy to distinguish AD from FTD and non-AD dementia. This AHRQ funded review concluded that FDG-PET was highly sensitive for neuropathologic AD diagnosis.[46]

We identified several systematic reviews describing the ability of FDG-PET to predict MCI conversion to AD. The most recent systematic review, Cotta Ramusin et al., 2024,[36] concluded that FDG-PET had moderate to good accuracy in predicting the progression of MCI to AD based on 25 studies (n = 6,803) with sensitivity and specificity ranging from 43% to 100% and 63% to 94%, respectively. Three other reviews reached similar findings.[42,44,50] Notably, the eligible reference standards for 2 of these reviews was not clearly reported.[42,44] Rice et al., 2017[50] found that FDG-PET alone had high sensitivity (92%) and specificity (89%) in predicting conversion to AD for patients with MCI though the authors noted the evidence base would be strengthened by studies with lengthier longitudinal follow-up. In contrast, Smailagic et al., 2015[52] found substantial variability in FDG-PET specificity values, heterogeneity in test, and lack of defined thresholds for determination of test positivity in the included studies. These authors concluded that the evidence did not support the routine use of FDG-PET in clinical practice but notably the search for this review was conducted in January 2013.[52]

Only 1 systematic review reported cost-effectiveness related outcomes (KQ6). Rice et al., 2017[50] reported that a U.S. based study found few benefits of FDG-PET at significant cost when introduced to the standard diagnostic regimes at AD centers. However, the decision-analytic model used by this study only included patients with moderate to severe AD. Rice et al., 2017 [50] added that a more recent study modelled the use of FDG-PET in relation to the validation scheme used for oncological biomarkers. The authors of that study argued that thorough cost/benefit quantification was hindered by the lack of research into its estimated impact on morbidity and disability, especially considering the recent FDA approval of potentially disease modifying drugs.

We did not identify any systematic reviews reporting outcomes for KQ1, KQ4, or KQ5 for FDG-PET.

3.3.2 SPECT

We identified 2 systematic reviews that assessed SPECT and reported evidence for the CQ.[46,47] Nihashi et al., 2020[47] included a total of 27 studies but only 2 studies had postmortem verification. Those 2 studies (n = 73) reported adjusted sensitivity of 0.83 and 0.87, respectively, and adjusted specificity of 0.84 and 0.81, respectively, for distinguishing DLB from non-DLB

dementia. Fink et al. assessed SPECT for distinguishing AD from non-AD dementias and included 3 studies (n = 205) with median sensitivity of 0.64 (range, 0.57 to 0.94) and median specificity of 0.83 (range, 0.76 to 0.92). This review concluded that SPECT had variable accuracy and was less accurate than FDG-PET and amyloid PET.[46]

We identified 3 systematic revies reporting KQ1 related outcomes for SPECT. All of these reviews had broader inclusion and exclusion criteria than the 2015 HTA and included studies with a reference standard of clinical diagnosis in addition to autopsy. McCleery et al. reported that they identified no studies with a neuropathological reference standard.[51] Athanasio, et al.[35] included 5 studies, with unclear reference standards, and found sensitivity of SPECT to distinguish AD and FTD ranged from 56% to 88% and specificity ranged from 51% to 93%. These authors concluded that SPECT had limited value in the diagnostic framework of FTD and suggested that it could be performed when FDG-PET was not available or in select cases when diagnosis using conventional methods was challenging.[35] An older review reached similar conclusions.[53]

We identified 2 reviews of SPECT reporting MCI conversion to AD.[36,42] Cotta Ramusino et al.[36] identified 9 studies (n = NR) with sensitivity and specificity ranging from 48% to 100% and 71% to 100%, respectively. This review concluded that SPECT was less accurate than FDG-PET and amyloid PET at predicting MCI conversion to AD.[36] Zhu et al.[42] identified 4 studies (n = NR) with sensitivity and specificity of 80.5% (95% CI, 78.3 to 90.1) and 74.3% (95% CI, 61.3 to 78.5), respectively. This review compared SPECT to FDG-PET and found that the sensitivity, specificity, and positive likelihood ratio of FDG-PET imaging for predicting MCI conversion to AD was significantly higher than that of SPECT and the difference was statistically significant ($P<0.05$).[42]

We did not identify any systematic reviews reporting outcomes for SPECT related to KQ3 or KQ6.

3.3.3 fMRI

We did not identify any systematic reviews reporting eligible outcomes related to fMRI. One systematic review focused on machine learning and deep learning techniques to diagnose AD from MRI and PET scan images and included fMRI as an eligible test; however, authors did not report any synthesized results or findings specific to fMRI alone.[41]

3.3.4 ASL-MRI

We identified a single systematic review comparing ASL-MRI to FDG-PET for diagnosing dementia.[39] This systematic review included a total of 14 studies but only one study (n = 9) had an eligible study design for the CQ. This retrospective cohort study found that the inter and intramodality agreements were insignificantly different between ASL-MRI and FDG-PET. The diagnostic accuracy of ASL MRI was 55% compared to 78% for FDG-PET. [39] The authors concluded that FDG-PET likely has an advantage over ASL-MRI, though this conclusion was driven by case-control studies.

3.3.5 Amyloid PET

The 2014 HTA excluded amyloid PET, which was a new technology at the time. Since then, evidence related to this imaging test has accumulated.[5] Thus, amyloid PET was added to the scope of this signal search. We identified 2 systematic reviews on amyloid PET reporting outcomes for the CQ. One review included 4 prospective and retrospective studies (n = 1,082) of amyloid PET for diagnosing AD with an autopsy reference standard.[37] Sensitivity and specificity ranged from 0.84 to 0.95 and 0.82 to 0.92, respectively. The authors of this review concluded that the performance of amyloid PET in diagnosing AD was favorable and added that employing machine learning analysis may improve diagnostic accuracy.[37] Similarly, an AHRQ funded review, identified 4 studies (n = 426) of amyloid PET to diagnose AD and reported a median sensitivity of 0.91 (range, 0.79 to 0.98) and a median specificity of 0.92 (range, 0.76 to 1.0). Fink et al. concluded that amyloid PET was highly sensitive for neuropathologic AD, though authors noted that the included studies were methodologically heterogeneous and had uncertain applicability to typical clinical settings.[46]

We identified 1 systematic review on amyloid PET reporting KQ1 outcomes. Ruan et al. included 1 study (n = 101) distinguishing AD from FTD that reported sensitivity of 0.93 (95% CI, 0.86 to 0.98) and specificity of 0.84 (95% CI, 0.75 to 0.92).[37]

We identified 1 systematic review on amyloid PET reporting outcomes for KQ2.[36,44] Cotta Ramusino et al. included 8 studies (n = 1,806) with a mean follow up of 36 months and found that specificity ranged from 64% to 94% and sensitivity ranged from 48% to 93% for predicting progression from MCI to AD.

We identified 3 systematic reviews on amyloid PET reporting outcomes for KQ3. Cotta Ramusino et al.[43] found that amyloid PET led to diagnostic revision in 19% to 79% of cases, an increase in diagnostic confidence in 9% to 49% of cases, and revised management plans in 24% to 89% of cases. They did not provide the exact number of studies or study participants supporting these estimates but cited 22 references to support these statements. Shea et al.[48] reported that across 13 studies (n = 1,489) the pooled percentage change for shift in diagnosis after amyloid PET was 35.2% (95% CI, 24.6% to 47.5%) and the range was 9% to 69%. This review identified 8 studies (n = 611) that reported changes in clinical management after amyloid PET. The pooled percentage change was 59.6% (95% CI, 39.4% to 77.0%) and the range was 25.4% to 81.3%. Notably, 1 of the studies included in this review reported a net decrease in the number of diagnostic investigations per patient following amyloid PET of 25% for structural imaging tests, 33% for neuropsychological testing, 95% for lumbar puncture, and 92% for FDG-PET.[48]

We identified 2 systematic review reporting outcomes for KQ4.[40,43] Couch et al.[40] found little evidence of an association between diagnostic disclosure of amyloid PET results and depression. Patients with MCI with elevated levels of amyloid had an increased risk of distress or anxiety compared with those without elevated amyloid. The objective of the review by Cotta Ramusino, 2024[36] was to determine how outcomes of clinical utility are operationalized in amyloid PET validation studies thus they reported how many studies measured psychological burden and did

not synthesize the findings. They found that most (6 of 8, 75%) amyloid PET validation studies quantified the psychological burden from the result disclosure.

We identified 1 systematic review for KQ6.[43] A review by Cotta Ramusino, 2024[43] categorizing outcomes reported in the literature found that health economics outcomes were included in 16% (5/32) of studies. These studies assessed costs in terms of time and healthcare resources spent to achieve a diagnosis (5/32, 16%), impact on quality of life and prognosis (1/32, 3%). They reported an increased mean life expectancy, quality-adjusted, by 0.008 to 0.150 years compared to patients undergoing the usual diagnostic workup, with cost savings of around $12,500 per patient over lifetime in medical care.[43]

3.3.6 Tau PET

We identified 2 systematic reviews for the CQ on tau PET.[38,45] Chavez-Fumagalli et al.,[45] included 7 studies (n = 1,102) and reported median sensitivity of 94% (95% CI, 76% to 97%) and median specificity of 88% (95% CI, 71% to 95%). Results showed that tau PET had higher performance compared to other diagnostic methods in their meta-analysis, which included EEG and MRI, but the authors noted that expense was a limiting factor for broader use of tau PET. Jin et al.[38] included 27 in their broader review but only 2 studies reported the diagnostic sensitivity and specificity of tau PET in differentiating progressive supranuclear palsy from healthy controls. The pooled sensitivity and specificity was 0.84 and 0.93, respectively.

Only Jin et al.[38] reported any findings related to KQ1 for tau PET. They found that the data on diagnostic performance of tau PET in distinguishing patients with progressive supranuclear palsy from other neurodegenerative diseases were absent, thus they could not perform relevant diagnostic performance meta-analysis.

Two systematic reviews included outcomes relevant to KQ2.[36,44] Cotta Ramusino et al.[36] included only one study on tau PET's ability to predict MCI progression to AD, which they included only in an exploratory analysis of studies with 20 to 50 participants. This study reported that tau PET could distinguish FTLD pathologies and could separate PSP and corticobasal degeneration (i.e., ratio of globus pallidus to red nucleus SUVR: AUC = 1). Ansart et al.,[44] Included studies predicting progression from MCI to AD using machine learning with a sample size of at least 30 subjects. They only identified 1 study of tau PET and were not able evaluate its performance.

We did not identify any studies of tau PET for KQ3 to KQ6.

3.3 Ongoing Studies

Searches of the clinicialtrials.gov trial registry retrieved 810 unique trial registrations. We found 33 to be potentially relevant to an update of the 2014 HTA. Among the 20 completed trials, 10 were retrieved by the PubMed search, 6 had no results posted or published, and 4 were published prior to 2014.

Table 3. Summary of clinical trials by imaging test and status

Imaging Test	Recruiting or enrolling	Active, not recruiting	Completed	Withdrawn or unknown status
Amyloid PET	2	1	14	3
Tau PET	2	0	2	2
FDG-PET	0	0	2	1
fMRI	0	1	1	0
SPECT	0	0	2	1
ASL-MRI	1	0	0	0
Total	**5**	**2**	**20***	**7**

*One trial included 2 imaging tests.

4. Discussion and Conclusions

We identified 33 systematic reviews that provided evidence related to the previous HTA's inclusion criteria and assessed evidence reported in 19 of these reviews. We found the greatest number of systematic reviews included FDG-PET (9 reviews), followed by amyloid PET (7 reviews), SPECT (7 reviews), tau PET (4 reviews), and ASL-MRI (1 review). We did not find any reviews reporting eligible outcomes related to fMRI. The most reported outcome was MCI progression to AD (KQ2), followed by ability to diagnose AD (CQ), and differential diagnosis (KQ1). Evidence for other KQs was sparse.

The most recent reviews of FDG-PET suggested that FDG-PET was highly sensitive for AD diagnosis[46] and had moderate to good accuracy in predicting the progression of MCI to AD.[36]Though studies included in these reviews did not clearly report reference standards and were methodologically heterogenous, findings were mostly consistent and suggested diagnostic accuracy. This may indicate that there is sufficient new evidence to conduct an updated HTA of FDG-PET. CMS has not updated its NCD for FDG-PET since 2004 but CMS does cover FDG-PET for the differential diagnosis of FTD and AD under specific circumstances.

Amyloid PET and tau PET were not included in the scope of the 2014 HTA because they were new technologies at that time. We found that evidence for these tests has accumulated since that time, especially for amyloid PET. Recent systematic reviews indicate that there is evidence that amyloid PET is sensitive and specific for diagnosis of AD and differential diagnosis of AD and FTD. There is also a large body of evidence pointing to changes in both diagnosis and clinical management of patients following amyloid PET. In October of 2023 CMS removed its previous NCD that limited use of amyloid PET and allowed an evidence-based process for coverage determinations. There is sufficient evidence to suggest amyloid PET should be reviewed. We found fewer systematic reviews on tau PET and many of the systematic reviews we identified documented that there were no eligible studies published. However, since tau PET was not included in the 2014 HTA and its use has become more widespread it may be reasonable to include in an updated HTA.

Evidence for SPECT was mixed and some systematic reviews found that it was less accurate than FDG-PET for diagnosing AD and predicting progression from MCI to AD. The accumulation of new evidence may suggest updating the HTA, but we did not find a strong

signal that there is new evidence indicating a change in coverage decision for SPECT. Likewise, evidence was extremely limited for fMRI and ASL-MRI. This may suggest that the field has moved on to focus on other modalities (e.g., FDG-PET and amyloid PET). We excluded some reviews of fMRI that assessed the use of machine learning and AI on the analysis of fMRI images because they did not include eligible comparators or report eligible outcomes.[68-70] This may be an area that warrants further exploration in the future.

4.1 Limitations

This signal search assessment has several limitations. First, we searched only 1 electronic database (PubMed); therefore, we may have missed relevant studies published in journals not indexed in PubMed. Second, we conducted a limited data abstraction and assessment of the evidence reported in the most recent systematic reviews; we did not conduct risk-of-bias assessments of the reviews we identified or of the primary studies included in those reviews. We also did not perform GRADE certainty of evidence assessments. Third, we found that many of the systematic reviews on this topic had broader inclusion and exclusion criteria than the 2014 HTA. Specifically, many permitted clinical diagnosis as an eligible comparator for diagnostic accuracy outcomes whereas the 2014 HTA was restricted to histopathological or genetic confirmation for the CQ and KQ1. Therefore, the conclusions of the systematic review authors were based on a broader evidence base that included less rigorous reference standards. Finally, systematic review authors also noted that the primary studies they included did not clearly define reference standard or diagnostic thresholds of tests. Some reviews may have included a combination of eligible and ineligible studies but did not report findings in way that we could separate the findings for eligible and ineligible studies.

4.2 Conclusion

We identified 33 relevant systematic reviews and abstracted data from 19 of those reviews. Most of these reviews (13 of 19) were published within the last 4 years (since 2020) and included studies published after the 2014 HTA. We found the greatest number of systematic reviews on FDG-PET (n = 9) and amyloid PET (n = 7). While these reviews noted the studies were heterogenous, they also generally found evidence of accuracy or utility for both tests. We also found 3 systematic reviews of tau PET that reflected a smaller evidence base for this test but still an evidence base that is new since the 2014 HTA. We found mixed evidence for SPECT and very limited or no evidence for ASL-MRI and fMRI, respectively. This may suggest an updated evidence review may be needed for FDG-PET, amyloid PET, and tau PET, in part because amyloid PET and tau PET were not within the scope of the previous HTA.

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Appendix A. Inclusion and Exclusion Criteria

Detailed inclusion and exclusion criteria from the 2014 review appear below. Note, we have revised the eligible index tests to include amyloid PET and tau PET, which are new since the prior HTA.

Appendix A Table 1. Summary of inclusion and exclusion criteria

Study Component	Inclusion	Exclusion
Population	Patients with dementia or mild cognitive impairment who have undergone a comprehensive initial diagnostic work-up (to include structural neuroimaging). Diagnoses of interest include primary neurodegenerative dementia, including: Alzheimer's Disease (AD), including atypical AD Lewy body dementia, including dementia with Lewy bodies (DLB) and Parkinson's Disease with dementia (PDD)) Frontotemporal dementia (FTD) disorders, including: behavioral variant FTD (bvFTD); FTD with motor neuron disease (FTD/MND); Pick's Disease; primary progressive aphasia (PPA); progressive supranuclear palsy (PSP) Mild cognitive impairment (MCI)	Asymptomatic or preclinical patients (i.e., without dementia or mild cognitive impairment) Patients who have not undergone a comprehensive initial diagnostic work-up (including structural neuroimaging) Vascular dementia in the absence of suspected AD or FTD Idiopathic Parkinson's Disease (i.e., Parkinson's Disease with movement disorders but not dementia) Huntington's disease FTD disorders without dementia (e.g., corticobasal degeneration) Creutzfeldt-Jakob disease Patients with other identifiable causes of dementia based on structural neuroimaging (e.g., subdural hematoma, tumor, normal-pressure hydrocephalus) Patients with other identifiable causes of dementia prior to neuroimaging (e.g., vitamin B12 deficiency as detected by bloodwork)
Index test	Diagnostic functional neuroimaging modalities of interest: PET (positron emission tomography) to measure glucose metabolism (e.g., 18F-FDG-PET) SPECT (single photon emission computed tomography) to measure cerebral perfusion (e.g., 99mTC-HMPAO-SPECT) and dopamine transporter uptake (e.g., 123I-ioflupane-SPECT/123I-FP-CIT-SPECT/Dat-SCAN/Dat-SPECT) fMRI (functional MRI) Arterial spin labelling (ASL) PET to assess the presence of beta-amyloid protein (e.g., PIB-PET, beta-amyloid-PET, Florbetapir PET) PET to estimate the density and distribution of aggregated tau neurofibrillary tangles (NFTs) (flortaucipir F18).	Functional neuroimaging used but no diagnosis made PET to assess the presence of beta-amyloid protein (e.g., PIB-PET, beta-amyloid-PET, Florbetapir PET) Structural neuroimaging (e.g., computed tomography (CT) including CT with contrast, magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), including voxel-based morphometry (VBM), deformation-based morphometry (DBM), tensor-based morphometry (TBM)) Neuroimaging for screening (i.e., asymptomatic patients) Brain electrical activity mapping (BEAM)/ quantitative electroencephalography (qEEG) Electroencephalography (V-EEG) Magnetoencephalography (MEG) Magnetic resonance spectroscopy (MRS) Near-infrared spectroscopy
Comparator test	KQ1: Gold standard (e.g., histopathological confirmation or genetic confirmation if applicable) KQ2 (i.e., portion of question that compares functional neuroimaging modalities): Direct comparison of functional neuroimaging methods with each other (e.g., FDG-PET vs HMPAO-SPECT)	KQ1: Clinical diagnosis (based on standardized comprehensive exam that may include patient history, cognitive testing, neurological exam, structural neuroimaging, and blood work) KQ2 (i.e., portion of question that compares functional neuroimaging modalities): Indirect comparisons of functional neuroimaging methods

Study Component	Inclusion	Exclusion
	KQ2 (first part), KQ3, KQ5, KQ6: Comprehensive initial diagnostic work-up (to include structural neuroimaging)	
Primary Outcomes	KQ 2, KQ5: Patient progression (e.g., functional and/or cognitive decline, as discussed below) Patient health outcomes, including: Function: (e.g., Alzheimer's Disease Co-operative Study – Activities of Daily Living Inventory (ADCS-ADL), Disability Assessment for Dementia (DAD), Cleveland Scale for Activities of Daily Living (CSALD)) Quality of life: (e.g., Dementia Quality of Life (DEMQOL), Quality of Life in Alzheimer's Disease (QOL-AD), Quality of Life in Late Stage Dementia (QUALID), Assessment of Quality of Life (AQoL)) Behavioral and psychological (e.g., Neuropsychiatric Inventory (NPI), Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD)) KQ 4, KQ 5: Harms (e.g., radiation exposure; magnetic field exposure; pain, redness, swelling at injection site; allergic reaction to tracer) KQ 6: Cost-effectiveness (e.g., cost per improved outcome), cost-utility (e.g., cost per quality adjusted life year (QALY), incremental cost effectiveness ratio (ICER)) outcomes	Technical efficacy (i.e., the ability of a diagnostic test to conform to technical specifications) Impact on diagnosis, therapeutic decisions, and clinical outcomes of patients with diagnosis other than primary neurodegenerative dementia or mild cognitive impairment (e.g., tumor) Contextual questions: First contextual question: inter-method reliability
Intermediate or Secondary Outcomes	KQ 1: diagnostic accuracy measures (e.g., sensitivity, specificity, likelihood ratios, predictive values, receiver operating curve characteristics (ROC)) KQ 2, KQ5: Cognition: (e.g., Modified Mini Mental Exam (3MS), Alzheimer's Disease Assessment Scale - Cognition (ADS-Cog)) Depression: (e.g., Cornell Scale for Depression in Dementia (CSDD), Geriatric Depression Scale (GDS)) Caregiver burden (Zarit Burden Interview (ZBI), Relative Stress Scale (RSS), Perceived Stress Scale (PSS), Kingston Caregiver Stress Scale (KCSS), Center for Epidemiologic Studies Depression Scale (CES-D), Screen for Caregiver Burden (CSB), Caregiver Strain Index (CSI), Burden Scale for Family Caregivers (BSFC), Burns Relationship Satisfaction Scale (BRSS)) Global: (e.g., Global Deterioration Scale (GDS), Clinical Dementia Rating (CDR), Dementia Severity Rating Scale (DSRS)) KQ 3: impact on therapeutic decisions or clinical management (e.g., treatments planned, treatments given) Contextual questions:	

Study Component	Inclusion	Exclusion
	First context question: intra-method reliability: inter-rater reliability and intra-rater (test-retest) reliability measures (kappa, percent agreement) Second contextual question: diagnostic accuracy measures (e.g., sensitivity, specificity, likelihood ratios, predictive values, receiver operating characteristics (ROC))	
Study Design	Focus will be on studies with the least potential for bias. KQ 1-5: Prospective studies will be sought. Retrospective studies will be considered only if there are insufficient prospective studies KQ 1-5: Studies must make a diagnosis/prediction based on functional neuroimaging scans using criteria specified *a priori.* KQ 1-5: High quality systematic reviews will be considered if available KQ 1, contextual question on accuracy: Studies directly comparing functional neuroimaging with the gold standard (e.g., histopathological or genetic confirmation) KQ 2 (first part), KQ 5: Longitudinal studies designed specifically to evaluate progression that provide sufficient information on baseline status and measurements, have sufficient follow-up time to evaluate progression, and clearly articulate changes from baseline KQ 2 (second part): Longitudinal studies directly comparing functional imaging modalities KQ 4-5: Studies that report on adverse events from functional neuroimaging in this patient population KQ5: Studies from KQ2/5 which stratify on patient or other characteristics and formally evaluate statistical interaction (effect modification) KQ 6: Only full, formal economic studies (i.e., cost-effectiveness, cost-utility, cost-minimization, and cost-benefit studies) will be considered.	KQ 1 and second contextual question: Studies comparing functional neuroimaging to clinical diagnosis KQ2, 3, 5: Prediction model generated in the same population it is then tested in. KQ 2, KQ 5: Longitudinal studies with less than 80% follow-up (excluding death) or less than 1 year follow-up KQ 2 (second part): indirect comparisons of functional imaging modalities KQ 6: Incomplete economic evaluations such as costing studies Studies with fewer than 10 patients Case reports Case control studies
Publication	Studies published in English in peer reviewed journals or publicly available FDA reports	Abstracts, editorials, letters Duplicate publications of the same study which do not report on different outcomes Single reports from multicenter trials White papers Narrative reviews Articles identified as preliminary reports when results are published in later versions

Appendix B. Search Strategy

Appendix B Table 1. Preliminary PubMed Search Detailed Results

Search date: April 5, 2024

#	Search Code	Number of Articles
1	"Dementia" OR Dementia[MeSH] OR Alzheimer* OR "Alzheimer Disease"[MeSH] OR "Lewy body dementia" OR (Lewy AND (disease OR dementia)) OR "Lewy Body Disease"[MeSH] OR "Frontotemporal dementia" OR "frontotemporal degeneration" OR (("FTD" OR "FTLD") AND "frontotemporal") OR "Frontotemporal Dementia"[MeSH] OR "Frontotemporal Lobar Degeneration"[MeSH] OR (frontotemporal AND (behavioral OR behavioural)) OR "bvFTD" OR "bvFTLD" OR "Pick's Disease" OR "Picks Disease" OR "Pick Disease" OR "Pick Disease of the Brain"[MeSH] OR "Primary Progressive Aphasia" OR "Aphasia, Primary Progressive"[MeSH] OR "Primary Progressive Nonfluent Aphasia"[MeSH] OR "Progressive supranuclear palsy" OR "Supranuclear Palsy, Progressive"[MeSH] OR Tauopathies[MeSH] OR "Neurofibrillary Tangles"[MeSH] OR "TDP-43 Proteinopathies"[MeSH] OR "mild cognitive impairment"	388,265
#2	"functional neuroimaging" OR "functional imaging" OR "PET" OR "positron emission tomography" OR "Positron-Emission Tomography"[MeSH] OR "SPECT" OR (Single AND Photon AND Emission AND Computed AND Tomography) OR "Tomography, Emission-Computed, Single-Photon"[MeSH] OR "fMRI" OR "functional MRI" OR "functional magnetic resonance imaging" OR "EEG" OR "electroencephalogram" OR "electroencephalograms" OR "electroencephalography" OR electroencephalography[MeSH] OR "MEG" OR "magnetoencephalogram" OR "magnetoencephalograms" OR "magnetoencephalography" OR magnetoencephalography[MeSH] OR "arterial spin labeling" OR "arterial spin labelling" OR "magnetic resonance spectroscopy" OR "magnetic resonance spectroscopy"[MeSH] OR "near infrared spectroscopy" OR "near-infrared spectroscopy" OR "spectroscopy, near infrared"[MeSH] OR (contrast AND (enhanced OR enhanced) AND (magnetic OR MR OR MRI)) OR Beta-amyloid PET OR amyloid PET OR TAU PET OR Tauvid OR flortaucipir F18	830,501
3	(#1 AND #2)	31,096
4	"diagnosis" OR "diagnoses" OR "diagnostic" OR "Diagnosis"[MeSH] OR "Diagnosis, Differential"[MeSH] OR "Diagnostic Imaging"[MeSH] OR "Diagnostic Techniques, Neurological"[MeSH] OR "Decision Support Techniques"[MeSH] OR "Early Diagnosis"[MeSH] OR "Delayed Diagnosis"[MeSH] OR "Decision Trees"[MeSH]	11,818,740
5	#3 AND #4	25,182
6	#5 NOT Case Reports[Publication Type]	22,527
	Published Since 1/1/2014	13,235
	Filter for SRs since 1/1/2014	234

Appendix C. Detailed Study Tables

Appendix C Table 1. Study and population characteristics for studies evaluating functional neuroimaging for dementia

Author Year Funder Included Imaging Tests	Evidence-base Used Included studies Search Date Range	Scope of Review	Outcomes Reported Results *Effect Estimate (95% CI)*	Review Authors' Conclusions
Ansart et al., 2021[44] French Government, European Union Tests reviewed: Amyloid PET FDG-PET Tau PET	29 studies (n = NR) Inception to December 2019	Included studies predicting progression from MCI to AD using machine learning with a sample size of at least 30 subjects. Note: This review also included ineligible tests and cognitive assessments.	KQ2 Progression of MCI to AD dementia Linear mixed-effect model results FDG-PET, 24 experiments (n = NR) Coefficient: 2.6 p-value: 0.023 Corrected p-value: 0.13 Amyloid PET, 5 experiments (n = NR) Coefficient: 1.3 p-value: 0.35 Corrected p-value: 0.78 Tau PET, 1 experiment Not able to evaluate impact on performance Amyloid PET did not have a significant impact on the prediction performance. Although amyloid load saturates several years before symptom onset, several studies show that MCI individuals who are amyloid positive are more likely to convert to dementia in the next 2 to 4 years than those who are amyloid negative.	This systematic and quantitative review on the automatic prediction of the evolution of clinical status of MCI individuals reported results from 234 experiments coming from 111 articles. We showed that studies using cognitive variables or FDG-PET reported significantly better results than studies that did not, and that including other feature types does not significantly improve performance compared to using cognition or FDG-PET alone.

Author Year Funder Included Imaging Tests	Evidence-base Used Included studies Search Date Range	Scope of Review	Outcomes Reported Results *Effect Estimate (95% CI)*	Review Authors' Conclusions
Athanasio et al., 2024[35] Brazilian National Council for Scientific and Technological Development Test reviewed: SPECT vs FDG-PET	35 studies (n = 3,142) Inception to July 2023	Clinical and observational studies published in English, French, Portuguese, or Spanish that investigated the diagnostic accuracy of brain SPECT in distinguishing FTD from AD and other dementias and included more than 10 FTD patients. Note: This review had broader inclusion and exclusion criteria and included a mix of studies with eligible an ineligible comparators and outcomes for our review.	KQ1 SPECT FTD vs AD, 5 studies Sensitivity range: 56% to 88% Specificity range: 51% to 93% FTD vs DLB, 6 studies (n = NR) No eligible outcomes summarized FTD vs PDD (n = NR) No eligible outcomes summarized	Brain perfusion SPECT has a limited value in the diagnostic framework of FTD. SPECT can be performed when FDG-PET is not available. SPECT is recommended only for selected cases when the diagnosis is challenging using conventional methods.
Archer et al., 2015[53] National Institute for Health Research Cochrane review Test reviewed: SPECT	11 studies (n = 1,117)	Included both case-control and cohort (delayed verification of diagnosis) studies. Where studies used a case-control design, included all participants who had a clinical diagnosis of FTD or other dementia subtype using standard clinical diagnostic criteria. For cohort studies, we included studies where all participants with suspected dementia were administered Regional cerebral blood flow SPECT at baseline. We excluded studies of participants from selected populations (e.g., post-stroke) and studies of participants with a secondary cause of cognitive impairment Note: Reference standards of included studies were not well reported, likely included studies that used clinical diagnosis.	KQ1 FTD vs non-FTD SPECT multiple-headed camera, 3 studies Sensitivity range: 0.73 to 1.00 Specificity range: 0.80 to 1.00 FTD vs AD SPECT multiple-headed camera, 3 cohort studies Sensitivity range: 0.73 to 1.00 Specificity range: 0.94 to 1.00	Due to small study numbers and large variation in how the studies were carried out, did not recommend the routine use of SPECT for diagnosing FTD in clinical practice. Most studies were at high risk of bias due to insufficient details on how participants were selected and how the SPECT scans were conducted and analyzed. The main limitations of the review were poor reporting, variability of study design and a lack of standardization of image interpretation between centers.

Author Year Funder Included Imaging Tests	Evidence-base Used Included studies Search Date Range	Scope of Review	Outcomes Reported Results *Effect Estimate (95% CI)*	Review Authors' Conclusions
Chavez-Fumagalli et al., 2021[45] NR Test Reviewed: Tau PET	13 studies (n = 1,012) January 1990 to April 2020	Studies reporting diagnostic accuracy of AD diagnosis in developed and developing countries. Note: Detailed inclusion criteria (e.g., study design or reference standard) were not well described.	CQ AD diagnosis Tau PET, 7 studies (n = 1,012) Sensitivity range: 76% to 97% Sensitivity median (95% CI): 94% (76% to 97%) Specificity range: 71% to 95% Specificity median (95% CI): 88% (71% to 95%) Amyloid PET, 2 studies (n = NR) Not included in the analyses due to limited number of studies	Results showed that Tau PET diagnosis had higher performance as compared to other diagnostic methods in this meta-analysis, which included EEG and MRI. Findings showed an important discrepancy in diagnostic data for AD between developed and developing countries, which can impact global prevalence estimation and management of AD. Also, our analysis found a better performance for the Tau PET diagnostic over other methods to diagnose AD patients, but the expense of Tau PET scan seems to be the limiting factor in the diagnosis of AD in developing countries such as those found in Asia, Africa, and Latin America.

Author Year Funder Included Imaging Tests	Evidence-base Used Included studies Search Date Range	Scope of Review	Outcomes Reported Results *Effect Estimate (95% CI)*	Review Authors' Conclusions
Cotta Ramusino et al., 2024[43] Italian Ministry of Health Test reviewed: Amyloid PET	32 studies Inception to April 2020	Included English language studies that reported outcomes of clinical utility. Papers including only clinical validity (e.g., diagnostic accuracy compared to a reference standard), but not clinical utility (e.g., practical impact on patients) measures, were excluded. There were no geographic or sample size limits. The objective of this review was to review how outcomes of clinical utility are operationalized in current amyloid PET validation studies, to prepare for formal assessment of clinical utility of amyloid PET based diagnosis.	KQ3: Amyloid PET led to diagnostic revision in 19–79% of cases and increased diagnostic confidence (9–49%). Amyloid PET led to revised management plans (24–89% of cases). KQ4: Most (6/8, 75%) quantified the psychological burden from the result disclosure. KQ6: Health economics-centered outcomes are included in 16% (5/32) of the studies and assessed the costs in terms of time and healthcare resources spent to achieve a high-confidence etiological diagnosis (5/32, 16%) and preliminarily impact on quality of life and prognosis (1/32, 3%); increased mean life expectancy, quality-adjusted, by 0.008–0.150 years compared to patients undergoing the usual diagnostic workup, with cost savings of around $12,500 per patient over lifetime in medical care. Note: Comparators and study design was not reported for the primary studies included in this review.	Current studies validating amyloid PET already assessed outcomes for clinical utility, although non-clinician-based outcomes were inconsistent. A wider participation of stakeholders may help produce a more thorough and systematic definition and assessment of outcomes of clinical utility and help collect evidence informing decisions on reimbursement of amyloid PET.

Author Year Funder Included Imaging Tests	Evidence-base Used Included studies Search Date Range	Scope of Review	Outcomes Reported Results *Effect Estimate (95% CI)*	Review Authors' Conclusions
Cotta Ramusino, et al., 2024[36] Review conducted for the European intersocietal task force and European Association of Nuclear Medicine (EANM) Supported by an unrestricted grant from F. Hoffmann-La Roche Ltd., Biogen International GmbH, Eisai Europe Limited, Life Molecular Imaging GmbH, and OM Pharma Suisse SA. Tests reviewed: FDG-PET Amyloid PET SPECT Tau PET	50 studies (n = NR overall) 2017 to 2022	Studies evaluating the accuracy of amyloid PET, tau PET, [18F]FDG-PET, or DaT-SPECT in predicting clinical progression to dementia that included a sample size of at least 50 patients with MCI, follow-up of at least 3 years, progression to dementia during follow-up or diagnosis on pathology as the gold standard, and critical outcome measures, e.g., sensitivity, specificity, accuracy, area under the receiver, or operating characteristic curve (ROC or AUC). If no eligible studies were identified for a given test, included accuracy outcomes from cross-sectional studies in a smaller sample of patients (n > 20, including subjects with mild dementia stage)	KQ2 Progression from MCI vs Reference Standard 18F-FDG-PET, 25 studies (n = 6,803) Mean follow up = 51 months (range: 24 to 120) Sensitivity range: 43% to 100% Specificity range: 63% to 94% Amyloid PET, 8 studies (n = 1,806) Mean follow up = 36 months Sensitivity range: 64% to 94% Specificity range: 48% to 93% DaT-SPECT, 9 studies (n = NR) Sensitivity range: 48% to 100% Specificity range: 71% to 100% TAU PET, 1 study (n = NR) Sensitivity and specificity = NR Study finding: Tau PET could distinguish FTD pathologies and could separate PSP and corticobasal degeneration (i.e., ratio of globus pallidus to red nucleus SUVR: AUC = 1). Note: DAT-SPECT and Tau PET analysis included exploratory analysis that permitted smaller sample study sample sizes.	Functional imaging has a moderate-to-good accuracy in predicting the progression of MCI to AD. [18F]FDG-PET and amyloid PET are the most accurate molecular imaging biomarkers in predicting MCI conversion to dementia, in particular to AD dementia, and in detecting AD co-pathology in DLB.

Author Year Funder Included Imaging Tests	Evidence-base Used Included studies Search Date Range	Scope of Review	Outcomes Reported Results *Effect Estimate (95% CI)*	Review Authors' Conclusions
Couch et al., 2024[40] NR Test Reviewed: Amyloid PET	10 studies (n range = 11 to 3690) Inception to October 2022	Included studies of participants with subjective cognitive decline, MCI or AD and related dementias, and/or their caregivers. Studies of cognitively healthy participants were included if subjective cognitive decline was explicitly stated as an inclusion criterion; (2) all study designs (with or without comparison groups) were included, however, outcomes were limited to those reported after the participant received the results from their own amyloid PET scan; (3) reported quantitative psychosocial and/or behavioral outcomes for patients or caregivers. Psychosocial outcomes were broadly defined as measures capturing mood, emotions, reaction to the scan, quality of life, and caregiver burden. Behavioral outcomes were broadly defined as changes in behavior, knowledge, or decision-making following amyloid disclosure; (4) studies published in English; and (5) studies published in peer reviewed journals.	Participants correctly recalled the scan results; however, it is unclear whether this led to an increased understanding of their diagnosis. We did not identify any studies measuring behavioral outcomes. KQ4: There was little evidence of an association between disclosure and depression. However, persons with MCI and their caregivers with elevated levels of amyloid had an increased risk of distress or anxiety compared with those without elevated amyloid.	We found mixed evidence on the relationship between amyloid scans and psychosocial and behavioral outcomes in people with cognitive impairment and caregivers. These findings highlight the need for more methodologically rigorous research on this topic.

Author Year Funder Included Imaging Tests	Evidence-base Used Included studies Search Date Range	Scope of Review	Outcomes Reported Results *Effect Estimate (95% CI)*	Review Authors' Conclusions
Fink et al., 2020[46] Agency for Healthcare Research and Quality Tests reviewed: Amyloid PET 18F-FDG-PET SPECT	15 studies (n = 1, 362) January 2012 to November 2019	Low or medium risk of bias English-language retrospective or prospective cohort studies with 25 or more participants evaluating the accuracy of brain imaging (amyloid PET, FDG-PET, SPECT) compared to an autopsy reference standard for distinguishing neuropathologically defined AD from non-AD among older adults with dementia.	CQ Amyloid PET, 4 studies (n = 426) AD vs non-AD Median sensitivity: 0.91 (range, 0.79 to 0.98) Median specificity: 0.92 (range, 0.76 to 1.0) 18F-FDG-PET, 2 studies (n=182) AD vs non-AD Median sensitivity: 0.89 (range, 0.84 to 0.94) Median specificity: 0.74 (range, 0.73 to 0.74) 18F-FDG-PET, 1 study (n = 45) AD vs FTD Median sensitivity: 0.97 (range, 0.96 to 0.98) Median specificity: 0.66 (range, 0.59 to 0.73) SPECT, 3 studies (n = 205) AD vs. non-AD Median sensitivity: 0.64 (range, 0.57 to 0.94) Median specificity: 0.83 (range, 0.76 to 0.92)	In methodologically heterogeneous studies of uncertain applicability to typical clinical settings, amyloid PET and 18F-FDG-PET were highly sensitive for neuropathologic AD. Amyloid PET, ^{18}F-FDG-PET, and CSF test combinations may add accuracy to clinical evaluation.

Author Year Funder Included Imaging Tests	Evidence-base Used Included studies Search Date Range	Scope of Review	Outcomes Reported Results *Effect Estimate (95% CI)*	Review Authors' Conclusions
Jin et al., 2023[38] Beijing Municipal Natural Science Foundation and Natural Science Foundation of China Test reviewed: Tau PET	2 studies (n = 126) Inception to April 2022	Included case–control studies or longitudinal studies of patients with a possible, probable, or definite diagnosis of PSP with Tau PET imaging; sufficient information of Tau tracer uptake for calculating effect sizes; studies performed regional analysis; studies written in English and published in peer-reviewed journal.	CQ Among the 27 studies included in the broader review, only 2 studies reported the diagnostic sensitivity and specificity of Tau PET in differentiating PSP from healthy controls. Pooled sensitivity: 0.84 Pooled specificity: 0.93 KQ1 The data on diagnostic performance of Tau PET in distinguishing patients with PSP from other neurodegenerative diseases were absent, so authors could not perform relevant diagnostic performance meta-analysis.	Due to the small number of articles and sample size, the 95% CIs were very wide, and the results of meta-analysis may not be convincing. More studies are needed to investigate the diagnostic performance of Tau PET imaging in differentiating PSP from HCs and other neurodegenerative diseases.
Haidar et al., 2023[39] Reported as "Not applicable" Tests reviewed: FDG-PET ASL-MRI	1 study (n = 9) Inception to May 2022	Included studies that involved dementia patients of any disease that were examined using both ASL-MRI and FDG-PET during the same interval of time. Included case-control studies and prospective or retrospective cohorts. Note: 12 of the 14 studies included in the review were case-control studies, 1 was a prospective cohort that did not report eligible outcomes, thus only 1 study included in this review would meet the HTA's review criteria.	CQ 1 retrospective cohort (n = 9 dementia patients)[71] Inter and intramodality agreements were insignificantly different between ASL-MRI and FDG-PET for AD vs non-AD Diagnostic accuracy: ASL-MRI: 55% (5 of 9) FDG-PET: 78 % (7 of 9)	Comparing the diagnostic value of FDG-PET and ASL-MRI, the results of this systematic review and meta-analysis indicate that FDG-PET still has an advantage over ASL-MRI, largely based on case-control studies. Such implication could be related to the technical differences relating to both modalities, with ASL-MRI having lower temporal resolution. It's worth mentioning that specificity was rather quite similar among both modalities and some studies found an overridden metabolic and perfused images.

Author Year Funder Included Imaging Tests	Evidence-base Used Included studies Search Date Range	Scope of Review	Outcomes Reported Results *Effect Estimate (95% CI)*	Review Authors' Conclusions
McCleery et al., 2015[51] Cochrane Review Test Reviewed: DAT-SPECT	1 study (n = 22) Inception to February 2013	Included test accuracy studies with delayed verification, diagnostic case-control studies, and two-gate studies with alternative diagnosis controls. Participants: (A) participants with dementia in secondary care, (B) participants in secondary care meeting consensus clinical criteria (other than the DAT imaging criterion) for possible or probable DLB, or both. Index test: SPECT or PET imaging of brain dopamine transporters. Reference standard: Neuropathological diagnosis at autopsy.	KQ1 Searched for and did not identify any studies with a neuropathological reference standard. Included 1 high risk of bias study that reported data on 22 participants who met consensus clinical criteria for DLB or NINCDS-ADRDA criteria for AD, or both (a two-gate design with alternative diagnosis controls). Diagnosis of DLB, 1 study (n = 22) SPECT analyzed semi quantitatively Sensitivity (95% CI): 1.00 (0.66 to 1.00) Specificity (95% CI): 0.92 (0.64 to 1.00) SPECT analyzed visually, 1 study (n = 19) Sensitivity (95% CI): 0.86 (0.42 to 1.00) Specificity (95% CI): 0.83 (0.52 to 0.98)	Only one study has used a neuropathological reference standard to assess the accuracy of DAT imaging for the diagnosis of DLB. The small size of the included study means that sensitivity and specificity estimates are imprecise. However, data from this study suggest that DAT imaging is more accurate than clinical diagnosis. Clinical diagnosis is therefore unsuitable to use as a reference standard for assessing the accuracy of DAT imaging. No studies using a neuropathological reference standard have directly addressed the common clinical scenario where the use of DAT imaging is considered as a diagnostic test in a person with possible DLB or assessed the accuracy of DAT imaging in people with mild dementia. However, the data from the included study suggest that, where there is moderately severe dementia and a strong pre-existing suspicion of DLB (probable DLB), then a normal (123)I-FP-CIT SPECT scan may be an accurate means of excluding the diagnosis.

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Nihashi et al., 2020[47] The Ministry of Education, Culture, Sports, Science, and Technology, Japan Test Reviewed: DAT-SPECT	2 studies (n = 73) Inception to March 2018	Included prospective or retrospective studies that evaluated the use of DAT-SPECT or MIBG scintigraphy in ≥ 10 adult patients (≥ 18 years of age) with dementia and used clinical and/or pathological diagnosis as the reference standard. When we encountered the same group of investigators in multiple studies that included overlapping patient cohorts, we included only the study with the largest sample size.	Among 27 studies included in the review, 2 included DAT-SPECT with postmortem neuropathological verification Thomas, 2017 n = 55 Adjusted Sensitivity (95% CI): 0.83 (0.70 to 0.92) Adjusted Specificity (95% CI): 0.84 (0.73 to 0.96) Jung, 2018 n = 18 Adjusted Sensitivity (95% CI): 0.87 (0.74 to 0.97) Adjusted Specificity (95% CI): 0.81 (0.63 to 0.95)	CQ In an adjusted analysis, DAT-SPECT had high diagnostic accuracy for detecting the hallmark pathology in the brain of Lewy bodies and for diagnosing the typical clinical syndrome. For diagnosing typical clinical DLB syndrome, evidence suggests that the reported high sensitivity and specificity of DAT-SPECT is plausible.

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Rice et al., 2017[50] Funding NR Tests Reviewed: Amyloid PET FDG-PET Note: We focused on FDG-PET in this abstraction since amyloid PET findings in this review focused on PIB, which has been replaced by a future generation of amyloid tracers.	Amyloid PET, 29 studies FDG-PET, 23 studies Both, 8 studies 2001 to 2016	Included studies that examined the current diagnostic use of amyloid and FDG-PET published in peer-reviewed scientific journals. Excluded articles that focused on drug trials and those that focused solely on other forms of dementia.	FDG-PET Qualitative Synthesis KQ2 Using FDG-PET in combination with other proven biomarkers of AD to predicted prognosis in MCI. FDG-PET alone had high sensitivity (92%) and specificity (89%) in predicting clinical outcome for those patients with MCI. KQ3 One study reported that at 18-month follow-up, the result of FDG-PET had led to a change in diagnosis in almost a third of the 94 patients. KQ6 FDG-PET has been reported by an American group to provide few benefits at a significant cost when introduced to the standard diagnostic regimes at AD centers. However, the decision-analytic model used by this study looked only at those patients who had moderate to severe AD at presentation. A more recent study modelled the use of FDG-PET in relation to the validation scheme used for oncological biomarkers. They argued that thorough cost/benefit quantification is hindered by the lack of research into its estimated impact on morbidity and disability.	Both amyloid PET and FDG-PET have been shown to detect AD with high sensitivity and specificity compared to other neurodegenerative processes and cognitively normal age-matched individuals. However, future studies with standardized, uniform thresholds and a lengthier longitudinal follow-up need to be conducted to allow us to make surer conclusions about the future role of PET in clinical practice. In addition, comparison with post-mortem diagnosis, rather than clinical diagnosis with its acknowledged flaws, would result in more powerful statistical outcomes – which is becoming increasingly important given that several disease-modifying AD drugs are now in phase 3 trials.

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Ruan et al., 2023[37] Key Medical and Health Projects in Xiamen, Grant Test reviewed: Amyloid PET	6 studies (n =1,362) Inception to January 2022	Included prospective and retrospective studies of amyloid PET for diagnosing AD or MCI progression to AD compared to an autopsy referencing standard. Note: This review included clinical diagnosis as an eligible comparator but only studies with an autopsy comparison are reported here.	CQ: AD vs non-AD, 4 studies (n = 1,082) Sensitivity range: 0.84 to 0.95 Specificity range: 0.82 to 0.92 AD vs Normal Controls, 1 study (n = 179) Sensitivity: 0.84 (95% CI, 0.78 to 0.90) Specificity: 0.86 (95% CI, 0.78 to 0.93) KQ1: AD vs FTD, 1 study (n = 101) Sensitivity: 0.93 (95% CI, 0.86 to 0.98) Specificity: 0.84 (95% CI, 0.75 to 0.92)	The overall performance of amyloid PET in diagnosing AD is favorable. A multimodal diagnostic approach and machine learning analysis may be effective in improving diagnostic accuracy.

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Shea et al., 2018[48] National Institute of Aging and Florida Alzheimer's Disease Research Center Test reviewed: Amyloid PET	13 studies (n = 1,489) January 2004 to February 2018	Included original research papers with a prospective or retrospective design or case series; involved patients seen in a specialty memory clinic setting; provided sufficient information to allow the calculation of crude percentage change in either diagnosis, management, or diagnostic confidence as study measures for the impact of amyloid PET; and published in English.	KQ3: Change in diagnoses after amyloid PET Range: 9% to 68.8% Pooled percentage change (95% CI): 35.2% (24.6% to 47.5%) Change from AD to non-AD, 13 studies (n = 872) Pooled percentage of diagnosis (95% CI): 22.7% (17.1% to 29.5%) Change from non-AD to AD diagnosis, 10 studies (n = 349) Pooled percentage of diagnosis (95% CI): 25.6% (17.6% to 35.8%) Change in clinical management, 8 studies (n = 611) Range: 25.4% to 81.3% Pooled percentage change (95% CI): 59.6% (39.4 to 77.0%) Numbers of diagnostic investigations per patient 1 study reported a net decrease in the following procedures Structural imaging: 24.4% Neuropsychological testing: 32.8% Lumbar puncture: 94.7% FDG-PET: 91.3%	Amyloid PET has a highly significant impact on both changes in diagnosis and management among patients being seen at a specialty memory clinic. The overall impacts of amyloid PET from the reported literature are a change of diagnosis and management in 35.2% and 59.6%, respectively.

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Smailagic et al., 2018[49] Update to 2015 Cochrane review National Institute for Health Research (NIHR) Test reviewed: FDG-PET	24 studies (n = 1,132) January 2013 to July 2017	Prospective longitudinal, nested case-control cohort studies and retrospective cohorts that contained sufficient data to construct two-by-two tables expressing FDG-PET results by disease status with a minimum of 1-year follow up published.	KQ2 MCI conversion to AD 18F-FDG-PET, 24 studies (n =1132) Sensitivity range: 25% to 100% Specificity range: 15% to 100% Number of studies with both sensitivity and specificity approximately 80% or higher: 14	Systematic and comprehensive assessment of studies of FDG-PET for prediction of conversion from MCI to AD dementia revealed that many studies have methodological limitations according to Cochrane diagnostic test accuracy gold standards, and shows accuracy remains highly variable, including in the most recent studies.
Smailagic et al., 2015[52] Cochrane Review National Institute for Health Research (NIHR) Test reviewed: FDG-PET	14 studies (n = 421) Inception to January 2013	Included studies that evaluated the diagnostic accuracy of FDG-PET to determine the conversion from MCI to AD or to other forms of dementia, i.e. any or all of vascular dementia, dementia with Lewy bodies, and FTD. These studies necessarily employ delayed verification of conversion to dementia and are sometimes labelled as delayed verification cross-sectional studies.	MCI to AD dementia, 14 studies (n = 421) Sensitivity range: 25% and 100% Median Sensitivity (95% CI): 76% (53.8 to 89.7) at the included study median specificity of 82% Specificity range: 15% and 100% Positive likelihood ratio (95% CI): 4.03 (2.97 to 5.47) Negative likelihood ratio (95% CI): 0.34 (0.15 to 0.75) Findings are based on studies with poor reporting, and the majority of included studies had an unclear risk of bias, mainly for the reference standard and participant selection domains. According to the assessment of Index test domain, more than 50% of studies were of poor methodological quality.	Given the considerable variability and specificity values, the heterogeneity in the conduct and interpretation of the test, and lack of defined thresholds for determination of test positivity in the included studies, the current evidence does not support the routine use of KLF-FDG-PET scan in clinical practice. KLF-FDG-PET scan is a high-cost investigation, and it is therefore important to clearly demonstrate its accuracy and to standardize the process of KLF-FDG-PET diagnostic modality prior to its being widely used. Future studies with more uniform approaches to thresholds, analysis and study conduct may provide a more homogeneous estimate than the one that has been available from the included studies we have identified.

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Zhu et al., 2022[42] Funding reported as "None". Test reviewed: FDG-PET SPECT	9 studies (n = NR) Inception to December 2020	Included diagnostic accuracy test studies of patients diagnosed with MCI without pathological type limitation; prognostic assessment was conducted through cerebral perfusion imaging, including FDG-PET and SPECT.	KQ2 Meta-analysis results, MCI to AD FDG-PET, 5 studies, n = NR Follow-up range: 12 to 36.5 months Sensitivity (95% CI): 87.2 (81.3 to 92.1) Specificity (95% CI): 89.4 (77.6 to 91.8) Positive likelihood ratio (95% CI): 5.973 (3.15 to 6.72) Negative likelihood ratio (95% CI): 0.132 (0.05 to 0.49) SPECT, 4 studies, n = NR Follow-up range: 12 to 36 months Sensitivity (95% CI): 80.5 (78.3 to 90.1) Specificity (95% CI): 74.3 (61.3 to 78.5) Positive likelihood ratio (95% CI): 2.637(1.38 to 4.81) Negative likelihood ratio (95% CI): 0.334 (0.18 to 0.50) The sensitivity, specificity, and positive likelihood ratio of FDG-PET imaging was significantly higher than that of SPECT and the difference was statistically significant (P<0.05).	This meta-analysis investigated the application value of cerebral perfusion imaging in the prognostic assessment of MCI. The results showed that cerebral perfusion imaging had good prognostic value in patients with MCI, and FDG-PET imaging had superior prognostic ability in patients with MCI.

Abbreviations: AD = Alzheimer's disease; ASL-MRI = Arterial Spin Labeling Magnetic Resonance Imaging; CQ = Contextual question; DaT = Dopamine transporter; DLB = Dementia with Lewy Bodies; EEG = Electroencephalography; FDG-PET = F-fluorodeoxyglucose Positron Emission Tomography; fMRI = Functional Magnetic Resonance Imaging; FTD = Frontotemporal dementia; HC = Healthy control; KQ = Key question; MCI = Mild cognitive impairment; MIBG = meta iodobenzylguanidin; MRI = Magnetic Resonance Imaging; NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NR = Not reported; PDD = Parkinson's Disease with dementia; PET = Positron Emission Tomography; PIB = Pittsburgh Compound-B; PSP = Progressive supranuclear palsy; SPECT = Single Photon Emission Computed Tomography.