

Functional Neuroimaging for Primary Degenerative Dementia or Mild Cognitive Impairment

Final Evidence Report

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Functional Neuroimaging for Primary Degenerative Dementia or Mild Cognitive Impairment

Provided by:



Prepared by:

Robin Hashimoto, PhD
Kathryn Mihalovich, BS
Haley Holmer, MPH
Andrea Skelly, MPH, PhD

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With assistance from:

Krystle Pagarigan, BS
Katie Moran, BS
Ned Sherry, BS
Erin Anthony-Fick
Joseph R. Dettori, PhD, MPH

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

The information in this assessment is intended to assist health care decision makers, clinicians, patients and policy makers in making sound evidence-based decisions that may improve the quality and cost-effectiveness of health care services. Information in this report is not a substitute for sound clinical judgment. Those making decisions regarding the provision of health care services should consider this report in a manner similar to any other medical reference, integrating the information with all other pertinent information to make decisions within the context of individual patient circumstances and resource availability.

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Abbreviations

- ¹¹C-DTBZ-PET:** Dihydratotetabenazine Positron Emission Tomography
- ¹²³I-FP-CIT-SPECT:** 2β-carbomethoxy-3β-(4-iodophenyl)-B: (3-fluoropropyl) nortropane
- ¹⁸F-FDG-PET:** Fluorodeoxyglucose positron emission tomography
- 3MS:** Modified Mini Mental Exam
- ⁹⁹Tc-HMPAO-SPECT:** 99-Technitium hexamethylpropylene amine oxime single photon emission computed tomography
- AAN:** American Academy of Neurology
- ACR:** American College of Radiology
- AD:** Alzheimer's Disease
- ADCS-ADL:** Alzheimer's Disease Co-operative Study – Activities of Daily Living Inventory
- ADNI:** Alzheimer's Disease Neuroimaging Initiative
- ADS-Cog:** Alzheimer's Disease Assessment Scale: Cognition
- AHRQ:** Agency for Health Research and Quality
- aMCI:** amnesic MCI
- APOE ε4:** Apolipoprotein E
- AQoL:** Assessment of Quality of Life
- ASL:** Arterial Spin Labeling
- BEHAVE-AD:** Behavioral Pathology in Alzheimer's Disease
- BRSS:** Burns Relationship Satisfaction Scale
- BSFC:** Burden Scale for Family Caregivers
- bvFTD:** Behavioral variant frontotemporal dementia
- CAMCOG:** Cambridge Cognitive Examination
- CASL:** Continuous arterial spin labeling
- CBD:** Corticobasal degeneration
- CCCDTD:** Canadian Consensus Conference on Diagnosis and Treatment of Dementia
- CDR:** Clinical Dementia Rating
- CES-D:** Center for Epidemiologic Studies Depression Scale
- CMS:** Centers for Medicare and Medicaid Services
- CoE:** Class of Evidence
- CSALD:** Cleveland Scale for Activities of Daily Living
- CSB:** Screen for Caregiver Burden
- CSDD:** Cornell Scale for Depression in Dementia
- CSI:** Caregiver Strain Index
- CT:** Computed Tomography
- DAD:** Disability Assessment for Dementia
- DEMQOL:** Dementia Quality of Life
- DLB:** Dementia with Lewy Bodies
- DPERG:** Diagnostic Pathway Expert Reference Group
- DSM-V:** Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
- DSRS:** Dementia Severity Rating Scale

Abbreviations, continued

EEG: Electroencephalogram

EFNS: European Federation of the Neurological Societies

F/U: Follow-up

FDA: Food and Drug Administration

fMRI: Functional magnetic resonance imaging

FN: False Negative

FP: False Positive

FTD: Frontotemporal dementia

FTD/MND: FTD with motor neuron disease

GDS: Geriatric Depression Scale

GRADE: Grades of Recommendation Assessment, Development and Evaluation Working Group

HUI: Health Utilities Index

ICER: Incremental cost effectiveness ratio

KCSS: Kingston Caregiver Stress Scale

KQ: Key Question

LR- : Negative Likelihood Ratio

LR+ : Positive Likelihood Ratio

MCI: Mild cognitive impairment

MEDLINE: Medical Literature Analysis and Retrieval System Online

MMSE: Mini Mental State Exam

MRI: Magnetic Resonance Imaging

NC: Normal Control

NCD: National Coverage Determination

Neuroimaging Draft Evidence Report: Abbreviations List

NGC: National Guideline Clearinghouse

NHS-England: National Health Service-England

NIA: National Institute on Aging

NICE-SCIE: National Institute for Health and Clinical Excellence, Social Care Institute for Excellence

NINCDS-ADRDA: National Institute of Neurological Disorders and Stroke – Alzheimer 's Disease and Related Disorders

NMDA: N-methyl D-aspartate

NPH: Normal pressure hydrocephalus

NPI: Neuropsychiatric Inventory

NR: Not Reported

OR: Odds Ratio

Oregon HERC: Oregon Health Evidence Review Commission

PASL: Pulsed arterial spin labeling

PD: Parkinson's Disease

PDD: Parkinson's Disease with Dementia

PET: Positron Emission Tomography

Abbreviations, continued

PIB-PET: Pittsburgh compound B- positron emission tomography

PMC: posteromedial cortex

PPA: Primary Progressive Aphasia

PSEN1: Presenilin-1

PSP: Progressive Supranuclear Palsy

PSS: Perceived Stress Scale

QALY: Quality adjusted life year

QHES: Quality of Health Economic Studies

TP: True Positive

QOL-AD: Quality of Life in Alzheimer's Disease

QUALID: Quality of Life in Late Stage Dementia

rCBF: regional cerebral blood flow

RCTs: Randomized Control Trials

RF: Radiofrequency

ROC: Receiver Operating Characteristics

ROIs: Regions of interest

RSS: Relative Stress Scale

SD: Semantic dementia

SD: Standard Deviation

SIGN: Scottish Intercollegiate Guidelines Network

SNCA: α -synuclein

SNM: Society of Nuclear Medicine

SoE: Strength of Evidence

SPECT: Single Photon Emission Computed Tomography

SR: Systematic Review

SRI: Spectrum Research, Inc.

SSP: Stereotactic surface projection

SSRIs: Selective serotonin reuptake inhibitors

SUVR: standardized uptake value ratio

TN: True Negative

VaD: Vascular Dementia

ZBI: Zarit Burden Interview

Executive Summary

Introduction

Condition/disease

Dementia is a condition in which mental capabilities have declined to the point that that it interferes with the ability to function on a daily basis. Dementia severity can range from mild to severe, and symptoms may include impaired reasoning, inability to handle complex tasks, lack of judgment, decreased visuospatial abilities, impaired language capacities, and behavioral and personality changes.⁹⁷ Although dementia may occur in individuals at any age, it typically affects the elderly; the aging of the global population is a key factor in the increasing number of people with this condition.¹⁴⁵ Of all diseases associated with age, dementia is the fastest growing with an estimated 24.3 million people worldwide having been diagnosed with the condition, with 4.6 million new cases diagnosed each year.⁵⁰ It is estimated that by 2050 the prevalence will have quadrupled, so that one in 85 individuals will be living with dementia.²⁴

AD is the most common type of dementia, accounting for 60-80% of cases.⁴ The estimated prevalence of AD is up to 40% in those over age 80.⁴⁷ It is one of the most devastating and costly disorders affecting the aging population with a financial cost to society that has been estimated to be between \$70 and \$100 billion annually.¹⁶³ AD develops gradually, with cognitive deficits worsening with time. The more common presentation of cognitive decline is amnesic in nature, with patients demonstrating impaired learning and short-term memory. Some patients have nonamnesic presentation and exhibit difficulties finding words, impaired visuospatial abilities, and impaired judgment and reasoning.⁹⁷ The brain pathology of AD patients is characterized by neuronal loss and by abnormal aggregations of proteins, which upon autopsy appear as deposits of the beta-amyloid protein (plaques) and twisted strands of the tau protein (neurofibrillary tangles).^{75,173}

DLB is considered to be the second most common type of neurodegenerative dementia following AD, accounting for approximately 4-30% of dementia cases.^{181,194} Core features of DLB include progressive cognitive decline and memory impairment; in addition, a decline in attention, executive function, and visuospatial abilities may be particularly evident. Patients may also exhibit disorders in REM sleep, frequent falls, and hallucinations.⁹⁵ DLB shares pathological and clinical features with other dementia subtypes such as AD, vascular dementia and Parkinson's disease (PD), which can make it difficult to distinguish in clinical practice. In addition to difficulties thinking and reasoning, patients with DLB often have movement difficulties (such as difficulty initiating movement, a shuffling gait, hunched posture, and muscle rigidity) similar to patients with PD. DLB is characterized pathologically by the presence of Lewy bodies, which are aggregates of α -synuclein and other proteins (e.g. ubiquitin, neurofilament protein, α B crystallin) in neurons of the cerebral cortex.^{15,129}

Frontotemporal dementia (FTD) is a group of disorders that affect areas of the brain associated with personality, language, and behavior. The prevalence of FTD has been estimated to be between 15-22 cases per 100,000 person-years and the estimated incidence is approximately 2.7-4.1 new cases per 100,000.^{83,130} Core features include behavioral disorder, affective symptoms, speech disorder, preserved spatial orientation, and specific physical signs (e.g. incontinence and low blood pressure).¹ FTD usually has an earlier onset than other types of dementia, often developing in the 50s and 60s,¹²⁰ and approximately 60% of all FTD cases occur in individuals aged 45-64 years.⁸³

MCI is not considered a type of dementia because it does not interfere with a person's functional independence. Instead, it is a term that has been used to describe a condition that may or may not eventually lead to dementia, and as a result the diagnosis of MCI is a difficult and controversial one.¹⁵⁶ It is estimated that 10-20% of people over the age of 65 have MCI,^{4,137} and although a clinical diagnosis of MCI is not a necessary as a precursor to dementia, it is a major risk factor for later progression, with an estimated 12% of MCI patients developing AD each year.¹³⁸ Various systematic reviews reported differences in annual conversion rates (ACRs) for MCI or aMCI patients progressing to AD or dementia ranging from 10.2% to 33.6% in studies with over one year of follow-up,¹⁸⁵ and 7% in studies of over three years of follow-up,¹⁰⁶ and 4.2% in studies with follow-up of five years or longer¹⁰⁵ indicating the risk for conversion lessens over time. There is no available diagnostic test for mild cognitive impairment (MCI); instead, evaluation of patient history and cognitive abilities may help clinicians come to a diagnostic consensus. MCI is considered to be the beginning stage of AD but often times other factors may be the cause of MCI. For this reason, it is important to determine what the cause of MCI is as it may be produced by issues that are not Alzheimer's related such as trauma or drug abuse. Further evaluation of cognition may show decline or problem areas within the individual that also help to diagnose MCI due to AD.

Diagnosis

Having an early and accurate diagnosis of the type of dementia from which an individual is suffering is important not only for management of the patient's symptoms, but also to allow provision of appropriate information to families and caregivers so that they know what to expect with regard to the course of the disease. Because different types of dementia often share common clinical, neuropsychological, and pathological characteristics, differentiating between the types of dementia can be challenging in clinical practice.¹⁶⁵ Patients presenting with symptoms of dementia ideally undergo an initial evaluation in the primary care setting, which consists of a thorough history, detailed cognitive testing and neurological examination. Most clinical practice guidelines recommend that patients meeting the clinical criteria for dementia undergo at least one structural neuroimaging exam (computed tomography (CT) scan or magnetic resonance imaging (MRI) scan) and laboratory testing to rule out any reversible causes of dementia, such as a vitamin deficiency or tumor. 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. Most often a diagnosis can be suggested following this initial workup; however, if following the initial clinical assessment the diagnosis remains unclear, patients may be referred for additional testing with functional neuroimaging.

To obtain a definite diagnosis of a specific type of dementia, histopathologic confirmation is required, however, this "gold standard" diagnosis is only available post-mortem and is therefore not helpful in the clinical situation. Studies have shown that the diagnostic accuracy of a diagnosis made from a standard clinical work-up compared to that based on the gold standard of autopsy is highly variable:

- **AD:** 78-97% sensitivity,^{59,77,81,123,160,166} 20-100% specificity^{81,123,166}
- **DLB:** 12-100% sensitivity,^{49,56,59,69,102,123,128,166,183,187} 79-100% specificity^{49,56,102,123,128,166,183,187}
- **FTD:** 62-100% sensitivity, 82-97% specificity (with higher values in more recent studies)^{54,64,166}

Technology: Functional Neuroimaging

Despite the development of consensus diagnostic criteria, many cases of dementia are missed.¹⁶⁵ When this happens, the use of other diagnostic strategies such as functional neuroimaging may be helpful in confirming a diagnosis of dementia. Functional neuroimaging is viewed as an add-on diagnostic test that is done if results from the clinical workup and structural neuroimaging exam are inconclusive. In

contrast to structural neuroimaging, which provides information on structural changes in the brain that may cause dementia symptoms, functional neuroimaging can provide information on how the brain is functioning. Functional neuroimaging can 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. Functional neuroimaging modalities of interest include single-photon emission computed tomography (SPECT), positron emission tomography (PET), and functional MRI (fMRI) which are briefly reviewed below.

Positron Emission Tomography (PET)

The detection of regional glucose metabolism with the ^{18}F -FDG radiopharmaceutical is considered by some to be the most widely available and useful biomarker for dementia diagnosis.⁷² PET is a diagnostic imaging test that uses a positron emitting radionuclide and a scanner to produce images of the brain or other part of the body being studied. In PET for dementia diagnosis, the radioactive particle most commonly used is [^{18}F] Fluorodeoxyglucose (^{18}F -FDG), which consists of fluorine-18, a positron-emitting radioactive isotope, incorporated into molecule glucose molecule. When this radioactive tracer is injected into the patient's bloodstream, it competes with glucose for absorption and metabolism in a variety of cell types, including neurons.⁶⁶ Subsequent scanning that demonstrates hypometabolism in specific regions can be indicative of specific types of neurodegenerative dementia, and can aid in the differentiation between AD and FTD.⁵¹

Single Photon Emission Computed Tomography (SPECT)

SPECT is another type of neuroimaging that is used to investigate changes in the function and molecular composition in the brains of patients with suspected neurodegenerative dementia. SPECT employs a radioactive tracer that remains in the bloodstream, allowing the visualization of blood flow to tissues and organs. In the case of dementia, SPECT is used to evaluate regional brain perfusion, and because cerebral blood flow correlates with brain metabolism, the images provide information regarding which regions of the brain are affected, which in turn aids with differential diagnosis. SPECT has a lower spatial resolution than FDG-PET; as with PET neuroimaging, patients with milder symptoms of dementia are less likely to have abnormal results.⁹⁰ Like FDG-PET, HMPAO-SPECT can help distinguish AD from FTD.⁵¹

SPECT may also be used to measure dopaminergic nigrostriatal denervation, which occurs in patients with DLB, using the radiolabeled dopamine transporter ligand ^{123}I -FP-CIT which is injected intravenously. ^{123}I -FP-CIT-SPECT is also known as DaTscan and Dat-SPECT and has been available in Europe since 2000 where it is indicated to help differentiate probable dementia with Lewy bodies (DLB) from Alzheimer's disease. Briefly, the ligand ^{123}I -FP-CIT is an analogue of the ligand for the dopaminergic presynaptic transporter (DAT). Because DAT loss is a consequence of the nigrostriatal degeneration that occurs with DLB (but not AD), ^{123}I -FP-CIT-SPECT can be used to distinguish DLB from AD.

Functional Magnetic Resonance Imaging (fMRI)

fMRI measures the changes in concentration of deoxyhemoglobin within active areas of the brain.³¹ As a neuron becomes active, blood flow and oxyhemoglobin supply increases in this stimulated area. When the supply of oxygen surpasses the active neurons' needs, the venous concentration of deoxyhemoglobin decreases and is detected by the fMRI.^{31,37,153} Individuals with AD usually experience damage to the medial temporal lobe, which may be imaged. Additionally, reduced functional activity of the default mode network (bilateral parietal cortex, precuneus and posterior cingulate cortex, anterior cingulate cortex, medial prefrontal cortex, hippocampus, and thalamus) has been shown to aid in distinguishing healthy individuals from those with AD^{8,19,62} or MCI.⁷⁶ The default mode network¹⁴² and the

posteromedial cortex¹⁴¹ have both been found to help predict progression of MCI to AD. However, fMRI is unable to distinguish if reduced functional activity is due to AD or another issue within the individual.

Policy context

There are significant questions related to the use of functional neuroimaging for the diagnosis of primary neurodegenerative dementia and mild cognitive impairment, specifically, there are medium concerns regarding safety, efficacy, and cost. The objective of this Health Technology Assessment was to systematically review, critically appraise, analyze and synthesize research evidence evaluating the ability of neuroimaging to differentially diagnose, predict progression and outcomes, and influence therapeutic decisions and clinical management for patients with primary neurodegenerative dementia or mild cognitive impairment. The differential effectiveness and safety of diagnostic neuroimaging for subpopulations was evaluated, as was the cost effectiveness of diagnostic neuroimaging. To that end, the Key Questions below were posed.

Key Questions

Contextual Questions:

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 DLB and 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).

Research Key Questions:

In patients with mild cognitive impairment or clinically diagnosed dementia who have completed a comprehensive initial diagnostic work-up (that included structural neuroimaging):

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)?
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?
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?
4. What are the short and long term harms of diagnostic functional neuroimaging?
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.

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

Inclusion and exclusion criteria are summarized as follows:

Population:

Patients with dementia or mild cognitive impairment who have undergone a comprehensive initial diagnostic work-up including 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); corticobasal degeneration (CBD); FTD with motor neuron disease (FTD/MND); Pick's Disease; primary progressive aphasia (PPA); progressive supranuclear palsy (PSP)
- Mild cognitive impairment (MCI)

Index test:

Diagnostic functional neuroimaging. Imaging modalities of interest include:

- PET (positron emission tomography) to measure glucose metabolism (e.g., ^{18}F -FDG-PET)
- SPECT (single photon emission computed tomography) to measure cerebral perfusion (e.g., $^{99\text{m}}\text{Tc}$ -HMPAO-SPECT) and dopamine transporter uptake (e.g., ^{123}I -FP-CIT-SPECT, ^{123}I -ioflupane-SPECT, Dat-SCAN)
- fMRI (functional MRI)

Comparator test(s):

- Gold standard (histopathological confirmation or genetic confirmation if applicable) (KQ1)
- Direct comparison of functional neuroimaging modalities with one another (e.g., FDG-PET vs HMPAO-SPECT) (KQ2)
- Comprehensive initial diagnostic work-up (to include structural neuroimaging (KQ2, KQ3, KQ5, KQ6))

Outcomes:

- Primary outcomes of interest: Patient progression; patient health outcomes including function, quality of life, behavioral and psychological outcomes; harms from neuroimaging procedure; cost-effectiveness
- Intermediate or secondary outcomes: Diagnostic accuracy measures; patient health outcomes including cognition, depression, caregiver burden, and global outcome measures; impact on therapeutic decisions or clinical management

Methods

The scope of this report and final key questions were refined based on input from clinical experts from a variety of disciplines and public comments received on draft key questions. Clinical expert input was sought to confirm primary outcomes on which to focus.

A formal, structured systematic search of the peer-reviewed literature across a number of databases including PubMed to identify relevant peer reviewed literature as well as other sources (National Guideline Clearinghouse, Center for Reviews and Dissemination Database) to identify pertinent clinical guidelines and previously performed assessments.

Studies were selected for inclusion based on pre-specified criteria detailed in the full report. All records were screened by two independent reviewers. Selection criteria included a focus on studies with the least potential for bias that were written in English and published in the peer-reviewed literature.

Pertinent studies were critically appraised independently by two reviewers based on Spectrum's Class of Evidence (CoE) system which evaluates the methodological quality and potential for bias based on study design as well as factors which may bias studies. An overall Strength of Evidence (SoE) combines the appraisal of study limitations with consideration of the number of studies and the consistency across them, directness and precision of the findings to describe an overall confidence regarding the stability of estimates as further research is available. Included economic studies were also formally appraised based on criteria for quality of economic studies and pertinent epidemiological precepts.

Results: Summary of the highest quality evidence on primary outcomes

A summary of the results for each key question are provided in the tables that follow the text summaries below with a focus on the primary outcomes described above. Details of these and other outcomes are available in the full report. RCTs and comparative nonrandomized controlled trials are the focus for this summary.

Context Question:

Provide a summary of the inter-rater and intra-rater diagnostic reliability (reproducibility) of functional neuroimaging to diagnose AD, FTD, and Lewy body dementia in symptomatic dementia patients based on an appropriate gold standard (e.g., autopsy, genetic confirmation).

- **FDG-PET:**
 - Evidence base: 7 studies (5 CoE I, 1 CoE II, 1 CoE III); N = 45-132.^{54,57,67,146,163,190,191}
 - Visual assessments of FDG-PET blinded to clinical information.
 - Inter-rater reliability for discriminating between AD and FTD :
 - Kappa ranged from 0.72-0.81 (3 studies (2 CoE I & 1 CoE II), 2-6 raters, N = 45-132)^{54,57,146}
 - Agreement between all raters: 76% of cases (1 study (CoE 1), 12 raters, N = 45)¹⁹⁰
 - Inter-rater reliability for distinguishing AD from other dementias:
 - Kappa ranged from 0.52-0.67 (2 studies (1 CoE I, 1 CoE III), 3 raters, N = 67-110)^{67,191}
 - Agreement between raters: 94% cases (1 study (CoE 1), 2 raters, N = 100)¹⁶³
 - Intra-rater reliability for diagnosing AD :
 - Mean kappa from 3 raters of 0.52 (range, 0.50, 0.94) (1 study, CoE II, N = 110).⁶⁷
- **¹¹C-DTBZ-PET:**
 - Evidence base: 1 study (CoE II); N = 27.⁸⁴
 - Inter-rater reliability for discriminating between AD, FTD, and DLB: Kappa: 0.85 (3 raters).

- Intra-rater reliability was not reported.
- **HMPAO-SPECT:**
 - Evidence base: 2 studies (CoE III); N = 16-57.^{41,100}
 - Inter-rater reliability for discriminating AD vs. FTD:
 - Kappa: 0.48 (1 study, 2 raters, N = 16).¹⁰⁰
 - Agreement between all raters: 35% cases. (1 study, 5 raters, N = 57)⁴¹
 - Intra-rater reliability for discriminating AD vs. FTD: not reported.
- **¹²³I-FT-CIT-SPECT:**
 - Evidence base: 2 studies (CoE I); N = 20-288.^{94,182}
 - Inter-rater reliability for differentiating between DLB and non-DLB dementias:
 - Kappa: 0.87 (95% CI, 0.79-0.94) (1 study, 3 raters, N = 288).⁹⁴
 - Agreement between all raters: 75% cases (1 study, 3 raters, N = 20).¹⁸²
 - Intra-rater reliability was not reported.
- **fMRI, ASL:** No studies identified.

Context Question:

Provide a summary of the sensitivity and specificity of functional neuroimaging to diagnose AD, FTD, and Lewy body dementia in symptomatic dementia patients based on an appropriate gold standard (e.g., autopsy, genetic confirmation).

- **FDG-PET:**
 - Evidence base: 2 retrospective studies (one CoE II, one CoE IV); N = 55-138.^{68,163}
 - Gold standard: autopsy.
 - Visual assessments of FDG-PET to diagnose AD had 93-95% sensitivity and 63-73% specificity (2 studies, N = 55-138).^{68,163}
 - Clinical diagnosis of probable or possible AD according to NINCDS-ADRDA criteria had 79% sensitivity; 88% specificity (1 CoE IV study, N = 55).⁶⁸
 - The diagnostic accuracy of the combination of FDG-PET + clinical diagnosis was not reported.
- **HMPAO-SPECT:**
 - Evidence base: 1 retrospective study (CoE IV); N = 73.²³
 - Gold standard: autopsy.
 - Visual assessments of HMPAO-SPECT to diagnose AD had 93% (95% CI, 81-98%) sensitivity and 85% (95% CI, 64-95%) specificity.²³
 - Diagnostic accuracy of clinical diagnosis alone or the combination of FDG-PET and clinical diagnosis was not reported.
- **¹²³I-FT-CIT-SPECT:**
 - Evidence base: 1 prospective study (CoE I); N = 20.¹⁸²
 - Gold standard: autopsy.
 - Visual assessments of FP-CIT-SPECT to diagnose DLB had 88% sensitivity; 83% specificity.¹⁸²
 - Semi-quantitative interpretations of FP-CIT-SPECT to diagnose DLB had 88% sensitivity and 100% specificity.¹⁸²

- Diagnostic accuracy of the combination of SPECT and clinical diagnosis was not reported.
- Clinical diagnosis of DLB according to the Consensus DLB criteria had 75% sensitivity and 42% specificity.¹⁸²
- ¹¹*C-DTBZ-PET, fMRI, ASL*: No studies identified.

Key Question 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)?

Summary

- **FDG-PET: AD vs. FTD**
 - Evidence base: 3 retrospective studies (two CoE II, one CoE III); N = 10-45.^{54,57,146}
 - Prevalence of AD: 30-68%
 - Gold standard: autopsy.
 - Diagnosis of AD with FDG-PET alone:
 - Visual assessments using SPM or SSP images only had 94-98% sensitivity and 73-76% specificity (2 CoE II studies, N = 90 total).^{54,57}
 - One additional CoE III study reported 67% sensitivity and 93% specificity (N = 10).¹⁴⁶
 - Automated classification of images had 67% sensitivity and 100% specificity (1 study (CoE III), N = 10).¹⁴⁶
 - Additional information for context:
 - Combination of FDG-PET (visual classification) + clinical diagnosis had 90% sensitivity and 86% specificity (1 study (CoE II), N = 45).⁵⁷
 - Clinical diagnosis of AD (methods varied) had 63-100% sensitivity and 79-100% specificity (3 studies, N = 10-45).^{54,57,146}
 - Note that sensitivity of an AD diagnosis is the same as the specificity of an FTD diagnosis (and vice versa).
- **HMPAO-SPECT: AD vs. FTD**
 - Evidence base: 1 retrospective study (CoE IV); N = 56.¹⁰⁰
 - Prevalence of AD: 55%
 - Gold standard: autopsy.
 - Diagnosis of AD with HMPAO-SPECT using visual classification had 65% sensitivity and 72% specificity.¹⁰⁰
 - Additional information for context:
 - Combination of SPECT + clinical diagnosis: 84% sensitivity & specificity.¹⁰⁰
 - Clinical diagnosis of AD after comprehensive work-up: 77% sensitivity, 88% specificity.¹⁰⁰
 - Note that sensitivity of an AD diagnosis is the same as the specificity of an FTD diagnosis (and vice versa).
- **FDG-PET: AD vs. DLB**
 - Evidence base: 2 retrospective studies (CoE III); N = 11-21.^{104,174}

- Prevalence of DLB: 45-52%
 - Gold standard: autopsy.
 - Diagnosis of DLB (alone or in combination with AD) (versus AD alone) had 80-90% sensitivity and 80-100% specificity (2 studies).^{104,174}
 - Additional information for context:
 - Diagnostic accuracy of clinical diagnosis either alone or in combination with SPECT was not reported.
 - Note that sensitivity of a DLB diagnosis is the same as the specificity of an AD diagnosis (and vice versa).
- ¹²³I-FP-CIT-SPECT, ¹¹C-DTBZ-PET, fMRI, ASL: No studies identified.

Strength of evidence table for the primary outcomes of interest:

Note that the focus is on the highest quality evidence for each test/outcome combination.

Details on how the final SoE was determined are available in the full report (see Section 5).

Imaging (Classification)	Outcome	Studies (CoE)	Findings	Final SoE
FDG-PET: AD vs. FTD				
Gold standard: autopsy				
FDG-PET (visual)	Sensitivity (AD diagnosis)	2 CoE II ^{54,57} N = 90	94 – 98%	Low
(SSP and/or SPM images only)	Specificity (AD diagnosis)	2 CoE II ^{54,57} N = 100	73 – 76%	Low
FDG-PET (automated)	Sensitivity (AD diagnosis)	1 CoE III ¹⁴⁶ N = 10	67%	Insufficient
	Specificity (AD diagnosis)		100%	Insufficient
HMPAO-SPECT: AD vs. FTD				
Gold standard: autopsy				
HMPAO-SPECT (visual)	Sensitivity (AD diagnosis)	1 CoE IV ¹⁰⁰ N = 56	65%	Insufficient
	Specificity (AD diagnosis)		72%	Insufficient
FDG-PET: DLB vs. AD				
Gold standard: autopsy				
FDG-PET (automated)	Sensitivity (DLB diagnosis)	2 CoE III ^{104,174} N = 32	80 – 90%	Insufficient
	Specificity (DLB diagnosis)		80 – 100%	Insufficient
¹²³I-FP-CIT-SPECT	No evidence			Insufficient
¹¹C-DTBZ-PET	No evidence			Insufficient
fMRI	No evidence			Insufficient
ASL	No evidence			Insufficient

Key Question 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?

Ability of functional neuroimaging to predict progression and clinical outcomes:

- **FDG-PET**

- Outcome: Patient progression (MCI to AD/dementia conversion)**

- Evidence base: 10 studies (2 CoE I, 8 CoE III); N = 12 – 128.^{39,43,48,65,80,85,134,144,164,175}
 - Baseline diagnosis: MCI or aMCI
 - CoE I/II studies (2 studies (CoE I); N = 17 – 30):^{43,48}
 - Length of follow-up: 1.3 – 1.6 years
 - Prediction of AD/dementia with FDG-PET using visual assessment (2 studies)^{43,48}
 - 25 – 40% progressed to AD/dementia
 - Prediction of AD or dementia with FDG-PET alone had 92-100% sensitivity and 75-89% specificity
 - Prediction of progressive cognitive decline with FDG-PET (1 study, N = 17):⁴⁸
 - 50% had cognitive decline
 - Prediction of decline with FDG-PET alone had 75% sensitivity and 88% specificity.
 - CoE III/IV studies (8 studies (CoE III); N = 12 – 128):^{39,65,80,85,134,144,164,175}
 - Length of follow-up: 1.3 – 3 years
 - Prediction of AD/dementia using automated assessment of FDG-PET scans (3 studies, N = 24 – 93):^{80,85,144}
 - 42 – 68% progressed to AD/dementia
 - Prediction of AD or dementia with FDG-PET alone: 33-45% sensitivity and 43-93% specificity
 - Prediction of AD/dementia using visual assessment of FDG-PET images (5 studies):^{39,65,134,164,175}
 - 11 – 68% progressed to AD/dementia
 - Prediction of AD or dementia with FDG-PET alone had 25-100% sensitivity and 24-83% specificity

- Outcome: Cognition (MMSE scores)**

- Evidence base: 1 study (CoE III); N = 167 (MMSE data available for subset of 95 patients)¹⁶⁴
 - Baseline diagnosis: MCI
 - Length of follow-up: 3.5 ± 1.0 years
 - MMSE scores:
 - Baseline: 24 ± 6.4 (n=95)
 - Prediction of progressive (n=67) vs. nonprogressive (n=28) dementia with FDG-PET using visual assessment: ~18 vs. ~25.5 ($P < 0.05$)

Outcomes related to function, quality of life, behavior, psychological status, depression, caregiver burden, and global health: No evidence identified.

- **SPECT (perfusion)**

- Outcome: Patient progression (MCI to AD/dementia conversion)**

- Evidence base: 3 studies (CoE III); N = 12 – 316.^{36,39,74}

- Ligands used: ⁹⁹Tc-HMPAO (2 studies), ¹²³I-IMP (1 study) (all measured cerebral blood flow)
- Baseline diagnosis: MCI or aMCI
- Length of follow-up: 1.3 – 4 years
- Prediction of AD using automated assessment of SPECT scans (1 study, N = 316):⁷⁴
 - 46.7% progressed to AD
 - Prediction of AD with SPECT alone: 58% sensitivity and 81% specificity
- Prediction of AD/dementia using visual assessment of SPECT images (3 studies):^{36,39,74}
 - 24.4 – 50% progressed to AD/dementia
 - Prediction of AD or dementia with SPECT alone had 36-76% sensitivity and 39-82% specificity

Outcomes related to function, quality of life, behavior, cognition psychological status, depression, caregiver burden, and global health: No evidence identified.

• **fMRI**

Outcome: Patient progression (MCI to AD/dementia conversion)

- Evidence base: 1 study (CoE III); N = 33¹⁴⁰
- Memory tasks given during scan
- Baseline diagnosis: MCI
- Length of follow-up: 2.5 ± 0.8 years
- Prediction of dementia using assessment of PMC activation as seen in fMRI scans:
 - 33% progressed to AD
 - Prediction of dementia with fMRI alone: 55% sensitivity and 73% specificity

Outcomes related to function, quality of life, behavior, cognition psychological status, depression, caregiver burden, and global health: No evidence identified.

- ¹²³I-FP-CIT-SPECT, ¹¹C-DTBZ-PET, ASL: No studies identified.

Ability of one type versus another type functional neuroimaging to predict progression and clinical outcomes: no evidence found.

Strength of evidence table for the primary outcomes of interest:

Note that the focus is on the highest quality evidence for each test/outcome combination.

Details on how the final SoE was determined are available in the full report (see Section 5).

Imaging (Classification)	Outcome	Studies (CoE)	Findings	Final SoE
FDG-PET: Patient progression (MCI to AD/dementia conversion)				
Reference standard: AD/dementia at follow-up				
FDG-PET (visual)	Sensitivity	2 CoE II ^{45,48} N = 47 F/U: 1.3-1.6 yrs.	92-100%	Moderate
	Specificity		75-89%	Moderate
FDG-PET (automated)	Sensitivity	3 CoE III ^{80,85,144} N = 136	33-45%	Insufficient

Imaging (Classification)	Outcome	Studies (CoE)	Findings	Final SoE
		F/U: 1.3-3 yrs.		
	Specificity		33-45%	Insufficient
FDG-PET: Patient progression (MCI to progressive cognitive decline) Reference standard: progressive cognitive decline at follow-up				
FDG-PET (visual)	Sensitivity	1 CoE I ⁴⁸ N = 17 F/U: 1.6 yrs.	75%	Low
	Specificity		88%	Low
FDG-PET: Cognitive decline				
FDG-PET (visual)	Cognition (MMSE scores)	1 CoE III ¹⁶⁴ N = 95	Patients predicted to have progressive dementia using to FDG-PET images had significantly lower MMSE scores at follow-up than did those predicted to have nonprogressive dementia (~18 vs. ~25.5, $P < 0.5$).	Insufficient
FDG-PET: prediction of outcomes related to function, behavior, psychological status, depression, caregiver burden, and global health: No evidence (insufficient evidence).				
HMPAO- or IMP-SPECT: Patient progression (MCI to AD/dementia conversion) Reference standard: AD/dementia at follow-up				
SPECT (automated)	Sensitivity	1 CoE III ⁷⁴ N = 316 F/U: 3 yrs.	58%	Insufficient
	Specificity		81%	Insufficient
SPECT (visual)	Sensitivity	3 CoE III ^{36,39,74} N = 454 F/U: 1.3 – 4.1 yrs.	36-76%	Insufficient
	Specificity		39-82%	Insufficient
SPECT: prediction of outcomes related to function, behavior, cognition, psychological status, depression, caregiver burden, and global health: No evidence (insufficient evidence).				

Imaging (Classification)	Outcome	Studies (CoE)	Findings	Final SoE
fMRI: Patient progression (MCI to dementia conversion)				
Reference standard: dementia at follow-up				
<i>fMRI (NR)</i>	Sensitivity	1 CoE III N = 33 F/U: 2.5 ± 0.8 yrs.	55%	Insufficient
	Specificity		73%	Insufficient
fMRI: prediction of outcomes related to function, behavior, cognition, psychological status, depression, caregiver burden, and global health: No evidence (insufficient evidence).				
¹²³ I-FP-CIT-SPECT		No evidence		Insufficient
¹¹ C-DTBZ-PET		No evidence		Insufficient
ASL		No evidence		Insufficient
<i>Comparisons of different types of neuroimaging to predict progression and patient outcomes</i>		No evidence		Insufficient

Key Question 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?

- No studies identified.

Key Question 4:

What are the short and long term harms of functional neuroimaging?

- **FDG-PET**
 - One study was identified (N = 36 dementia/MCI patients) and reported short-term harms as identified by patients on a follow-up telephone call.⁸⁹ No adverse events assessed were reported to occur, including injection site pain, tenderness, redness, or swelling; or new fever, rash, breathing difficulties, diarrhea, headache, or muscle pain.
- **¹²³I-FP-CIT-SPECT (DaTscan)**
 - One study was identified (N = 326 dementia patients) and reported procedural and postprocedural harms only.⁹⁴ Adverse events attributed to the ¹²³I-FP-CIT injection occurred in 9 patients (10 events), including nausea (3 events), injection site hemorrhage (2 events), injection site erythema (2 events), dry mouth (1 event), vomiting (1 event), and headache (1 event).

- **HMPAO-SPECT, ¹¹C-DTBZ-PET, fMRI, ASL:**
 - No evidence identified.

Strength of evidence table for the primary outcomes of interest:

Note that the focus is on the highest quality evidence for each test/outcome combination.

Details on how the final SoE was determined are available in the full report (see Section 5).

Imaging	Outcome	Studies (CoE)	Findings	Final SoE
FDG-PET	Injection-related short-term harms*	1 CoE III ⁹⁹ N = 36	0%	Insufficient
¹²³I-FP-CIT-SPECT	Injection-related harms** (procedural and post-procedural harms only)	1 CoE III ⁹⁴ N = 326	2.8% patients (10 events)	Insufficient
FDG-PET, ¹²³I-FP-CIT-SPECT	Other harms, including long-term harms and effect of missed diagnosis, false negative, or false positive	0 studies		Insufficient
<p>No evidence (i.e., Insufficient SoE) found for of the following diagnostic tests:</p> <ul style="list-style-type: none"> • HMPAO-SPECT • ¹¹C-DTBZ-PET • fMRI • ASL 				

Key Question 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.

- No studies identified.

Key Question 6:

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

- **FDG-PET:**
 - One cost-utility study⁹⁹ and two cost effectiveness studies^{109,162} explored the addition of FDG-PET to the conventional clinical work-up for the diagnosis of AD.
 - All studies based on a simulated cohort of hypothetical dementia patients.
 - The cost utility study concluded that FDG-PET was more costly (imaging costs, additional travel days, caregiver time and consultation fees) and provided no benefit in QALYs, thus FDG-PET was not cost effective as an add-on in the diagnosis of AD. An 18-month time horizon was used, and the study was conducted in the US.

- Conversely, the cost effectiveness studies^{109,162} found that the use of FDG-PET, when deemed appropriate, in addition to a conventional clinical evaluation, to be cost-effective for the diagnosis of AD, particularly because it was less costly and had increased accuracy over the conventional work-up. One study used a 6-month time horizon and was conducted in the US. The other study was conducted with a European perspective, and the time horizon was not clear in the other study.
- **SPECT (visual and computed)**
 - Two cost-utility studies^{98,99} examined the use of SPECT as an add-on functional imaging modality to a conventional clinical work-up, compared with the conventional work-up alone.
 - Both studies based on a simulated cohort of hypothetical dementia patients.
 - The studies found that SPECT was not cost-effective as an add-on to the conventional clinical evaluation in the diagnosis of AD based on increased costs and similar QALYs. Both studies were conducted in the US and an 18 month time horizon was used.
- ¹¹**C-DTBZ-PET, fMRI:** No studies identified.

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1. Appraisal

1.1. Rationale

Dementia is a condition in which mental capabilities have declined severely enough such that it interferes with the ability to function on a daily basis. Dementia can range in severity from mild to severe and may impact people differently, depending on the area of the brain affected. Impairment of memory is one of the most common deficits, but language, praxis, visual-perceptive and executive functions may also be affected.¹⁶ Although dementia may occur in individuals at any age, it is typically a condition that affects the elderly and the aging of the global population is a key factor in the increasing number of people with this condition.¹⁴⁵

Of all diseases associated with age, dementia is the fastest growing with an estimated 24.3 million people worldwide having been diagnosed with the condition, with 4.6 million new cases diagnosed each year.⁵⁰ It is estimated that by 2050 the prevalence will have quadrupled, so that one in 85 individuals will be living with dementia.²⁴ Although the prevalence of dementia and its associated disability increases considerably with age,^{32,150} the focus of research and of clinical care has shifted toward achieving a diagnosis in younger individuals when the cognitive decline is in the earlier stages.¹⁵¹

Dementia can be caused by a number of conditions and diseases. The most common cause of dementia is Alzheimer's Disease (AD), which is most prevalent in older people. Other causes of dementia include vascular dementia (VaD), Lewy body dementia (which includes dementia with Lewy bodies (DLB) as well as Parkinson's Disease with dementia (PDD)), and frontotemporal dementia (FTD). Mixed dementia can also occur, in which patients have a combination of two or more types of dementia. Some forms of dementia can be reversed or treated with appropriate treatment including normal pressure hydrocephalus, subdural hematoma, tumor, thyroid problems, and vitamin B deficiency.

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. Most clinical practice guidelines recommend that patients who meet clinical criteria for dementia undergo at least one structural neuroimaging procedure (computed tomography (CT) or magnetic resonance imaging (MRI) scan) and laboratory testing to exclude reversible causes of dementia such as subdural hematoma or tumor. Structural neuroimaging may also aid in the diagnosis of dementia subtype based on patterns of atrophy. After this initial comprehensive work-up, a specific diagnosis is generally able to be made. However, in some patients the diagnosis remains unclear and additional testing with functional imaging may be conducted in order to make an accurate diagnosis.

Functional neuroimaging is an add-on diagnostic test that is typically only done in addition to structural neuroimaging if needed to confirm a diagnosis. In contrast to structural imaging, functional neuroimaging can provide specific information regarding specific brain functions. Functional neuroimaging involves the injection of radiolabeled ligands, which are then detected by the scanner. Types of functional neuroimaging include single-photon emission computed tomography (SPECT), positron emission tomography (PET), and functional MRI (fMRI). SPECT can measure dopaminergic nigrostriatal denervation, which occurs in patients with DLB, using the radiolabeled dopamine

transporter ligand ^{123}I -FP-CIT (2 β -carbomethoxy-3 β -(4-iodophenyl)-B- (3-fluoropropyl) nortropane). SPECT can also assess cerebral blood flow using $^{99\text{m}}\text{Tc}$ -HMPAO (hexamethylpropylene amine oxime). Because cerebral blood flow correlates with brain metabolism, the images provide information regarding which regions of the brain are affected, which in turn aids with differential diagnosis. FDG (fluorodeoxyglucose) PET also provides information regarding brain metabolism by measuring glucose uptake.

Functional neuroimaging has the capability of aiding in the differential diagnosis of AD, DLB, and FTD disorders, and may be of particular use when the clinical diagnosis remains unclear. While functional imaging is typically not used to diagnose mild cognitive impairment, it may predict future conversion to AD and thus would help patients plan for the future. However, there are significant questions related to the use of functional neuroimaging for the diagnosis of primary neurodegenerative dementia and mild cognitive impairment, specifically, there are medium concerns regarding safety, efficacy, and cost. The objective of this Health Technology Assessment was to systematically review, critically appraise, analyze and synthesize research evidence evaluating the ability of neuroimaging to differentially diagnose, predict progression and outcomes, and influence therapeutic decisions and clinical management for patients with primary neurodegenerative dementia or mild cognitive impairment. The differential effectiveness and safety of diagnostic neuroimaging for subpopulations was evaluated, as was the cost effectiveness of diagnostic neuroimaging. To that end, the Key Questions below were posed. Note that Key Questions are shown in terms of an analytic framework which guided the HTA in Figure 1.

1.2. Key Questions

Contextual Questions:

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 DLB and 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).

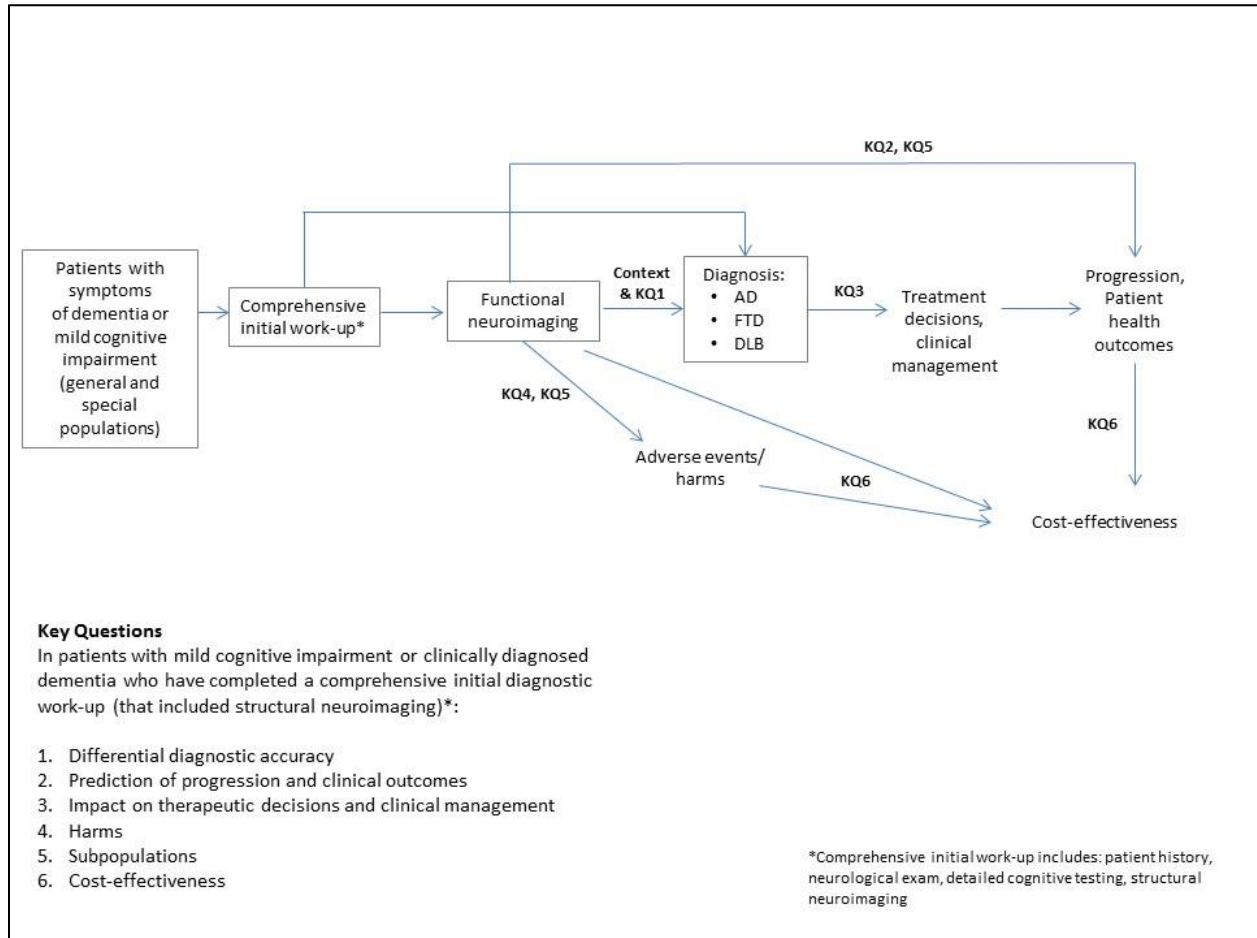
Research Key Questions:

In patients with mild cognitive impairment or clinically diagnosed dementia who have completed a comprehensive initial diagnostic work-up (that included structural neuroimaging):

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)?
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?
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?
4. What are the short and long term harms of diagnostic functional neuroimaging?

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

Figure 1. Analytic framework



1.3. Outcomes Assessed

Diagnostic test performance measures were used in this report. Briefly:

- **Kappa statistic:** represents the extent to which the agreement observed exceeds that which would be expected by chance alone, and can be calculated as follows:

$$\text{Kappa} = \frac{(\% \text{ agreement observed}) - (\% \text{ agreement expected by chance alone})}{100\% - (\% \text{ agreement expected by chance alone})}$$
 - Kappa has been interpreted according to the guidelines suggested by Landis and Koch⁸⁶:
 - 0.81 – 1.0: almost perfect agreement
 - 0.61 – 0.80: substantial agreement
 - 0.41 – 0.60: moderate agreement

- 0.21 – 0.40: fair agreement
- 0 – 0.20: slight agreement
- <0: no agreement
- **True positive (TP):** patients who test positive and who have the disease
- **False positive (FP):** patients who test positive but do not have the disease
- **False negative (FN):** patients who test negative but do have the disease
- **True negative (TN):** patients who test negative and do not have the disease
- **Sensitivity** (true positive rate) measures the ability of a diagnostic test to correctly identify patients with the disease, and can be calculated as follows: $TP/(TP + FN)$
- **Specificity** (true negative rate) measures the ability of a diagnostic test to minimize false positives, and can be calculated as follows: $TN/(FP + TN)$
- Note that sensitivity and specificity are negatively correlated with one another: if the threshold of a positive test is set higher to maximize sensitivity, specificity will be lower, and vice versa.⁷
- **Prevalence** indicates the percentage of patients who have the disease according to the reference standard: $(TP + FN)/(TP + FP + FN + TN)$

A list of the outcome measures used in studies included in this report is provided in Table 1.

Table 1. Outcome measures used in included studies

Outcome Measure	Patient Or Clinician Reported	Components	Score Range	Interpretation
Cognition				
Mini Mental State Exam (MMSE) ⁵³	Clinician	8 categories (30 items): <ul style="list-style-type: none"> • Complex commands (6 points) • Orientation to time (5 points) • Orientation to place (5 points) • Attention and calculation (5 points) • Registration (repeating named prompts) (3 points) • Recall (3 points) • Language (2 points) • Repetition (1 point) Each item has a minimum score of 0 and a maximum score of 1.	0 to 30 points	The lower the score, the greater the cognitive impairment. Score classification regarding cognitive impairment: <ul style="list-style-type: none"> • 27-30: normal • 19-24: mild • 10-18: moderate • 0-9: severe
Modified Mini Mental Exam (3MS) ¹⁷²	Clinician	15 subscales (48 items): <ul style="list-style-type: none"> • Place and date of birth • Registration • Mental reversal • First recall • Temporal orientation • Spatial orientation • Naming 	3MS total score: 0 to 100 points	The lower the score, the greater the cognitive impairment. 3MS total score < 79: cognitive impairment

Outcome Measure	Patient Or Clinician Reported	Components	Score Range	Interpretation
		<ul style="list-style-type: none"> • Four-legged animals • Similarities • Repetition • Read and obey • Writing • Copying two pentagons • Three-stage command • Second recall <p>Each item has a minimum score of 0 and a variable maximum score of 1 to 8.</p>		3MS total score < 48: severe impairment
Alzheimer's Disease Assessment Scale - Cognition (ADS-Cog) ¹⁵⁴	Clinician	<p>11 items:</p> <ul style="list-style-type: none"> • Word recall • Naming objects and fingers • Commands • Constructional praxis • Ideational praxis • Orientation • Word recognition task • Language • Comprehension of spoken language • Word finding difficulty • Remembering test instructions <p>Each item has a minimum score of 0 and a variable maximum score of 5 to 12.</p>	Total score: 0 to 70 points	The higher the score, the greater the cognitive impairment.
Cambridge Cognitive Examination (CAMCOG) ¹⁵⁵	Clinician	<p>8 subscales (67 items):</p> <ul style="list-style-type: none"> • Orientation • Language • Memory • Attention • Praxis • Calculation • Abstraction • Perception <p>59 of 67 items scored on a 0 to variable maximum 1 to 3 points scale.</p>	Total score: 0 to 107 points	The lower the score, the greater the cognitive impairment.

Outcome Measure	Patient Or Clinician Reported	Components	Score Range	Interpretation
Global				
Clinical Dementia Rating (CDR) ¹⁰⁷	Clinician	<p>6 subscales (84 items) including the following:</p> <ul style="list-style-type: none"> • Memory • Orientation • Judgment and Problem Solving • Community Affairs • Home and Hobbies • Personal Care <p>Each subscale scored on a 0 to 3 point scale.</p>	<p>Total score: 0 to 18 points</p> <p>Global score: 0 to 3 points</p>	<p>The higher the score, the greater the dementia severity.</p> <p>The global CDR is derived from the scores of the six subscales; Memory ("M") is considered the primary category and the others are secondary. If at least 3 subscales are scored the same as M, then the global CDR = M. If three or more subscales are scored greater or less than M, then the global CDR = the score of the majority of secondary categories on whichever side of M has the greater number of secondary categories.</p>

1.4. Key considerations highlighted by clinical experts:

1.4.1. Key Concepts

When determining which functional neuroimaging technique should be used to diagnose primary neurodegenerative dementia, two topics are important to consider include: (1) How well an imaging modality deciphers two similar disorders from one another; and (2) The advantages and disadvantages of using a particular imaging modality for diagnosis.

1.4.2. Patient Workup

Patients presenting with symptoms or complaints suggestive of dementia ideally undergo an initial evaluation consisting of a thorough history with both the patient and a corroborating informant,

detailed cognitive testing, and neurological examination. However, patients may not receive such a thorough work-up unless they are referred for neurological or dementia specialty evaluation, as primary care physicians may not have the time and/or training for this level of assessment. Patients who meet criteria for dementia undergo CT or MRI neuroimaging (per AAN guideline recommendations) and reversible dementia lab workup. This structural neuroimaging is mainly done to rule out subdural hematomas, which can cause cognitive symptoms and are treatable, but also helps to identify contributions from cerebrovascular disease and evaluate patterns of atrophy, etc. A diagnosis is generally able to be made based on this initial evaluation, and only a very small percentage of patients evaluated in the dementia specialty clinic require additional testing with functional imaging. Patients who present with atypical features such as younger onset of symptoms, rapid progression, and symptoms that straddle multiple diagnoses (i.e., features of both AD and FTD) are generally those who undergo functional neuroimaging for a more helpful diagnosis.

Functional neuroimaging is an add-on diagnostic test that should be done in addition to structural neuroimaging when needed. Typically, functional neuroimaging is most useful when trying to determine FTD (of any type, including semantic dementia, progressive nonfluent aphasia, and behavioral variant (bvFTD)) from AD. The advantage of functional versus structural neuroimaging is that it gives information regarding brain metabolism/function, which can be abnormal prior to structural brain changes such as atrophy. The addition of functional neuroimaging to structural neuroimaging would not change management and treatment for the majority of patients with typical dementia phenotypes, particularly classic AD. For someone with atypical features, clarification of AD versus FTD can be helpful in both treatment and counseling/prognosis. Even if an accurate diagnosis is not obtained, functional imaging can sometimes be helpful in determining whether or not a neurodegenerative disease is likely present. This would help guide treatment and management of atypical patients.

Both technological and economic factors contribute to choosing an imaging technique for diagnosis. For example, PET scans are covered by Medicare, while SPECT scans are not. Additionally, occipital abnormalities in DLB are more visible on FTG-PET, which makes it useful when sorting out AD or FTD versus DLB by allowing assessment of overall brain function rather than just dopaminergic activity.

In summary, functional neuroimaging can be an important diagnostic tool for primary neurodegenerative dementias and especially in atypical populations. Additionally, choice of functional imaging technique is multifaceted, and all factors (i.e., accuracy, reliability, cost, etc.) should be taken into consideration when choosing a diagnostic test.

1.4.3. Diagnoses of Interest

In terms of primary neurodegenerative dementia, the following diagnoses can be made with the help of functional neuroimaging: Alzheimer's disease (AD), dementia with Lewy bodies (DLB), and frontotemporal dementia (FTD).

Functional neuroimaging is typically not used to diagnose mild cognitive impairment (MCI). However, if effective therapies are discovered, they are likely going to be most effective in earlier stages of the disease and functional imaging for those with mild cognitive impairment would become very important.

1.4.4. Reference Standards

Two gold standards currently exist for diagnosis of primary neurodegenerative dementia: genetic confirmation for hereditary forms in symptomatic patients and pathology from biopsy/ autopsy. Clinical diagnosis is considered to be second best as it is more practical but less certain. Structural neuroimaging, different types of functional neuroimaging, and same type of functional imaging but different ligand used are excluded diagnostic comparators. Over the past 20 years, diagnostic standards for AD, FTD, and DLB have not changed significantly. The primary change is the description of FTD subsets: PPA, bvFTD, and semantic dementia.

1.4.5. Outcomes of interest

The primary outcomes of importance in this patient population include function, quality of life, and behavioral and psychological outcomes. Highlighted outcome measures include:

- 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 outcomes (e.g., Neuropsychiatric Inventory (NPI), Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD))

Secondary outcomes of importance include cognition, depression, caregiver stress and burden, global outcome measures, and mortality. Highlighted outcome measures include:

- 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))
- Global outcome measures (e.g., Global Deterioration Scale (GDS), Clinical Dementia Rating (CDR), Dementia Severity Rating Scale (DSRS))

Intermediate outcomes of interest included diagnostic sensitivity and specificity.

1.4.6. Harms/ Safety Issues from Functional Neuroimaging

Functional neuroimaging is generally considered fairly safe.

1.5. Washington State utilization and cost data

The following data were provided from the Washington State Health Care Authority and represent estimates for costs and utilization from the Uniform Medical Plan, Labor and Industry and Medicaid.

Figure 1 –Agency Costs and Counts – Dementia and Cognitive Tests, 2010-2013

Public Employee Benefits (PEBB), Uniform Med Plan (UMP)	2010	2011	2012	2013	4 Year Total	Avg % Change	
PEBB/UMP Average Annual Members	213,487	212,596	212,684	222,339		1.4%	
Dementia Diagnosed Member Counts	1874	2038	2224	2347	5833	6.4%	*
Cognitive Testing Patients	684	704	767	761	2916	2.4%	*
Nuclear Imaging(NI) for Dementia (All members)†	15	26	21	29	91		
SPECT Scans (78607) (% Medicare)	5 (60%)	2 (50%)	3 (33.3%)	1 (0%)	11 (45.4%)		
PET Scans (78608) (% Medicare)	10 (80%)	24 (66.7%)	18 (77.8%)	28 (75.0%)	80 (73.8%)		
NI Scans Total Cost (Direct cost by code)Non-medicare only	\$3,286	\$7,905	\$7,122	\$10,647	\$28,960		
NI Scans Total Cost (Non-medicare only) (Day of procedure related charges)**	\$5,005	\$9,264	\$7,368	\$10,956	\$32,593		
Medicaid Fee for Service (FFS) and Managed Care							
Medicaid Average Annual Members (FFS)	474,676	473,356	477,727	442,698		-2.2%	
Medicaid Average Annual Members (Managed Care)	680,785	695,591	730,250	800,096		5.6%	
Dementia Diagnosed Member Counts (FFS)	6200	6272	5516	5456	23,444	-1.6%	*
Dementia Diagnosed Member Counts (Managed Care)	1017	1101	1248	1601	4,967	10.3%	*
Cognitive Testing Patients (FFS + Managed Care)	69	58	49	72	248	8.8%	*
Nuclear Imaging(NI) for Dementia(FFS + Managed Care)†	12	15	9	7	43		
SPECT Scans (78607)	5	5	4	2	16		
PET Scans (78608)	7	10	5	5	27		
NI Scans Total Cost (Direct cost by code)	\$3,876	\$2,814	\$851	\$648	\$8,189		
NI Scans Total Cost (Day of procedure related charges)**	\$4,110	\$3,399	\$1,070	\$683	\$9,262		
L&I							
L&I Average Annual Members	122,712	121,043	121,660	123,159		0.0%	
Dementia Diagnosed Member Counts	96	80	90	88	354	-2.3%	*
Cognitive Testing Patients	1303	1157	1207	1078	4744	-6.0%	*

*Population Adjusted Average % Change, Average % change not calculated for nuclear tests due to variability of low volume events.

**Day of procedure charges include radioisotopes, structural imaging. See Figure 4 for a breakdown of day of procedure charges by category.

†Test counts and patient counts are equal in Medicaid data (no repeated functional imaging). In PEBB data, 3 patients had a repeated procedure of the same type.

NOTE: L&I data included 22 nuclear imaging encounters, but none with a dementia diagnoses.

Figure 2: Agency Fee Schedules

Current pricing for Functional Brain Imaging as available on Agency web sites:

CPT Codes	CPT Code Descriptions	Current Agency Fees (Allowed)		
		PEBB/UMP*	L&I†	Medicaid‡
70554	FUNCTIONAL MRI,BRAIN, W/O PHYSICIAN	\$767.66	\$0.00	\$0.00
70555	FUNCTIONAL MRI,BRAIN, W/ PHYSICIAN	\$1067.29	\$0.00	\$0.00
78607	SPECT imaging of brain	\$526.41	\$609.23	\$218.74
78608	PET imaging of brain	\$1,685.99	\$2,832.22	\$948.07

*Regence Blue Shield Provider Fee Schedule – effective January 1 2013, MD/DO/DPM Provider rates, Maximum Allowable fee, http://www.hca.wa.gov/ump/documents/Regence_Professional_Fee_Schedule_Jan_2013.pdf, Accessed 10/13/2014. Payment based on the Regence Fee Schedule is subject to all of the terms and conditions of the applicable Regence BlueShield provider agreement, member benefits, Regence BlueShield policies, and all published Regence BlueShield administrative guidelines. Therefore, the appearance of fees for particular procedure codes does not guarantee coverage. Some providers may have contracted fees at different rates.

†Washington State Labor and Industries Fee Schedules and Payment Policies (MARFS), Fee Schedules and Payment Policies for: 2014, <http://www.ini.wa.gov/apps/FeeSchedules/>, Accessed 10/13/2014

‡Washington State Medicaid Rates Development Fee Schedule, July 1, 2014 Physician and Related Services Fee Schedule (Updated October 1, 2014), <http://www.hca.wa.gov/medicaid/rbrvs/pages/index.aspx#P>, Accessed 10/13/2014.

Figure 3a. PEBB/UMP Neuroimaging for Dementia Patients by Age and Gender, 2010-2013

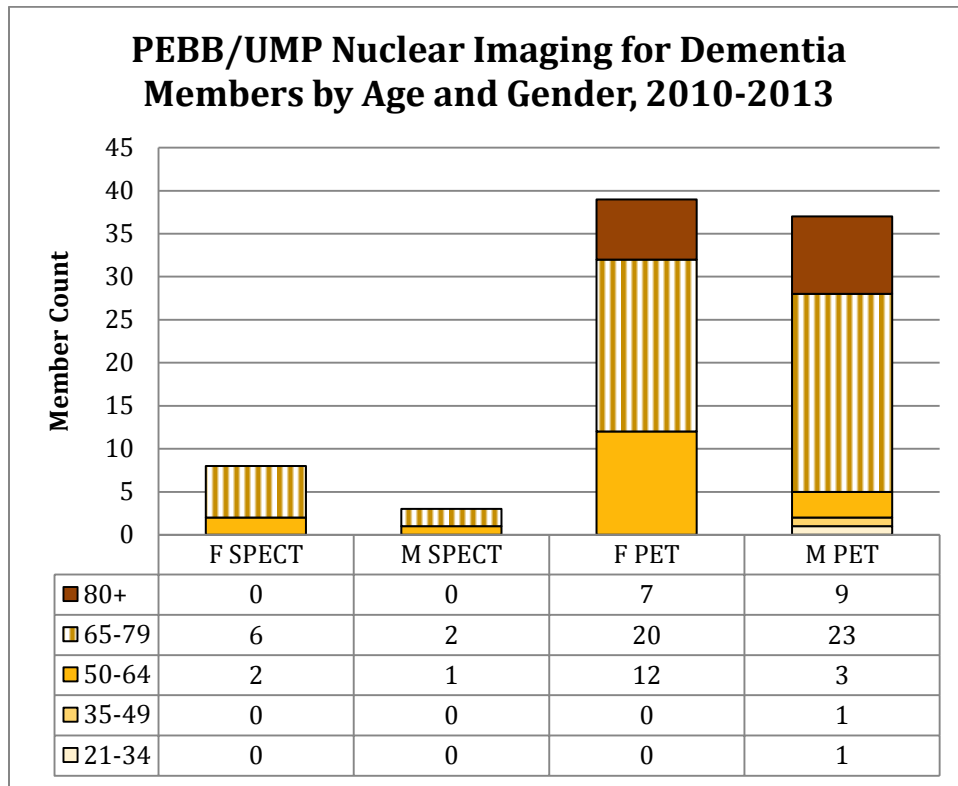


Figure 3b. Medicaid Neuroimaging for Dementia Patients by Age and Gender, 2010-2013

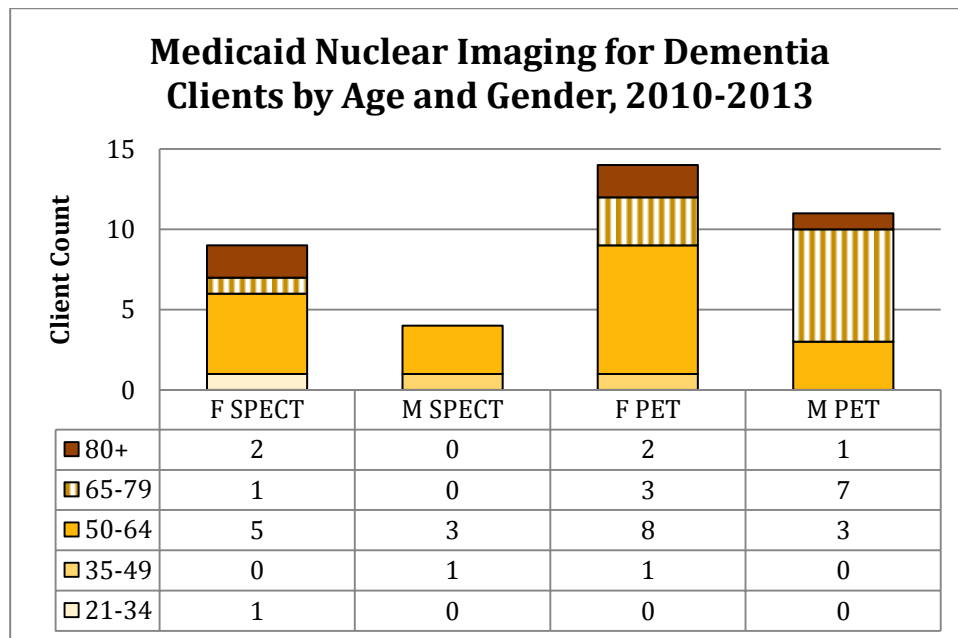


Figure 4. Day of Imaging Charges, Allowed Amounts

Agency and Image Type	PEBB/UMP PET	PEBB/UMP SPECT	Medicaid PET	Medicaid SPECT
Day of Service Charge Breakdowns, Allowed Amounts	Non-Medicare Allowed Amounts, n=13	Non-Medicare Allowed Amounts, n=3	FFS only, Allowed Amounts, n=25*	FFS only, Allowed Amounts, n=11*
by Type of Charge				
Nuclear Imaging for Dementia	\$2,266	\$1,359	\$1,212	\$527
Other Imaging	\$19	\$590	\$7	\$264
Other Care/Psych Care	\$76	\$0	\$6	\$8
Radiopharmaceuticals	\$56	\$0	\$268	\$52
Other Tests	\$30	\$0	\$0	\$0
Total	\$2,447	\$1,949	\$1,493	\$851
by Facility vs Provider				
Facility	\$1,989	\$1,840	\$237	\$742
Provider	\$458	\$109	\$1,255	\$109
Total	\$2,447	\$1,949	\$1,493	\$851

Allowed amounts are the maximum responsibility of the payer and are more representative of cost. Paid \$ are reported in Table 1, and exclude client/member contributions.

Figure 5a. PEBB/UMP SPECT Imaging for Dementia Patients by Diagnosis, 2010-2013

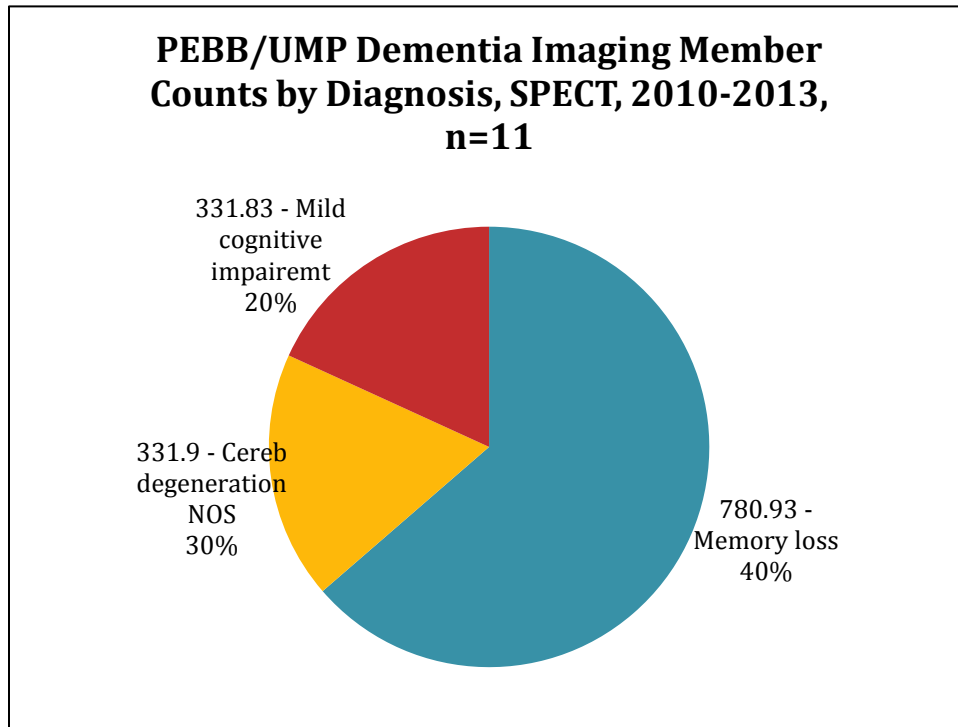


Figure 5b. PEBB/UMP PET Imaging for Dementia Patients by Diagnosis, 2010-2013

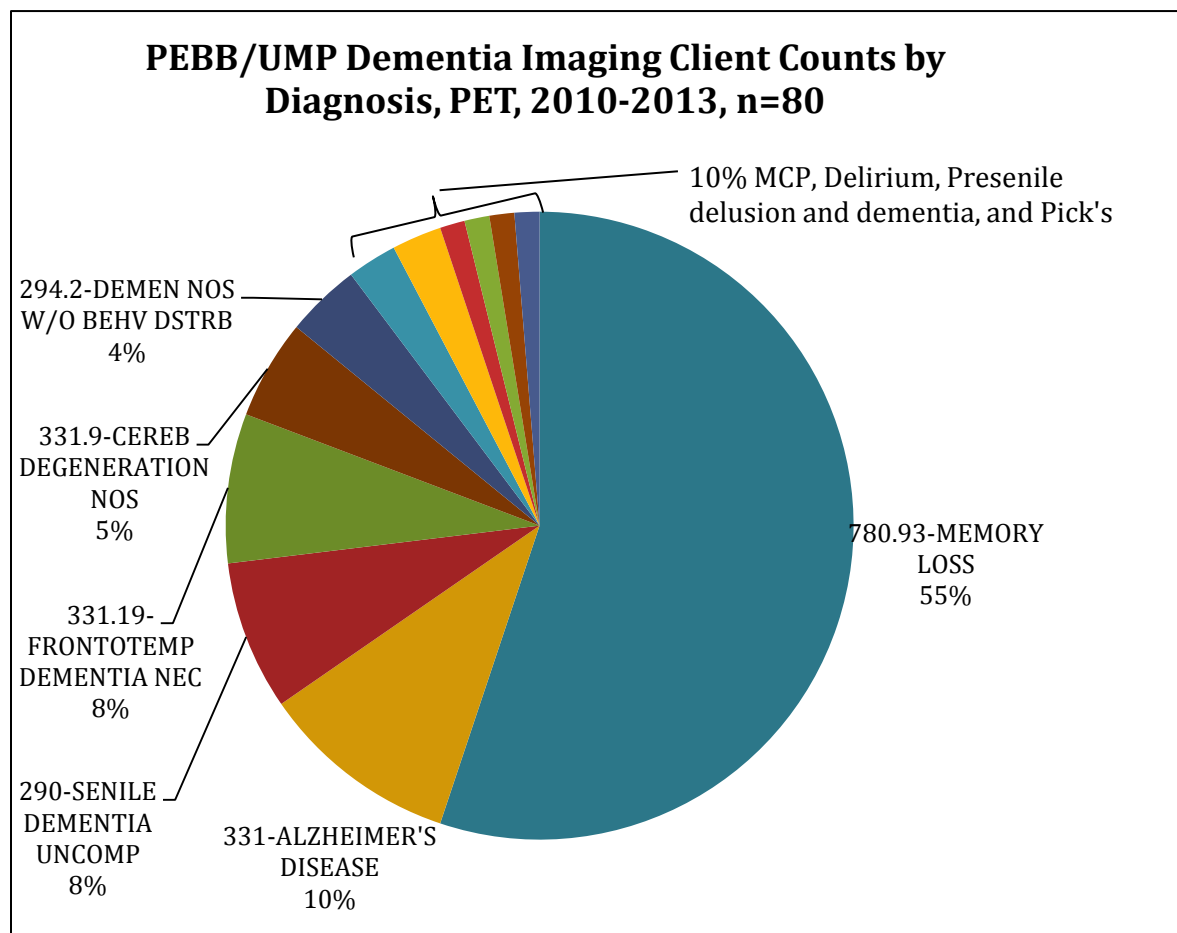


Figure 5c. Medicaid SPECT Imaging for Dementia Patients by Diagnosis, 2010-2013

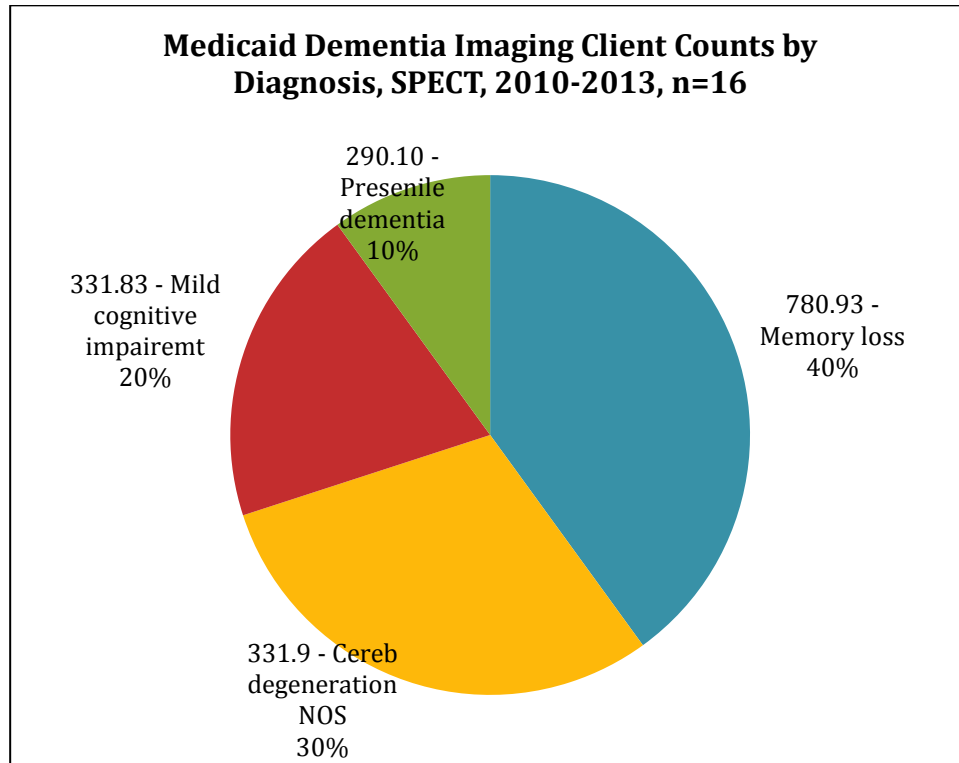


Figure 5d. Medicaid PET Imaging for Dementia Patients by Diagnosis, 2010-2013

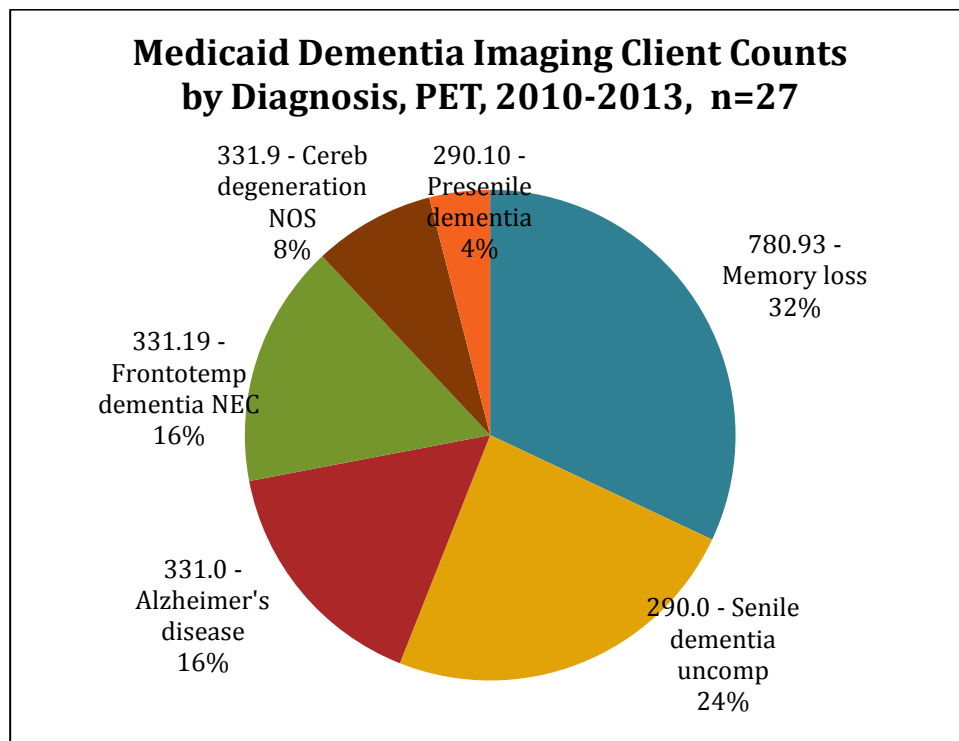
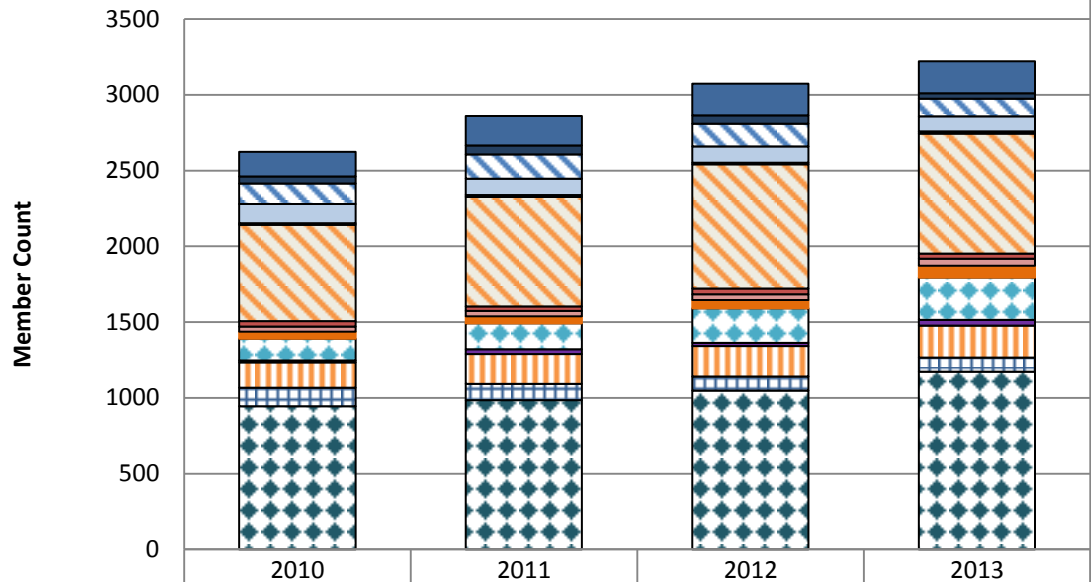


Figure 6a PEBB/UMP Dementia Patients by Diagnosis

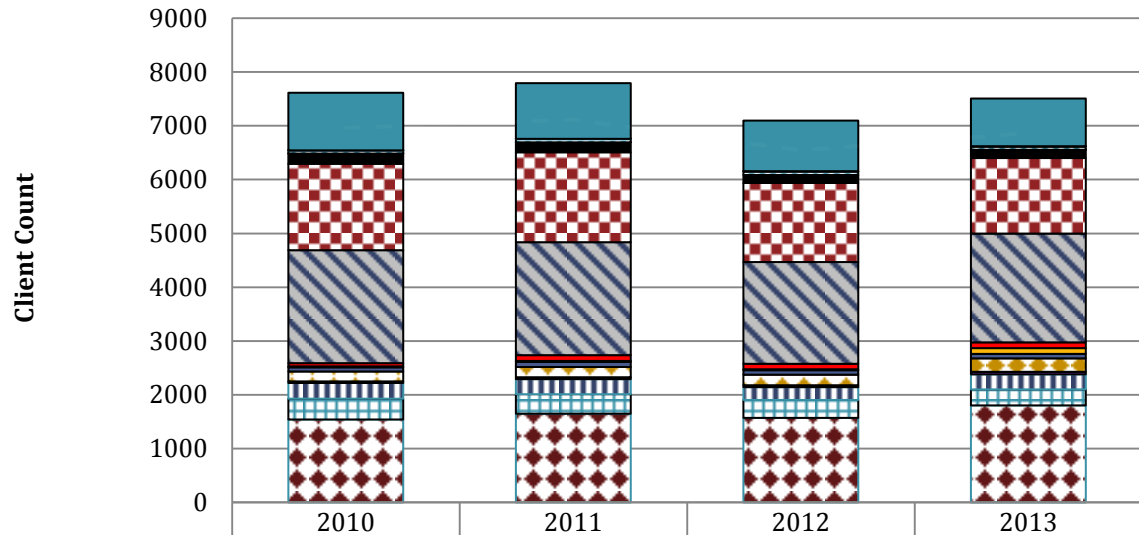
PEBB/UMP Neurocognitive Diagnoses by Year, 2010-2013



290 - SENILE DEMENTIA, UNCOMPLICATED	163	194	208	211
290.1x - PRESENILE DEMENTIA, Various	46	60	56	35
290.2x - SENILE DEMENTIA WITH DELUSIONAL FEATURES, Various	136	160	150	116
290.4 - VASCULAR DEMENTIA, Various	127	107	107	100
290.8&9 - Other Senile Psychotic Cond	11	14	11	14
331 - ALZHEIMER'S DISEASE	634	722	819	793
331.1x - PICK'S & OTHER FRONTOTEMPORAL DEMENTIA	37	30	38	34
331.2-.7 - SENILE DEGENERATION OF BRAIN, Various	34	35	38	47
331.82 - DEMENTIA WITH LEWY BODIES	45	46	55	77
331.83 - MILD COGNITIVE IMPAIREMT	145	172	228	280
331.89 - OTHER CEREBRAL DEGENERATION	12	31	22	37
331.9 - UNSPECIFIED CEREBRAL DEGENERATION	167	196	200	212
438 - LATE EF CV DIS-COGNF DEF	122	108	92	93
780.93 - MEMORY LOSS	945	985	1049	1172
Members, any dementia diagnosis	1874	2038	2224	2347

Figure 6b Medicaid FFS and Managed Care Dementia Patients by Diagnosis

Medicaid FFS and Managed Care Neurocognitive Diagnoses by Year, 2010-2013



	2010	2011	2012	2013
290 - SENILE DEMENTIA, UNCOMP	1069	1031	939	888
290.1x - PRESENILE DEMENTIA	1	1	0	0
290.2x - SENILE DEMENTIA W/DELUSION	2	3	6	1
290.3 - SENILE DELIRIUM	57	62	61	61
290.4 - VASCULAR DEMENTIA	4	1	0	2
290.8&9 - OTHER SENILE PSYCH COND	187	186	153	153
294.xx-DEMENTIA IN COND ELSEWH	1604	1671	1466	1402
331 - ALZHEIMER'S DISEASE	2103	2100	1891	2026
331.1x - PICK'S & OTHER FRONTOTEMPORAL DEMENTIA	57	104	102	103
331.2-.7 - SENILE DEGENERATION OF BRAIN, Various	21	20	20	106
331.82 - DEMENTIA W/ LEWY BODIES	73	95	79	88
331.83 - MILD COGNITIVE IMPAIREMT	188	190	200	246
331.89 - OTHER CEREBRAL DEGEN	28	36	32	50
331.9 - UNSP CEREBRAL DEGEN	292	278	243	278
438 - LATE EF CV DIS-COGNF DEF	385	363	331	298
780.93 - MEMORY LOSS	1543	1650	1571	1804
Members, any dementia diagnosis	6957	7111	6544	6866

Related Medical Codes

Code Type	Codes	Short Description	Code Chgs
Dementia Diagnosis	331.0	ALZHEIMER'S DISEASE	
	331.11	PICK'S DISEASE	
	331.19	OTHER FRONTOTEMPORAL DEMENTIA	
	331.2	SENILE DEGENERATION OF BRAIN	
	331.6	CORTICOBASAL DEGENERATION	
	331.7	CEREBRAL DEGENERATION IN DISEASES CLASSIFIED ELSEWHERE	
	331.82	DEMENTIA WITH LEWY BODIES	
	331.83	MILD COGNITIVE IMPAIRMENT	
	331.89	OTHER CEREBRAL DEGENERATION	
	331.9	UNSPECIFIED CEREBRAL DEGENERATION	
	438.0	Late effects of cardiovascular disease – Cognitive deficits	
	780.93	Memory loss (amnesia/memory loss NOS)	
	290.0- 290.9	Senile dementia	
	294.10 - 294.11	Dementia in conditions classified elsewhere	
Functional Neuroimaging CPT Codes			
	70554	FUNCTIONAL MRI,BRAIN, W/O PHYSICIAN	
	70555	FUNCTIONAL MRI,BRAIN, W/ PHYSICIAN	
	78607	SPECT imaging of brain	
	78608	PET imaging of brain	
Cognitive Assessment CPT Codes			
	96116	Neurobehavioral status testing	
	96118	Neuropsych test by psych/phys	
	96119	Neuropsych test by tech	

2. Background

2.1. Epidemiology and Burden of disease

Dementia is a condition in which mental capabilities have declined severely enough such that it interferes with the ability to function on a daily basis. Dementia severity can range from mild to severe, and symptoms may include impaired reasoning, inability to handle complex tasks, lack of judgment, decreased visuospatial abilities, impaired language capacities, and behavioral and personality changes.⁹⁷ Although dementia may occur in individuals at any age, it typically affects the elderly; the aging of the global population is a key factor in the increasing number of people with this condition.¹⁴⁵

Of all diseases associated with age, dementia is the fastest growing with an estimated 24.3 million people worldwide having been diagnosed with the condition, with 4.6 million new cases diagnosed each year.⁵⁰ It is estimated that by 2050 the prevalence will have quadrupled, so that one in 85 individuals will be living with dementia.²⁴ Although the prevalence of dementia and its associated disability increases considerably with age,^{32,150} the focus of research and of clinical care has shifted toward achieving a diagnosis in younger individuals when the cognitive decline is in the earlier stages.¹⁵¹

Patients with dementia experience serious declines in cognition, behavior, and function which can be difficult for the patient, their family, and primary caregiver.⁴⁰ Symptoms of dementia such as delusions, hallucinations, wandering, and changes in mood can be very frightening and distressing for an individual with dementia.¹⁰¹ Often, stress of patient leads to burden on caregiver and vice versa which generates a debilitating cycle.⁴⁰ Caregivers of individuals with dementia are at especially high risk for depression. More than one third (39%) of caregivers for individuals with dementia are depressed compared to 17% of non-caregivers.^{17,159} Approximately 55% of caregivers are taking care of their parents.⁵² These family members tend to show high percentages of clinical depression due to the caregiving.⁴⁶ AD patients undergo severe personality changes, which are reported to be the most difficult for familial caregivers.¹³² The most stressful time reported is the year before the individual's death when 59% of caregivers report working all hours of the day.¹⁵⁸ Caregiving for patients with dementia may also cause physical harms to the caregiver. These individuals are more likely to experience health issues induced by caregiving than other caregivers, and pay an estimated 8% more on health care than non-caregivers.¹¹

Dementias are classified in a variety of ways and are often grouped together by the aspect of brain function that is affected, or by whether or not the dementia is progressive and will worsen with time. Some dementias are transient and do not worsen, such as those caused by an adverse reaction to a medication, nutritional deficiency, infection or tumor, and may be reversible once the condition is treated. Other types of dementias are caused by neurodegeneration and are characterized by progressive deterioration in cognitive ability and capacity for independent living. These types of neurodegenerative dementias are included in this report and are described below

2.2. Dementia and Mild Cognitive Impairment

2.2.1. *Alzheimer's disease (AD)*

AD is the most common type of dementia. It accounts for approximately 60-80% of cases⁴ and has an estimated prevalence of up to 40% in those over age 80.⁴⁷ It is one of the most devastating and costly disorders affecting the aging population with a financial cost to society that has been estimated to be between \$70 and \$100 billion annually.¹⁶³

Before symptoms occur, histologic changes may be present in asymptomatic individuals, and such subclinical involvement may last for more than 10 years.^{82,139} The genotype APOE ϵ 4 and mutations to genes amyloid beta (A4) precursor protein (APP), presenilin 1 (PSEN 1), and presenilin 2 (PSEN2) have been found to contribute to the development of AD.¹⁸ The brain pathology of AD patients is characterized by neuronal loss and by abnormal aggregations of proteins, which upon autopsy appear as deposits of the beta-amyloid protein (plaques) and twisted strands of the tau protein (neurofibrillary tangles).^{75,173} Early changes seen on structural imaging include hippocampal and mesial temporal lobe atrophy, with global/generalized atrophy occurring later with disease progression. These asymptomatic histologic changes are followed by a gradual progression of symptoms; the initial symptom of which is often mild cognitive impairment, which is distinguished from dementia by the absence of functional disability.¹³⁵ When other symptoms of dementia finally do arise, the disease progresses through increasing levels of cognitive disability and gradual loss of functional independence. Symptoms of AD likely contribute to death. For example, individuals with AD experience swallowing issues which may lead to malnutrition and help to explain why AD patients are at higher risk for death due to circulatory and respiratory issues, particularly bronchopneumonia and ischemic heart disease.^{6,26}

The National Institute on Aging (NIA) and the National Institute of Neurological Disorders and Stroke – Alzheimer’s Disease and Related Disorders (NINCDS-ADRDA) are two organizations that have provided criteria widely used by clinicians to diagnose both probable and possible AD.^{44,97} A third source of diagnostic criteria commonly used in clinical practice is the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V), which outlines criteria for the diagnosis of major or mild neurocognitive disorder due to AD.⁵ Details of these common diagnostic criteria are provided in Appendix H.

2.2.2. *Dementia with Lewy Bodies (DLB)*

DLB is considered to be the second most common type of neurodegenerative dementia following AD, accounting for approximately 4-30% of dementia cases.^{181,194} However, some research has suggested that the incidence of DLB may actually be lower than previously thought, with 3.5 cases per 100,000 people per year.¹⁵⁷ The difficulty in establishing consistent epidemiological data on DLB highlights the challenges that exist in defining it as a disease entity that is distinct from other degenerative dementias, such as the closely related Parkinson’s disease dementia (PDD), which is considered to be a type of dementia with Lewy bodies.

A core feature of DLB is progressive cognitive decline, with impairment of attention, executive function, and visuospatial abilities particular evident in the early stages of the disease. Patients may also exhibit disorders in REM sleep, frequent falls, and hallucinations.⁹⁵ DLB shares pathological and clinical features with other dementia subtypes such as AD, vascular dementia and Parkinson’s disease (PD), which can make it difficult to distinguish in clinical practice. DLB is characterized pathologically by the presence of Lewy bodies, which are aggregates of α -synuclein and other proteins (e.g. ubiquitin, neurofilament protein, α B crystallin) in neurons of the cerebral cortex.^{15,129} Although most patients with DLB have high levels of amyloid plaques as do patients with AD, the presence of neurofibrillary tangles is more varied and may more directly influence the presence of AD- or DLB-like symptoms.^{55,96} Studies on the diagnostic use of structural neuroimaging to identify cortical and subcortical atrophy in patients with suspected DLB have given inconsistent results, perhaps due to the pathologic heterogeneity of DLB.¹⁷¹ Genetic factors similar to that of AD (mutations to APOE ϵ 4⁸⁸ and PSEN1⁷³) and Parkinson’s disease (mutations to α -synuclein [SNCA]^{187,195}) are also present in DLB. Additionally, the 2q35-q36 locus has been found to be a potential genetic link in DLB.²⁰

In addition to dementia, other distinctive clinical features of DLB (and often PDD) include visual hallucinations, parkinsonism, fluctuations with cognition and alertness, sleep behavior disorder, and visuospatial disturbances significant enough to interfere with daily life.^{96,110} To distinguish DLB from PDD, clinicians typically use what is referred to as ‘the one-year rule’: If the dementia begins within one year of the parkinsonism symptoms, they diagnose DLB; if the onset of dementia occurs after more than one year, PDD is diagnosed. However, this distinction between DLB and PDD on the basis of dementia onset is often considered arbitrary as the length of time that dementia precedes other symptoms has not been shown to correlate with pathologic differences.⁹³

The most commonly used criteria to diagnose DLB were developed by the DLB Consortium in 2005. For patients to receive a clinical diagnosis of DLB, they must have the central feature of dementia, as well as various other core features, suggestive features and supportive features⁹⁶ (detailed description of DLB Consortium criteria are provided in Appendix H. Other criteria used in clinical practice include criteria set forth in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V), which outlines criteria for the diagnosis of major or mild neurocognitive disorder with Lewy bodies.⁵ Criteria specific to the diagnosis of PDD were developed by the Movement Disorder Society Task Force and include diagnostic criteria for probable and possible PDD.⁴⁵ Details of these diagnostic criteria are also provided in Appendix H.

2.2.3. *Frontotemporal Dementia (FTD)*

Originally referred to as Pick’s disease, FTD refers to a group of disorders that affect areas of the brain associated with personality, language, and behavior. The prevalence of FTD has been estimated to be between 15-22 cases per 100,000 person-years and the estimated incidence is approximately 2.7-4.1 new cases per 100,000.^{83,130} FTD usually has an earlier onset than other types of dementia, often developing in the 50s and 60s.¹²⁰ Approximately 60% of all FTD cases occur in individuals aged 45-64 years.⁸³ Many individuals report a family history of FTD, however, only around 10% of FTD occurrences are inherited in a dominant manner.⁶¹ Mutations to genes tau (MAPT), chromosome 9 open reading frame 72 (C9ORF72), and progranulin (GRN) have all been found to be associated with neurodegeneration and dementia which is characteristic of FTD.⁶¹

FTD is a disease process that is associated with atrophy and neuronal loss in the frontal and temporal lobes of the brain. The neuropathological features of FTD include abnormal deposits and neuritic tangles of the tau and ubiquitin proteins, however, there is histologic heterogeneity in FTD patients.²⁹ Signs and symptoms of FTD appear gradually, and can include inappropriate behaviors, language problems, difficulties with thinking and concentration, and movement problems.¹ FTD progresses faster than AD; patients with FTD tend to lose basic skills like grooming and dressing oneself quicker and live shorter lives than patients with AD.¹⁴⁹

Although there is debate about how to classify the various syndromes that comprise the FTD disorders, FTD is often categorized into 3 subgroups: (1) Behavioral variant (bvFTD), (2) semantic dementia (SD), and (3) progressive nonfluent aphasia. The behavioral variant is the most common type of FTD, representing approximately 60% of all FTD cases.⁷⁸ This variant is characterized by its negative impact on social skills, self-awareness and personal conduct. Some behaviors that individuals with bvFTD may exhibit are a lack of inhibition or judgment, neglect of personal hygiene, and apathy. Semantic dementia is a second form of FTD that is caused by damage to the left temporal lobe and is characterized by difficulty remembering the meaning of words. In other cases of SD, individuals have damage to the right temporal lobe, which results in difficulties matching names to faces and understanding emotion. Eventually the degeneration occurs in both lobes, and patients have symptoms affecting both language

and social skills. The third subgroup of FTD, progressive nonfluent aphasia, is also characterized by difficulty with language, however, patients with this type of FTD do not have trouble with the meaning of words, but rather they lose the ability to communicate effectively. Often patients with progressive nonfluent aphasia speak slowly and lose their ability to pronounce words, and may eventually lose their ability to speak altogether. This type of FTD is also associated with motor symptoms such as stiffness of the limbs and muscle weakness.

The diagnostic criteria most commonly used for the clinical diagnosis of FTD are outlined by the Lund and Manchester groups and include both core diagnostic features and supportive diagnostic features.¹ Core features include behavioral disorder, affective symptoms, speech disorder, and preserved spatial orientation.. A second source of commonly used diagnostic criteria for FTD is the DSM-V, which includes criteria for major or mild frontotemporal neurocognitive disorder.⁵ Full details of these diagnostic criteria are provided in Appendix H.

2.2.4. *Mild Cognitive Impairment (MCI)*

MCI is not considered a type of dementia because it does not interfere with a person's functional independence. Instead, it is a term that has been used to describe a condition that may or may not eventually lead to dementia, and as a result the diagnosis of MCI is a difficult and controversial one.¹⁵⁶ It is estimated that 10-20% of people over the age of 65 have MCI,^{4,137} and although a clinical diagnosis of MCI is not a necessary as a precursor to dementia, it is a major risk factor for later progression, with an estimated 12% of MCI patients developing AD each year.¹³⁸ Various systematic reviews reported differences in annual conversion rates (ACRs) for MCI or aMCI patients progressing to AD or dementia ranging from 10.2% to 33.6% in studies with over one year of follow-up,¹⁸⁵ and 7% in studies of over three years of follow-up,¹⁰⁶ and 4.2% in studies with follow-up of five years or longer¹⁰⁵ indicating the risk for conversion lessens over time. These studies also indicate a difference in conversion rates depending on if studies used clinic or community samples.^{105,106,185}

MCI consists of a heterogeneous pathology, and MCI due to AD, also referred to as prodromal AD, is thought to be a transitional stage between aging and AD.⁷² The neuropathology of MCI is not well established and does not appear to follow a linear course, but MCI is thought to have a lesser degree of pathology similar to AD and other dementias.¹¹¹ MCI also has similar genetic markers to AD such as the APOE ε4 genotype which may help to predict progression of MCI into AD.¹³⁸ Clinically, patients with MCI differ from patients with other forms of dementia in that cognitive deficits are restricted to memory alone and patients maintain their ability to function independently.⁷⁵ Common symptoms of MCI include frequently losing items, forgetting events, and difficulty following conversations. These symptoms may remain unchanged for years, may progress to AD, or in rare instances, may even improve.

2.3. Treatment Options

Alzheimer's disease (AD)

There are currently no pharmacologic or nonpharmacologic treatments that can reverse or stop the biological progression of AD, however, acetylcholinesterase inhibitors as well as N-methyl D-aspartate (NMDA) antagonists may improve cognitive symptoms and therefore can improve quality of life while decreasing caregiver burden.^{58,148} Common side effects of acetylcholinesterase inhibitors include nausea, vomiting, diarrhea, insomnia, muscle cramps, and fatigue.¹¹⁷ NMDA antagonists often cause constipation, dizziness, somnolence, hypertension, instability, and headache.^{116,117} Combinations of

acetylcholinesterase inhibitors and NMDA antagonists show promise in short-term symptom reduction for patients with AD, but still pose risks for adverse events like headache and confusion.¹⁷⁰ Non-pharmacological therapies such as memory training and physical exercise have been suggested for increasing quality of life and reducing anxiety and depression.²⁸ Many therapies aimed at slowing or halting the progression of AD are currently being researched, and the effectiveness of these treatments varies across populations.

Dementia with Lewy Bodies (DLB)

Treatment of DLB is primarily symptomatic and aimed at managing specific manifestations of the disease. Cholinesterase inhibitors have been shown to improve cognitive and neuropsychiatric symptoms and to be generally well tolerated by most patients,⁹³ however, clinical improvement may be more pronounced in patients with PDD rather than DLB.^{93,152} Patients with DLB who also experience psychotic symptoms are often more difficult to treat, as antipsychotics tend to exacerbate motor functioning and increase risk of mortality or stroke.^{92,118} Rivastigmine, an acetylcholinesterase inhibitor, has been suggested for patients with DLB because it may help lessen psychotic symptoms without worsening motor symptoms.¹¹⁴ Side effects such as nausea, weight loss, tiredness, and vomiting have been observed in patients with DLB treated with rivastigmine.¹¹⁴ Behavioral strategies targeted to treat environmental stressors may also be used, as well as physical therapy and/or mobility aids to manage parkinsonism symptoms.

Frontotemporal Dementia (FTD)

There are currently no treatments that can slow or halt the progression of FTD, however, research into the condition is expanding and clinicians are gaining a better understanding of the various FTD disorders. Selective serotonin reuptake inhibitors (SSRIs) have been recommended for reduction of behavioral symptoms and care-giver burden, but have not been seen to help cognitive symptoms.¹²⁶ Acetylcholinesterase inhibitors and NMDA antagonists are not recommended as treatment for FTD because they have not been shown to improve symptoms.¹¹⁸ Current treatment is focused on managing a patient's symptoms through the use of speech and language pathologists, physical therapists, neuropsychologists, nurses and social workers.

Mild Cognitive Impairment (MCI)

There are no pharmacological treatments currently available to treat the condition of MCI; however, due to the high rate of conversion to AD, this is an active area of research. It has been suggested that donepezil, an acetylcholinesterase inhibitor, reduces the rate of conversion of MCI to AD; however, these effects are only present short term (up to 36 months).¹⁴⁸ Otherwise, there is evidence that cholinesterase inhibitors do not help in symptom reduction for patients with MCI.¹²⁶ Some changes to lifestyle may slow or reverse the progression of the disease, such as improvements in exercise, diet and cardiovascular health. Referral for extensive neuropsychologic testing, with follow-up intervals of six to nine months, is suggested for patients with mild or borderline cognitive deficits.¹³⁸

2.4. Diagnosis of Dementia and Mild Cognitive Impairment

Dementia is currently a provisional diagnosis based on persistent and significant impairments of intellectual function identified during a clinical workup. To obtain a definite diagnosis of a specific type of dementia, histopathologic confirmation is required, however, this "gold standard" diagnosis is only available post-mortem and is therefore not helpful in the clinical situation.

Having an early and accurate diagnosis of the type of dementia from which an individual is suffering is important not only for management of the patient's symptoms, but also to allow provision of appropriate information to families and caregivers so that they know what to expect with regard to the course of the disease. Because different types of dementia often share common clinical, neuropsychological, and pathological characteristics, differentiating between the types of dementia can be challenging in clinical practice.¹⁶⁵ Although the clinical presentation may vary from patient to patient depending on the etiology of the dementia, the diagnostic features are usually constant.

In order to establish the presence of dementia and to differentiate between the different sub-types, standard diagnostic criteria are used. There are various clinical criteria used in the diagnosis of dementia; however, there is no single reliable test. The most common diagnostic criteria are listed in Table 2 below, and full diagnostic criteria are provided in Appendix H.

There is no available diagnostic test for mild cognitive impairment (MCI); instead, evaluation of patient history and cognitive abilities may help clinicians come to a diagnostic consensus. MCI is considered to be the beginning stage of AD but often times other factors may be the cause of MCI. For this reason, it is important to determine what the cause of MCI is as it may be produced by issues that are not Alzheimer's related such as trauma or drug abuse. Further evaluation of cognition may show decline or problem areas within the individual that also help to diagnose MCI due to AD. Appendix H contains the complete diagnostic criteria.

Table 2. Commonly used diagnostic criteria

Disease classification	Diagnostic Criteria
Dementia	<ul style="list-style-type: none"> National Institute on Aging (NIA) & Alzheimer's Association workgroups (2011)⁹⁷: All-cause dementia DSM-V¹³: major neurocognitive disorder
Alzheimer's disease	<ul style="list-style-type: none"> National Institute of Neurological Disorders and Stroke – Alzheimer's Disease and Related Disorders (2007) (NINCDS-ADRDA)⁴⁴: probable AD and definite AD National Institute on Aging (NIA) & Alzheimer's Association workgroups (2011)⁹⁷: probable AD and possible AD DSM-V¹³: major or mild neurocognitive disorder due to AD
Frontotemporal dementia	<ul style="list-style-type: none"> Lund-Manchester Criteria (1994)²⁵ DSM-V¹³: major or mild frontotemporal neurocognitive disorder
Dementia with Lewy bodies	<ul style="list-style-type: none"> DLB Consortium (2006)⁹⁵ DSM-V¹³: major or mild neurocognitive disorder with Lewy bodies Movement Disorder Society Task Force: probable and possible PDD
Mild cognitive Impairment	<ul style="list-style-type: none"> National Institute on Aging (NIA) & Alzheimer's Association workgroups (2011)¹⁰: MCI due to AD

Patients presenting with symptoms of dementia typically undergo an initial evaluation in the primary care setting, which may consist of a thorough history, detailed cognitive testing and neurological examination. This work-up is likely to be more thorough in patients referred to neurological or dementia specialists than it is in the primary care setting, however. Most clinical practice guidelines recommend that patients meeting the clinical criteria for dementia undergo at least one structural neuroimaging exam (computed tomography (CT) scan or magnetic resonance imaging (MRI) scan) and laboratory

testing to rule out any reversible causes of dementia, such as a vitamin deficiency or tumor. Structural neuroimaging may also aid in the differential diagnosis of the specific subtype of dementia based on patterns of atrophy in the brain. Most often a diagnosis can be made following this initial workup; however, if following the initial clinical assessment the diagnosis remains unclear, patients may be referred for additional testing with functional neuroimaging.

2.5. Technology: Functional Neuroimaging

Despite the development of consensus diagnostic criteria, many cases of dementia are missed.¹⁶⁵ When this happens, the use of other diagnostic strategies such as functional neuroimaging may be helpful in confirming a diagnosis of dementia. Functional neuroimaging is viewed as an add-on diagnostic test that is done if results from the clinical workup and structural neuroimaging exam are inconclusive. In contrast to structural neuroimaging, which provides information on structural changes in the brain that may cause dementia symptoms, functional neuroimaging can provide information on how the brain is functioning. Functional neuroimaging can 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.

Functional neuroimaging involves the injection of radiolabeled ligands, which are then detected by a scanner. Types of functional neuroimaging included in this report and summarized below are: positron emission tomography (PET), single-photon emission computed tomography (SPECT) (including DaTscan), functional MRI (fMRI), and arterial spin labeling (ASL).

2.5.1. Types of Functional Neuroimaging

Positron Emission Tomography (PET)

The detection of regional glucose metabolism with the ¹⁸F-FDG radiopharmaceutical is considered by some to be the most widely available and useful biomarker for dementia diagnosis.⁷² However, because this type of functional neuroimaging does not detect other pathological abnormalities that can cause dementia (e.g. the presence of a hematoma, vascular dementia, or a brain tumor), imaging with FDG-PET occurs after an initial exam with structural neuroimaging, such as an MRI or CT scan.

PET is a diagnostic imaging test that uses a positron-emitting radionuclide and a scanner to produce images of the brain (or other part of the body being studied). In PET for dementia diagnosis, the radioactive particle most commonly used is ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG), which is incorporated into the ¹⁸FDG molecule. When this radioactive tracer is injected into the patient's bloodstream, it competes with glucose for absorption and metabolism in a variety of cell types, including neurons, allowing it to serve as a marker for glucose metabolism.⁶⁶ FDG-PET scans demonstrating hypometabolism in specific regions can be indicative of specific types of neurodegenerative dementia.

According to the European Federation of the Neurological Societies (EFNS) 2012 guidelines on the use of neuroimaging in the diagnosis of dementia⁵¹:

- The following metabolic phenotype is distinctive of AD: “the overall regional pattern of metabolic impairment of the posterior cingulate/precuneus and lateral temporoparietal

cortices [that is] more accentuated than frontal cortex deficits, together with the relative preservation of the primary sensorimotor and visual cortices, basal ganglia and cerebellum.”

- In MCI patients, the AD-distinctive pattern is “predictive of conversion to AD within a few years.”
- AD and FTD have distinct metabolic phenotypes: in contrast to the AD-distinctive pattern described above, “a disproportionate reduction in frontal metabolism” is more commonly found in FTD.
- AD and DLB may not be adequately distinguishable with FDG-PET: although occipital hypometabolism may be more common with DLB versus AD, these diseases often appear identical on individual scans. Because occipital hypometabolism is not specific for DLB and can also occur in AD patients, FDG-PET is not recommended to differentiate between these diseases.
- Finally, dementia patients with normal FDG-PET scans are less likely to have a neurodegenerative diagnosis.

Further, the 2007 NINCDS-ADRA criteria for the diagnosis of AD considers “reduced glucose metabolism in bilateral temporal parietal regions” to be a supportive feature of probable AD (at least one supportive feature is required for a diagnosis of probable AD).⁴⁴

After scanning, images must be processed, reconstructed, and displayed; a number of methods and software programs are available to do this. More recent software allows for three-dimensional display of reconstructed images. Hypometabolism signals may be referenced against different regions of the brain or against a database of normal healthy controls. Interpretation of FDG-PET images can be done either visually, often using transverse images and with reference to structural images, or in an automated manner, which calculates hypometabolism in specific regions of interest compared to a reference standard. In the latter method, various thresholds may be used to determine whether regional hypometabolism is clinically significant.¹⁸⁶

Single Photon Emission Computed Tomography (SPECT)

SPECT is another type of neuroimaging that is used to investigate changes in the function and molecular composition in the brains of patients with suspected neurodegenerative dementia.

SPECT is a technique that employs a radioactive tracer, which remains in the bloodstream and allows the visualization of blood flow to tissues and organs. In the case of dementia, SPECT is used to evaluate regional brain perfusion, and because cerebral blood flow correlates with brain metabolism, the images provide information regarding which regions of the brain are affected, which in turn aids with differential diagnosis. SPECT has a lower spatial resolution than FDG-PET; as with PET neuroimaging, patients with milder symptoms of dementia are less likely to have abnormal results.⁹⁰

A technetium-based lipid soluble radionuclide, such as hexamethylpropylene amine oxime (HMPAO) is injected intravenously and crosses the blood brain barrier in proportion to cerebral blood flow.¹²² Once in the brain, the radioactive tracer undergoes a transformation that fixes it for several hours until the imaging can be performed; therefore HMPAO SPECT provides a ‘snapshot’ of cerebral blood flow shortly after the ligand is injected into the patient’s bloodstream. Emission data are then collected using a rotating gamma camera and a perfusion image is generated, which then may be evaluated semi-quantitatively by regions of interest (ROIs). Relative regional cerebral blood flow (rCBF) may be calculated for each ROI based on mean counts compared to a reference area such as the cerebellum which may aid in the differential diagnosis of AD dementia.¹⁴³

According to the EFNS 2012 guidelines on the use of neuroimaging in the diagnosis of dementia⁵¹:

- AD and FTD have distinct phenotypes: while “posterior temporal and parietal brain hypoperfusion... is predictive of a pathological diagnosis of AD”, “a disproportionate reduction in frontal perfusion” is more commonly found in FTD.

SPECT may also be used to measure dopaminergic nigrostriatal denervation, which occurs in patients with DLB, using the radiolabeled dopamine transporter ligand ¹²³I-FP-CIT (2β-carbomethoxy-3β-(4-iodophenyl)-B- (3-fluoropropyl) nortropine), which is injected intravenously. ¹²³I-FP-CIT-SPECT is also known as DaTscan and Dat-SPECT. DaTscan has been available in Europe since 2000 where it is indicated to help differentiate probable dementia with Lewy bodies (DLB) from Alzheimer's disease. Briefly, the ligand ¹²³I-FP-CIT is an analogue of the ligand for the dopaminergic presynaptic transporter (DAT). Because DAT loss is a consequence of the nigrostriatal degeneration that occurs with DLB (but not AD), ¹²³I-FP-CIT-SPECT can be used to distinguish DLB from AD.

According to the EFNS 2012 guidelines on the use of neuroimaging in the diagnosis of dementia⁵¹:

- AD versus DLB: “Dopaminergic SPECT is useful to distinguish DLB from AD, especially when there are no clear extrapyramidal symptoms and signs. However, a negative ¹²³I-FP-CIT scan does not necessarily exclude a diagnosis of probable DLB, as around 20% of individuals with probable DLB appear to have normal scans.”

SPECT images are processed much in the same way as described for FDG-PET (see above).^{38,79}

Functional Magnetic Resonance Imaging (fMRI)

fMRI measures the changes in concentration of deoxyhemoglobin within active areas of the brain.³¹ As a neuron becomes active, blood flow and oxyhemoglobin supply increases in this stimulated area. When the supply of oxygen surpasses the active neurons' needs, the venous concentration of deoxyhemoglobin decreases and is detected by the fMRI.^{31,37,153} Functional MRI may be completed passively or actively (ie. with or without active stimulation) to help determine the cognitive ability of the individual.^{37,153} The lack of harmful radiation allows multiple fMRI images to be taken over time, and thus, changes within the brain may be tracked more frequently and accurately.¹⁵³

Generally a structural MRI is completed prior to a functional MRI to direct the fMRI based on any identified structural issues.^{31,37,153} Individuals with AD usually experience damage to the medial temporal lobe, which may be imaged. Additionally, reduced functional activity of the default mode network (bilateral parietal cortex, precuneus and posterior cingulate cortex, anterior cingulate cortex, medial prefrontal cortex, hippocampus, and thalamus) has been shown to aid in distinguishing healthy individuals from those with AD^{8,19,62} or MCI.⁷⁶ The default mode network¹⁴² and the posteromedial cortex¹⁴¹ have both been found to help predict progression of MCI to AD. However, fMRI is unable to distinguish if reduced functional activity is due to AD or another issue within the individual. The European Federation of the Neurological Societies (EFNS) 2012 guidelines on the use of neuroimaging in the diagnosis of dementia⁵¹ discuss functional MRI under a section on “future tools” and recommend that “at present, [it] does not have a role in the diagnosis or routine assessment or monitoring of neurodegenerative dementia. [Further,] the reliability and reproducibility of advanced MRI techniques requires further evaluation...”

Arterial Spin Labeling (ASL)

MRI with ASL uses electromagnetically labeled arterial water as a tracer for measuring perfusion within the brain.³⁵ A radiofrequency (RF) pulse is applied and magnetizes the blood water. The magnetized

blood water moves to the target area which in turn alters the magnetization of the tissue.³⁵ The change in tissue magnetization generates an MR signal and thus, an image of brain activation. A second image must be taken as a comparison using control labeling which generally is an image lacking tracer. These two images are then subtracted from one another to create a map of cerebral blood flow.¹⁸⁸ Two types of ASL are used: continuous (CASL) and pulsed (PASL). CASL generates a higher perfusion contrast by continuously labeling arterial blood water through a labeling plane;¹⁸⁴ this allows the same area to be imaged for several seconds at a time.¹⁸⁸ PASL sends short and rapid radiofrequency pulses rather than a singular long pulse.¹⁸⁸

Common blood flow changes in AD patients include decreased flow in the precuneus and posterior cingulate gyrus, lateral parietal cortex, left middle temporal cortex, and inferior temporal cortex.^{12,33,71} AD patients also showed increased blood flow in areas of the frontal lobe.^{12,33,71} In MCI patients, changes are observed in the posterior cingulate, which is in agreement with PET findings.¹² Increased blood flow to left hippocampus, right amygdala, and rostral head of the right caudate nucleus has been observed in MCI patients, in addition to decreased blood flow in the posterior cingulate gyrus.³³ ASL imaging of FTLD has shown decreased blood flow to areas the frontal lobe and increased blood flow to the posterior cingulate and medial parietal/ precuneus areas.⁷¹ Discriminating between healthy individuals and different types of dementia are still difficult for ASL neuroimaging and require more testing to generate better reference standards.

The European Federation of the Neurological Societies (EFNS) 2012 guidelines on the use of neuroimaging in the diagnosis of dementia⁵¹ have the same recommendations for arterial spin labeling as they do for functional MRI (above).

2.6. Reference Standards

Gold Standard: Histopathological Confirmation

The clinical criteria that define AD and other dementias are not the ideal gold standard because the clinical diagnosis does not always conform to the pathological diagnosis. The perfect gold standard for the definitive diagnosis of specific types of dementia is the histopathological examination of brain tissue at autopsy.

Research on diagnostic neuroimaging has usually been validated against clinical diagnosis. It is believed that this may introduce difficulty into the interpretation of the comparison, since there may be a variable error associated with a subjective clinical diagnosis.¹⁸⁹ Studies have shown that the diagnostic accuracy of a diagnosis made from a standard clinical work-up compared to that based on the gold standard of autopsy is highly variable:

- **AD:** 78-97% sensitivity,^{59,77,81,123,160,166} 20-100% specificity^{81,123,166}
- **DLB:** 12-100% sensitivity,^{49,56,59,69,102,123,128,166,183,187} 79-100% specificity^{49,56,102,123,128,166,183,187}
- **FTD:** 62-100% sensitivity, 82-97% specificity (with higher values in more recent studies)^{54,64,166}

Because clinical diagnosis is not as accurate as histopathological diagnosis, the latter was chosen to be the main comparator for the purposes of this health technology assessment, with the knowledge that there are likely to be less studies with fewer patients available than would be for studies that use clinical diagnosis as the reference standard.

2.7. Potential Complications/Harms of Functional Neuroimaging

Both PET and SPECT involve injection of radiolabeled tracers into the bloodstream. Radiation doses range between various nuclear imaging modalities and procedures. For the neuroimaging modalities of interest, administered doses are typically around 740 MBq¹⁰³ (and recommended doses range from 111-1110 MBq)^{38,79,186} with effective doses reported to range from 5.7 – 25 mSv.^{103,147} In contrast, a head CT is associated with an average effective dose of 2 mSv and a chest CT has a mean effective dose of 7 mSv,^{103,147} while the average effective dose per year for people living at sea level is 3 mSv.^{147,179} Note that all effective doses vary depending on the size of the patient and the size of the body part being imaged.¹⁷⁹ The FDA estimates that an amount of 10 mSv increases the risk of death from cancer by 1 in 2000, and states that “for any one person the risk of radiation-induced cancer is much smaller than the natural risk of cancer” but notes that “this small increase in radiation-associated cancer risk for an individual can become a public health concern if large numbers of the population undergo increased numbers of CT screening procedures of uncertain benefit.”¹⁷⁹ The FDA has developed an initiative to reduce the risk of radiation exposure and maximize the benefit of nuclear imaging, and states that the imaging procedure should be considered to do more good than harm for the patient, the test should only be performed when considered medically necessary, and that doses should be optimized so that the patient is exposed to the lowest radiation dose necessary.¹⁸⁰

Administered doses of ¹⁸F-FDG range from 185 – 740 MBq, with doses at/near the upper end of this range being more common than lower doses. The resulting effective dose ranges from 3.5 – 14.1 mSv.^{103,186} Because any ¹⁸F-FDG not used in glucose metabolism is excreted through the urine,¹⁷⁶ the urinary bladder receiving the highest dose.¹⁰³ Cardiac tissues are cleared of the tracer at least 96 hours after injection, whereas non-cardiac tissues are cleared between three and twenty-four hours after injection.¹⁷⁶ Adverse events resulting from ¹⁸F-FDG administration are minimal, with many studies reporting no events. One small subset of 42 patients who underwent FDG-PET for epilepsy reported transient hypotension, hypo- or hyperglycemia, or transient increases in alkaline phosphatase.¹⁷⁶ Other reported adverse reactions to ¹⁸F-FDG have included allergic reaction, erythema/ flushing, hypertension, tachycardia, and diaphoresis.¹⁶¹ One systematic review of FDG-PET for imaging dementia patients reported that “no safety issues have been raised in the multitude of papers that have studied the application of ¹⁸F-FDG-PET in AD, AD-related dementias, or other neurodegenerative disorders...”²¹

Administered doses of Tc-99m HMPAO range from 555 – 1110 MBq, with resulting effective doses ranging from 5.2 – 10.3 mSv.^{79,103} The Society for Nuclear Medicine reports that the kidneys receive the highest radiation dose,⁷⁹ while FDA found the lachrymal glands, gallbladder wall, and kidney (0.13 rad/mCi) to have the highest absorbed radiation doses.¹⁷⁸ Adverse events stemming from Tc-99m HMPAO have been reported to include fever, nausea, erythema/ flushing, rash, hypertension, hypotension, respiratory reaction, seizure, diaphoresis, cyanosis, anaphylaxis, facial swelling, and abdominal pain.¹⁶¹

The recommended administered dosage of ¹²³I-iodoflupane is 111 – 185 MBq, with an effective dose of 2.3 – 4.4 mSv.^{38,177} DaTscan has been associated with headache, vertigo, dry mouth, nausea, and dizziness of mild to moderate severity.¹⁷⁷ The highest observed levels of absorbed radiation reported by the FDA were in the bladder wall, lungs, lower large intestine, and the upper large intestine.¹⁷⁷

Functional MRI utilizes a powerful magnetic field, so the most serious incidents are related to presence of metal in the testing area. These events may be easily avoided through attentive behavior of the technician and thorough prior screening for metal implants/ devices within the patient. Vertigo,

tiredness, disorientation, slight nausea, or tingling sensations have been experienced during or after an fMRI scan.¹⁶⁹ Feelings of claustrophobia and anxiety may be experienced while undergoing an fMRI screening due to the shape and size of the machine, but they do not pose any threat to safety of the individual.

ASL is generally considered safe. It uses water molecules as a tracer, so no injection of foreign material is necessary. The lack of injected radiotracer also means that ASL can be completed multiple times without the risk of accumulating radiation or other potentially harmful substances. Arterial-spin labeling is completed using MRI, thus similar safety risks apply (i.e., confined imaging space, adverse events in those with metal implants).

2.8. FDA-Approved Functional Neuroimaging Ligands

Of the functional neuroimaging modalities included in this report, three have received FDA approval for general use in clinical areas other than dementia; none have received FDA approval for explicit use in the diagnosis of dementia. 18F-FDG was approved in 2004 for assessment of abnormal glucose metabolism to assist in the evaluation of malignancy and epileptic seizures. Ceretec (^{99m}Techetium HMPAO) was approved in 2005 for use as an adjunct in the detection of altered cerebral perfusion in stroke or as an adjunct in the localization of intra-abdominal infection and inflammatory bowel disease. DaTscan (¹²³I-Ioflupane) is a radiopharmaceutical agent that was approved in 2011 to help differentiate essential tremor from tremor due to Parkinsonian syndromes. Additional details regarding FDA approval can be found in Appendix I.

2.9. Clinical Guidelines

The National Guideline Clearinghouse (NGC), major bibliographic databases, professional societies, and Medline were searched for guidelines related to functional neuroimaging for the diagnosis of dementia. Key word searches were performed: “functional neuroimaging” OR “functional imaging” OR “PET” OR “positron emission tomography” OR “Positron-Emission Tomography” OR “SPECT” OR (Single AND Photon AND Emission AND Computed AND Tomography) OR “Tomography, Emission-Computed, Single-Photon” OR “fMRI” OR “functional MRI” OR “functional magnetic resonance imaging.” Sixteen documents were recovered that contained specific recommendations regarding this topic.

Guidelines from the following sources are summarized:

- European Federation of the Neurological Societies
- The National Institute on Aging, Alzheimer’s Association
- Canadian Consensus Conference on Diagnosis and Treatment of Dementia (imaging group)
- National Guideline Clearinghouse

In addition, one guideline was identified during the literature search and was included, and one statement was identified from the “Choosing Wisely” campaign and is noted below.

A brief synopsis of each guideline is included below. Details of each included recommendation for functional neuroimaging, including the class/grade of recommendation and the level of evidence, can be found in Table 3 that follows.

The Society of Nuclear Medicine, 2012³⁸: *SNM Practice Guideline for Dopamine Transporter Imaging with ¹²³I-ioflupane SPECT 1.0*. DaT-SPECT is recommended for differentiating between dementia with Lewy Bodies or Alzheimer's disease.

European Federation of the Neurological Societies, 2012⁵¹: *EFNS task force: the use of neuroimaging in the diagnosis of dementia*. Routine functional neuroimaging may not be beneficial in typical cases of dementia, but are recommended in cases where the diagnosis remains in doubt after clinical and structural imaging. Functional neuroimaging may help to differential different kinds of dementia from other pathologies.

The National Institute on Aging, Alzheimer's Association, 2011⁹⁷: *The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease*. Biomarker evidence from FDG-PET imaging are not recommended for the diagnosis of AD.

The National Institute on Aging, Alzheimer's Association, 2011⁹: *The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease*. The definitive absence of evidence of neuronal injury (FDG-PET) strongly suggests that the MCI syndrome is not due to AD.

Clinical Research Center for Dementia of South Korea, 2011¹¹³: *Clinical Practice Guideline for Dementia; Part I: Diagnosis and Evaluation*. Functional imaging is not recommended as the only imaging measure, but may be useful in cases where diagnostic uncertainty remains after other work up.

National Institute for Health and Clinical Excellence, Social Care Institute for Excellence, 2007¹⁴: *A NICE-SCIE Guideline on supporting people with dementia and their caregivers in health and social care*. Functional neuroimaging is recommended for use in differentiating different types of dementia, if the diagnosis is in doubt.

American College of Radiology, 2010¹¹²: *ACR Appropriateness Criteria dementia and movement disorders*. FDG-PET and HMPAO SPECT may be appropriate in cases of probable and possible Alzheimer's disease, suspected frontotemporal dementia and suspected vascular dementia (or mixed VAD and AD), for "problem solving." fMRI is usually not appropriate.

Scottish Intercollegiate Guidelines Network, 2006¹¹⁹: *Management of patients with dementia. A national clinical guideline*. SPECT may be used with CT to aid in the differential diagnosis of dementia, when in doubt.

Regional Health Council (Italy), 2011¹¹⁵: *Dementia. Diagnosis and Treatment*. PET and SPECT should not be routinely used in assessing dementia.

European Federation of Neurological Societies, 2010⁷⁰: *EFNS guidelines for the diagnosis and management of Alzheimer's disease*. FDG-PET and SPECT are recommended adjuncts when the diagnosis remains in doubt. Dopaminergic SPECT is useful to differentiate AD from DLB. EEG is recommended in differential diagnosis of atypical clinical presentations of AD.

European Federation of Neurological Societies, 2012¹⁶⁷: *EFNS guidelines on the diagnosis and management of disorders associated with dementia.* SPECT is recommended for distinguishing DLB and AD dementias. SPECT and PET techniques are useful in FTLD diagnosis.

Diagnostic Pathway Expert Reference Group, 2013¹²⁵: *Guidance on the use of neuroimaging in the assessment of dementia in Primary Care (NHS-England).* FDG-PET, HMPAO-SPECT and DaTscans can assist in the diagnosis of dementia, but due to the cost of these interventions they recommended reserving their use in a specialist memory assessment service.

Canadian Consensus Conference on Diagnosis and Treatment of Dementia (imaging group), 2013¹⁶⁸: *Clinical applications of neuroimaging in patients with Alzheimer's disease: a review from the Fourth CCCDTD 2012.* FDG-PET is recommended for differential diagnosis purposes; SPECT rCBF if an FDG-PET scan is not available. There was inadequate consensus on imaging for the use of a functional imaging modality in patients with MCI.

Canadian Consensus Conference on Diagnosis and Treatment of Dementia (imaging group), 2013²⁷: *Role of emerging neuroimaging modalities in patients with cognitive impairment: a review from the CCCDTD 2012.* fMRI is not recommended for the clinical investigation of patients presenting with cognitive impairment.

Dementia with Lewy bodies Consortium, 2005²²: *Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium.* SPECT and PET imaging is recommended, based on their suggestive and supportive features towards DLB diagnosis. DAT scanning is useful to distinguish DLB and AD disorders.

"Choosing Wisely" statement from The Society of Nuclear Medicine and Molecular Imaging, 2013³⁰: *Five things physicians and patients should question:* Don't use PET imaging in the evaluation of patients with dementia unless the patient has been assessed by a specialist in this field. Without objective evidence of dementia, the potential benefit of PET is unlikely to justify the cost or radiation risk. Dementia subtypes have overlapping patterns in PET imaging. Clinical evaluation and imaging often provide additive information and should be assessed together to make a reliable diagnosis and plan care.

Table 3. Clinical Guidelines

Organization(S) Title (Year)	Search Dates	Functional Neuroimaging; Diagnosis Evaluated	Evidence Base Available	Recommendations	Class/ Grade Of Recommendation	Level Of Evidence
The Society of Nuclear Medicine (SNM) <i>SNM Practice Guideline for Dopamine Transporter Imaging with ¹²³I-ioflupane SPECT 1.0 (2012)³⁸</i>	No systematic literature search performed	¹²³ I-ioflupane SPECT Diagnoses included: DLB, AD	NR	¹²³ I-ioflupane SPECT can be used to help differentiate between DLB and AD. <ul style="list-style-type: none">AD exhibits normal to mildly diminished striatal bindingDLB exhibits significantly decreased striatal binding	NR	NR
European Federation of the Neurological Societies (EFNS) <i>EFNS task force: the use of neuroimaging in the diagnosis of dementia (2012)⁵¹</i>	Through April 2012	Functional neuroimaging (SPECT, PET) Diagnoses included: Alzheimer's disease (AD), vascular brain diseases, dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), primary progressive aphasia (PPA)	Articles published in English (including but not limited to meta-analyses, systematic reviews, and evidence-based management guidelines).	Consensus recommendations were given and graded according to the EFNS guidance regulations. "Good practice points" were stated as opinion when there was lack of evidence but consensus amongst experts was reached. Recommendations for functional imaging: <ol style="list-style-type: none">Although typical cases of dementia may not benefit from routine SPECT or PET imaging, these tools are recommended in those cases where diagnosis remains in doubt after clinical and structural MRI work-up and in particular clinical settings.Functional imaging can be of value to diagnose (or exclude) a neurodegenerative dementia in those subjects with cognitive impairment presenting with severe psychiatric disturbances (including depression and agitation) and in	NR* Good practice point	class II, level A* NR

Organization(S) Title (Year)	Search Dates	Functional Neuroimaging; Diagnosis Evaluated	Evidence Base Available	Recommendations	Class/ Grade Of Recommendation	Level Of Evidence
				cases where proper cognitive testing is difficult, that is, with no language in common with the patient.		
				3. Normal FDG PET scan findings, in the presence of the suspicion of dementia, make a neurodegenerative diagnosis less likely.	NR	class II, level A
				4. The overall regional pattern of metabolic impairment of the posterior cingulate/precuneus and lateral temporoparietal cortices, more accentuated than frontal cortex deficits, together with the relative preservation of the primary sensorimotor and visual cortices, basal ganglia and cerebellum defines the distinct metabolic phenotype of AD.	NR	class II, level A
				5. AD-like metabolic patterns in patients with MCI are predictive of conversion to AD within several years.	NR	class II, level A
				6. Occipital hypometabolism, particularly in the primary visual cortex, may be more common in DLB than AD on a group basis. However, on individual scans, the appearance of DLB and AD can be identical. Moreover, occipital hypometabolism is not a specific marker for DLB and can be associated with AD.	NR Good practice point	class II, level B NR
				7. Although an overlap of functional abnormalities between FTD and AD has been shown to occur, the presence of posterior temporal and parietal brain hypoperfusion or hypometabolism is predictive of a pathological diagnosis of AD, whereas a disproportionate reduction in frontal	NR	class II, level A

Organization(S) Title (Year)	Search Dates	Functional Neuroimaging; Diagnosis Evaluated	Evidence Base Available	Recommendations	Class/ Grade Of Recommendation	Level Of Evidence
				<p>perfusion/metabolism is more common in FTD.</p> <p>8. In PPA patients, bilateral posterior temporoparietal hypometabolism (PET) or hypoperfusion (SPECT) is predictive of AD pathology; normal bilateral posterior temporoparietal function is specific for FTLD.</p> <p>9. Dopaminergic SPECT is useful to distinguish DLB from AD, especially when there are no clear extrapyramidal symptoms and signs. However a negative 123I-FP-CIT scan does not necessarily exclude a diagnosis of probable DLB, as around 20% of individuals with probable DLB appear to have normal.</p> <p>10. Dopaminergic SPECT can be useful in differentiating DLB from long-term psychiatric patients on neuroleptic drugs, who's parkinsonism may be drug-induced.</p> <p>Recommendations for non-conventional MRI:</p> <p>1. At present, advanced MRI techniques do not have a role in the diagnosis or routine assessment or monitoring of neurodegenerative dementia.</p> <p>2. The reliability and reproducibility of advanced MRI techniques requires further evaluation, and serious efforts are under way to achieve harmonization of both acquisition and post-processing procedures.</p>	<p></p> <p>NR</p> <p>NR</p> <p>NR</p> <p>Good practice point</p> <p>Good practice point</p> <p>NR</p>	<p></p> <p>class III, level C</p> <p>class I, level A</p> <p>class I, level A</p> <p>NR</p> <p>Class IV</p> <p>NR</p>
The National Institute on Aging The Alzheimer's Association	No systematic literature search performed	PET Diagnoses included: AD	NR	Recommendations for functional imaging: In persons who meet the core clinical criteria for probable AD dementia biomarker evidence (i.e., biomarkers of downstream neuronal degeneration such as FDG-PET) may increase the certainty that the	NR	NR

Organization(S) Title (Year)	Search Dates	Functional Neuroimaging; Diagnosis Evaluated	Evidence Base Available	Recommendations	Class/ Grade Of Recommendation	Level Of Evidence
<p>The diagnosis of dementia due to Alzheimer’s disease: Recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease (2011)⁹⁷</p>				<p>basis of the clinical dementia syndrome is the AD pathophysiological process. However, we do not advocate the use of AD biomarker tests for routine diagnostic purposes at the present time for the following reasons:</p> <ol style="list-style-type: none"> 1. The core clinical criteria provide very good diagnostic accuracy and utility in most patients; 2. More research needs to be done to ensure that criteria that include the use of biomarkers has been appropriately designed; 3. There is limited standardization of biomarkers from one locale to another; 4. Access to biomarkers is limited to varying degrees in community settings. <p>Presently, the use of biomarkers to enhance certainty of AD pathophysiological process may be useful in three circumstances:</p> <ul style="list-style-type: none"> • Investigational studies • Clinical trials • Optional clinical tools for use where available and when deemed appropriate by the clinician. <p>Further studies are needed to prioritize biomarkers and to determine their value and validity in practice and research settings.</p>		
<p>The National Institute on Aging The Alzheimer’s Association</p>	<p>No systematic literature search performed</p>	<p>FDG-PET, SPECT Diagnoses included: MCI due to AD</p>	<p>NR</p>	<p>For MCI subjects whose clinical and cognitive MCI syndrome is consistent with AD as the etiology, the addition of biomarkers (e.g. biomarkers of neuronal injury such as hypometabolism or hypoperfusion on PET or SPECT) may affect levels of certainty that the AD pathophysiological process is the underlying</p>	<p>NR</p>	<p>NR</p>

Organization(S) Title (Year)	Search Dates	Functional Neuroimaging; Diagnosis Evaluated	Evidence Base Available	Recommendations	Class/ Grade Of Recommendation	Level Of Evidence
The diagnosis of mild cognitive impairment due to Alzheimer’s disease: Recommendations from the National Institute on Aging- Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease (2011) ⁹				cause of the MCI syndrome. The definitive absence of evidence of neuronal injury strongly suggests that the MCI syndrome is not due to AD. In such situations, search for biomarkers that reflect alternative pathological processes should be considered. Such biomarkers are not as well established as those for AD. They may include: (1) prominent frontal or frontotemporal hypometabolism, hypoperfusion, or atrophy that often reflects frontotemporal lobar degeneration, (2) loss of dopamine transporters seen with SPECT imaging, often seen in DLB.		
Clinical Research Center for Dementia of South Korea Clinical Practice Guideline for Dementia; Part I: Diagnosis and Evaluation (2011) ¹¹³	CPGs: 1997-2007 SRs: 2007-NR	FDG-PET, SPECT Diagnoses included: AD, VaD, DLB, FTD, Huntington’s disease, NPH	4 CPGs selected to adapt to the guideline (of 22 CPGs reviewed), SRs	Structural and functional brain imaging should be performed for the diagnosis of dementia. As functional brain imaging, (FDG) PET or (HMPAO) SPECT can be used together with structural imaging. Functional imaging may be useful in those cases where diagnostic uncertainty remains after clinical and structural imaging work up. They should not be used as the only imaging measure.	NR NR	A ⁺ B
National Institute for Health and Clinical Excellence – Social Care Institute	Database inception-March 2006	FDG-PET, SPECT, FP-CIT SPECT Diagnoses	Observational case-control and cohort studies, details	Perfusion HMPAO SPECT should be used to help differentiate AD, VaD and FTD if the diagnosis is in doubt.	NR	NR

Organization(S) Title (Year)	Search Dates	Functional Neuroimaging; Diagnosis Evaluated	Evidence Base Available	Recommendations	Class/ Grade Of Recommendation	Level Of Evidence
for Excellence (NICE-SCIE) A NICE-SCIE Guideline on supporting people with dementia and their carers in health and social care (2007) ¹⁴		included: AD, VaD, DLB, FTD, delirium	NR	FDG-PET should be used to help differentiate AD, VaD and FTD if the diagnosis is in doubt and HMPAO SPECT is unavailable.	NR	NR
				FP-CIT SPECT should be used to help establish the diagnosis in those with suspected dementia with DLB if the diagnosis is in doubt.	NR	NR
				EEG should not be used as a routine investigation in people with dementia.	NR	NR
				EEG should be considered if a diagnosis of delirium or FTD is suspected, or in the assessment of associated seizure disorder in those with dementia.	NR	NR
American College of Radiology ACR Appropriateness Criteria dementia and movement disorders (2010) ¹¹²	Dates NR	fMRI, FDG-PET, HMPAO SPECT Diagnoses included: AD, FTD, DLB, VaD	NR	FDG-PET may be appropriate in cases of probable AD, for “problem solving”.	6*	NR
				FDG-PET is usually appropriate in cases of possible AD, for “problem solving”.	7	NR
				HMPAO SPECT may be appropriate in cases of probable AD, for “problem solving”.	5	NR
				HMPAO SPECT may be appropriate in cases of possible AD, for “problem solving”.	6	NR
				fMRI is usually not appropriate in cases of probable AD, for “research purposes”.	2	NR
				fMRI is usually not appropriate in cases of possible	2	NR

Organization(S) Title (Year)	Search Dates	Functional Neuroimaging; Diagnosis Evaluated	Evidence Base Available	Recommendations	Class/ Grade Of Recommendation	Level Of Evidence
				AD.		
				FDG-PET is usually appropriate in cases of suspected FTD, for “problem solving”.	7	NR
				HMPAO SPECT may be appropriate in cases of suspected FTD, for “problem solving”.	6	NR
				fMRI is usually not appropriate in patients with suspected FTD.	2	NR
				FDG-PET is usually appropriate in cases of suspected DLB, for “problem solving”.	7	NR
				HMPAO SPECT is usually appropriate in cases of suspected DLB, for “problem solving”.	7	NR
				fMRI is usually not appropriate in cases of suspected DLB.	2	NR
				FDG-PET may be appropriate in cases of suspected VaD or mixed VaD and AD, for “problem solving”.	6	NR
				HMPAO SPECT may be appropriate in cases of suspected VaD or mixed VaD and AD, for “problem solving”.	5	NR
				fMRI is usually not appropriate in cases of suspected VaD or mixed VaD and AD.	2	NR

Organization(S) Title (Year)	Search Dates	Functional Neuroimaging; Diagnosis Evaluated	Evidence Base Available	Recommendations	Class/ Grade Of Recommendation	Level Of Evidence
Scottish Intercollegiate Guidelines Network (SIGN) Management of patients with dementia. A national clinical guideline (2006) ¹¹⁹	1994-2004	SPECT, EEG Diagnoses included: AD, VaD, DLB, FTD	SRs and cohort studies, details NR	SPECT may be used in combination with CT to aid the differential diagnosis of dementia when the diagnosis is in doubt.	C [§]	2+ to 2++ [§]
				There is not enough evidence to support the routine use of EEG to assess dementia.	B [§]	2+ [§]
Regional Health Council (Italy) Dementia. Diagnosis and treatment (2011) ¹¹⁵	No systematic search performed	PET, SPECT Diagnoses included: NR	DSM-IV	PET and SPECT should not be routinely used in assessing dementia.	NR	NR**
European Federation of Neurological Societies (EFNS) EFNS guidelines for the diagnosis and management of Alzheimer's disease (2010) ⁷⁰	Before May 2009	FDG-PET, SPECT, EEG Diagnoses included: AD, DLB	Original research articles, meta-analysis, and systematic reviews; details NR	FDG-PET and perfusion SPECT are useful adjuncts when diagnosis remains in doubt.	B*	NR*
				Dopaminergic SPECT is useful to differentiate AD from DLB.	A	NR
				EEG is recommended in differential diagnosis of atypical clinical presentations of AD.	NR	Good practice point
European Federation of Neurological Societies (EFNS)	Before June 2011	SPECT, PET Diagnoses included: AD, FTD, FTLD, DLB	NR	SPECT perfusion is useful to distinguish DLB and CBS from AD.	NR	Good practice point
				SPECT pre-synaptic dopamine transporter imaging is	B	NR

Organization(S) Title (Year)	Search Dates	Functional Neuroimaging; Diagnosis Evaluated	Evidence Base Available	Recommendations	Class/ Grade Of Recommendation	Level Of Evidence
EFNS guidelines on the diagnosis and management of disorders associated with dementia (2012) ¹⁶⁷				useful to distinguish DLB from non-DLB dementias.		
				SPECT and PET perfusion and metabolic techniques are highly useful in FTLD (other dementia) diagnosis.	C	III
Diagnostic Pathway Expert Reference Group (DPERG){NHS England: Strategic Clinical Networks Guidance on the use of neuro-imaging in the assessment of dementia in Primary Care (NHS-England) (2013){NHS England: Strategic Clinical Networks (South West), 2013 #19656}	No systematic search performed	FDG-PET, HMPAO-SPECT Diagnoses included: AD, FTD, DLB	NR	FDG-PET or HMPAO-SPECT can help in diagnosing and differentiating AD from FTD and DaTscans™ can assist in the diagnosis of DLB. Given the cost of these interventions, we would suggest they are reserved for use in a specialist memory assessment service.	NR	NR
Canadian Consensus Conference on Diagnosis and Treatment of Dementia, imaging group (CCDTD)	January 2006 – January 2012	FDG-PET, SPECT, PET amyloid imaging, dopamine presynaptic imaging agents	208 articles for PET and 98 articles for SPECT	For a patient whose underlying pathological process is still unclear (after clinical and structural imaging evaluations), preventing adequate clinical management, we recommend that the specialist obtains an 18F-FDG PET scan for differential diagnosis purposes.	Grade 1B**	NR**

Organization(S) Title (Year)	Search Dates	Functional Neuroimaging; Diagnosis Evaluated	Evidence Base Available	Recommendations	Class/ Grade Of Recommendation	Level Of Evidence
Clinical applications of neuroimaging in patients with Alzheimer’s disease: a review from the Fourth CCCDTD 2012 (2013) ¹⁶⁸		Diagnoses included: AD		<p>If such a patient cannot be practically referred for a FDG-PET scan, we recommend that a SPECT rCBF study be performed for differential diagnosis purposes.</p> <p>There was only partial consensus for the proposition that for a patient with MCI evaluated by a dementia specialist and in whom clinical management would be influenced by evidence of an underlying neurodegenerative process, an ¹⁸F-FDG PET scan be performed or, if not available, then a SPECT rCBF study be performed.</p>	Grade 2C NR	NR NR
Canadian Consensus Conference on Diagnosis and Treatment of Dementia, imaging group (CCCDTD)	January 2006 – April 2012	fMRI Diagnoses evaluated: AD, MCI	NR	fMRI is not currently recommended for the clinical investigation of patients presenting with cognitive impairment.	NR NR	3b ⁺⁺ 3b
Role of emerging neuroimaging modalities in patients with cognitive impairment: a review from the CCCDTD 2012 (2013) ²⁷					NR	3b

Organization(S) Title (Year)	Search Dates	Functional Neuroimaging; Diagnosis Evaluated	Evidence Base Available	Recommendations	Class/ Grade Of Recommendation	Level Of Evidence
Dementia with Lewy bodies Consortium (DLB) Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium (2005) ²²	No systematic search performed	DAT, PET, SPECT Diagnoses evaluated: DLB	NR	Suggestive features for DLB ^{††} : <ul style="list-style-type: none"> Low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging 	NR	NR
				Supportive features for DLB ^{§§} : <ul style="list-style-type: none"> Generalized low uptake on SPECT/PET perfusion scan with reduced occipital activity 	NR	NR
				Low striatal DAT activity also occurs in DLB but is normal in AD, making DAT scanning particularly useful in distinguishing between the two disorders.	NR	NR

* EFNS class/grade of recommendation and level of evidence was not defined in great detail. The scientific evidence were evaluated according to pre-specified levels of certainty (classes of evidence I, II, III, and IV) by the expert group members, and the recommendations were graded according to the strength of evidence (grade A, B, or C), using the definitions given in the EFNS guidance. In addressing important clinical questions, for which no evidence was available, ‘good practice points’ were recommended based on the experience and consensus of the expert task force group.

† Clinical Research Center for Dementia of South Korea based on Brainin et al. (2004) level of evidence – Level A: rating (established as useful/predictive or not useful/predictive) requires at least one convincing class I study or at least two consistent, convincing class II studies; Level B: rating (established as probably useful/predictive or not useful/predictive) requires at least one convincing class II study or overwhelming class III evidence; Level C: rating (established as possibly useful/predictive or not useful/predictive) requires at least two convincing class III studies.

‡ ACR class/grade of recommendation based on modified Delphi technique (1-9 scale divided into 3 categories) to determine the appropriateness of an imaging or therapeutic procedure for a specific clinical scenario – 1-3 defined as “usually not appropriate”; 4-6 defined as “may be appropriate”; 7-9 defined as “usually appropriate”.

§ SIGN level of evidence – 1++: High quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias; 1+: Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias; 1-: Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias; 2++ High quality systematic reviews of case control or cohort studies OR High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal; 2+: Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal; 2-: Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal; 3: Non-analytic studies, e.g. case reports, case series; 4 Expert opinion.

SIGN grade of recommendation – Grade A: At least one meta-analysis, systematic review of RCTs, or RCT rated as 1++ and directly applicable to the target population; or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results; Grade B: A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+; Grade C: A body of evidence including studies rated as 2+, directly applicable

to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++; Grade D: Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+.

Regional Health Council levels of evidence and grade of recommendation based on the National Guidelines System – SNLG. Levels of evidence – Level I: Evidences from randomized controlled clinical trials and/or systematic reviews of randomized trials; Level II: Evidences from one single adequately designed randomized trial; Level III: Evidences from non-randomized cohort studies with concurrent or historical control or their meta-analysis; Level IV: Evidences from non-controlled retrospective case-control studies; Level V: Evidences from non-controlled case-series studies; Level VI: Evidences from experts’ opinions or opinions from panels as indicated in guidelines or consensus conferences, or based on opinions from members of the work group responsible for this guideline. Regional Health Council grades of recommendation – Grade A: Carrying out the specified procedure or diagnostic test is strongly recommended. The recommendation is supported by good-quality evidences, even if not necessarily type I or II; Grade B: It would be inappropriate to always recommend the specified procedure or intervention, considered the still existing doubts, but it should anyway carefully considered; Grade C: Significant uncertainties exist against recommending to carry out the specified procedure or intervention; Grade D: The specified procedure is not recommended; Grade E: The specified procedure is strongly not recommended.

** CCCDTD: *Clinical applications of neuroimaging in patients with Alzheimer’s disease: a review from the Fourth CCCDTD 2012* recommendations were graded by consensus of clinicians in attendance at the conference. No other scoring details were reported.

†† CCCDTD: *Role of emerging neuroimaging modalities in patients with cognitive impairment: a review from the CCCDTD 2012* level of evidence ratings were graded using the Oxford Centre for Evidence-Based Medicine guidelines, http://www.cebm.net/mod_product/design/files/CEBM-Levels-of-Evidence-2.1.pdf. No definition was listed for the “b” rating.

‡‡ Suggestive features for the clinical diagnosis of DLB: If one or more of these is present in the presence of one or more core features, a diagnosis of probable DLB can be made. In the absence of any core features, one or more suggestive features is sufficient for possible DLB. Probable DLB should not be diagnosed on the basis of suggestive features alone.

§§ Supportive features for the clinical diagnosis of DLB: Commonly present but not proven to have diagnostic specificity.

2.10. Previous Systematic Reviews/Technology Assessments

A total of four Health Technology Assessments (HTAs)^{2,3,91,131} and 11 high-quality systematic reviews (SRs)^{21,34,42,60,82,135,165,189,192,193,196} provided data on diagnostic functional neuroimaging for mild cognitive impairment or dementia. These reports are summarized in Table 4.

FDG-PET

Overall, four HTAs^{2,3,91,131} and nine SRs^{21,34,60,82,135,165,189,193,196} provided data on FDG-PET for diagnosing patients with suspected primary degenerative dementia or mild cognitive impairment.

- The sensitivity and specificity for the ability of FDG-PET to predict MCI conversion to AD was 72 – 95% and 70 – 85%, respectively. These values were obtained from two HTAs^{91,131} and two SRs.^{193,196}
- The sensitivity and specificity for the ability of FDG-PET to differentiate AD from non-AD dementias was 86 – 92% and 85 – 89%, respectively. These values were obtained from one HTA² and two SRs.^{34,135}
- The sensitivity and specificity for the ability of FDG-PET to differentiate between unspecified dementia subtypes was 86 – 96% and 16 – 87%, respectively. These values were obtained from one HTA¹³¹ and one SR.²¹
- The sensitivity and specificity for the ability of FDG-PET to differentiate between AD versus DLB was 77 – 92% and 71 – 80%, respectively. The value for sensitivity was obtained from two SRs,^{165,189} and the value for specificity was obtained from one SR.¹⁶⁵
- The sensitivity and specificity for the ability of FDG-PET to provide an early AD diagnosis was 96% and 90%, respectively. These values were obtained from one SR.³⁴
- Finally, the sensitivity and specificity for the ability of FDG-PET to differentiate AD patients from healthy normal controls was 93 – 96% and 63 – 90%, respectively. These values were obtained from two SRs.^{21,189}

HMPAO SPECT

Overall, two HTAs^{3,91,131} and six SRs^{42,82,165,189,192,193} provided data on HMPAO-SPECT for diagnosing patients with suspected primary degenerative dementia or mild cognitive impairment.

- The sensitivity and specificity for the ability of HMPAO SPECT to provide differential diagnosis of dementia sub-types was 71 – 77% and 76 – 89%, respectively. These values were obtained from one HTA.¹³¹
- The sensitivity and specificity for the ability of HMPAO SPECT to provide differential diagnosis of AD from DLB was 65 – 85% and 76.2 – 87%, respectively. These values were obtained from two SRs.^{165,192}
- The sensitivity and specificity for the ability of HMPAO SPECT to detect MCI conversion to AD was 83.8% and 90.4%, respectively. These values were obtained from one SR.¹⁹³
- The sensitivity and specificity for the ability of HMPAO SPECT to provide differential diagnosis of AD from non-AD dementias was 65.7 – 95% and 42 – 79.1%, respectively. These values were obtained from two SRs.^{42,82}
- The sensitivity and specificity for the ability of HMPAO SPECT to provide differential diagnosis of AD vs. FTD was 71.5 – 79.7% and 78.2 – 97.9%, respectively. These values were obtained from two SRs.^{42,192}
- The sensitivity and specificity for the ability of HMPAO SPECT to provide differential diagnosis of dementia from healthy controls was 77.1% and 89.0%, respectively. These values were obtained from one SR.⁴²

- The sensitivity and specificity for the ability of HMPAO SPECT to provide differentiation of medial temporal lobe dementias from healthy controls was 89% and 80%, respectively. These values were obtained from one HTA.⁹¹

DaTscan SPECT

One SR provided data on the ability of DaTscan SPECT to diagnose patients with suspected primary degenerative dementia or mild cognitive impairment.¹⁶⁵

- The sensitivity and specificity of DaTscan SPECT to provide differential diagnosis of AD from DLB was 78 – 88% and 94 – 100%, respectively.¹⁶⁵
- The sensitivity and specificity of DaTscan SPECT to provide differential diagnosis of DLB from non-DLB dementias was 86.5% and 92.6%, respectively.¹⁶⁵

Table 4. Previous Health Technology Assessments and Systematic Reviews

Assessment (Year)	Functional Imaging	Reference Standard	Lit Search Dates	Critical Appraisal	Evidence Base And Outcomes	Conclusion
PREVIOUS HTAs						
FDG-PET						
AHRQ (2004) (update to 2001 version) ⁹¹	FDG-PET	Histopathologic or clinical diagnosis	2001 - 2004	Classification Categories [†]	<p>AD vs. PPD <u>Evidence base:</u> 1 study (study design NR) <u>Outcomes:</u> Low acetylcholine levels as measured by PET is more characteristic of patients with PPD than those with AD.</p> <p>MCI conversion to AD <u>Evidence base:</u> 3 studies (study design NR) <u>Outcomes:</u> Data only provided for 1/3 studies: Sensitivity: 95% (95% CI, 90%, 100%) Specificity: 79% (95% CI, 66%, 92%)</p>	<p>Overall Treatment without further PET testing is superior to treatment with further PET testing.</p> <p>AD vs. PPD This study examined a variant of PET involving a radioligand other than FDG and thus is not clearly relevant to current or near-term clinical practice.</p> <p>MCI conversion to AD FDG-PET could be valuable for distinguishing patients with MCI who rapidly convert to frank AD.</p>

Assessment (Year)	Functional Imaging	Reference Standard	Lit Search Dates	Critical Appraisal	Evidence Base And Outcomes	Conclusion
Oregon HERC Evidence Review for Coverage Guidance (2012) ¹³¹	FDG-PET	Clinical diagnosis	NR	NR	<p>MCI Conversion to AD <u>Evidence base:</u> 1 meta-analysis, 6 case series <u>Outcomes:</u> Sensitivity: 72 -89% Specificity: 70 -85% LR+: 2.56 – 4.61 LR-: 0.15 – 0.37 OR: 9.2 – 40.1</p> <p>Differential Diagnosis of Dementia Sub-Types <u>Evidence base:</u> NR <u>Outcomes:</u> Sensitivity: 86 – 96% Specificity: 16 – 87%</p>	<p>Overall No evidence for improved outcomes from any functional neuroimaging intervention.</p> <p>MCI conversion to AD PET may have a small to moderate ability to predict MCI conversion to AD.</p> <p>Differential Diagnosis of Dementia Sub-Types NR</p>
Ontario (2006) ²	FDG-PET	Clinical diagnosis	2004 – September 2006	NR	<p>AD vs. non-AD dementia <u>Evidence base:</u> 3 studies (study design NR) <u>Outcomes:</u> Sensitivity: ~92 % Specificity: ~89%</p>	<p>AD vs. non-AD dementia While there is evidence to suggest PET can accurately diagnose AD, there is no evidence to suggest that it changes patient outcomes.</p>
Swedish Council (2008) ³	FDG-PET	Neuropathologic or clinical diagnosis	1980 – July 2004	Internal Quality Assessment [‡] AND To evaluate each modality: Classification of Evidence [§]	<p>AD vs. Control <u>Evidence base:</u> 10 studies (study design NR) <u>Outcomes:</u> LR+ (median): 4.2ⁱ LR- (median): 0.18</p> <p>AD vs. non-AD Dementia <u>Evidence base:</u> 2 cross-sectional studies, 1 cross-sectional longitudinal study, 19 study</p>	<p>AD vs. Control, AD vs. non-AD Dementia There is moderate evidence supporting the use of PET to differentiate between controls and AD subtypes.</p>

Assessment (Year)	Functional Imaging	Reference Standard	Lit Search Dates	Critical Appraisal	Evidence Base And Outcomes	Conclusion
					design NR <u>Outcomes:</u> PET detection of glucose metabolism contributes to differential dementia diagnosis.	
SPECT						
AHRQ (2004) (update to 2011 version) ⁹¹	SPECT (2/3 studies Tc HMPAO SPECT)	Histopathologic or clinical diagnosis	1966 – January Week 2 2004	Classification Categories ⁺	Medial Temporal Lobe Dementias vs. Control <u>Evidence base:</u> 1 study (study type NR) <u>Outcomes:</u> Sensitivity: 89% Specificity: 80%	Medial Temporal Lobe Dementias vs. Control NR
Oregon HERC Evidence Review for Coverage Guidance (2012) ¹³¹	SPECT	NR	NR	NR	Differential diagnosis of dementia sub-types <u>Evidence base:</u> NR <u>Outcomes:</u> Sensitivity: 71 -77% Specificity: 76 – 89%	Overall No evidence for improved outcomes from any neuroimaging intervention. Differential diagnosis of dementia sub-types NR
Swedish Council (2008) ³	SPECT	Histopathologic or clinical diagnosis	1980 – July 2004	Internal Quality Assessment [‡] AND To evaluate each modality: Classification of Evidence [§]	AD vs. Control, AD vs. non-AD dementia <u>Evidence base:</u> 10 studies 9 cross-sectional studies, 1 cross-sectional longitudinal study, 9 study design not reported AD vs. Control <u>Outcomes:</u> LR+ (median): 4.2 LR- (median): 0.18	AD v. controls, AD v. non-AD dementia There is moderate evidence supporting the use of SPECT to differentiate between controls and AD subtypes.

Assessment (Year)	Functional Imaging	Reference Standard	Lit Search Dates	Critical Appraisal	Evidence Base And Outcomes	Conclusion
					AD vs. non-AD dementia: <u>Outcomes:</u> NR	
PREVIOUS SRs AND META-ANALYSES						
Bohnen (2012) ²¹	FDG-PET	Histopathologic diagnosis	2000-2012	Detailed-review quality score ⁺⁺ , AAN Levels of Diagnostic Evidence	<p>AD vs. Controls <u>Evidence base:</u> 5 cross sectional case-control studies <u>Outcomes:</u> Accuracy: 93% Sensitivity: 96% Specificity: 90%</p> <p>Differential Diagnosis of AD v. Other Dementias <u>Evidence base:</u> 1 prospective cohort study, 1 historical cohort study, 1 multicenter retrospective analysis, 2 retrospective studies <u>Outcomes:</u> Diagnostic Accuracy: 85% Sensitivity: 87% Specificity: 81%</p>	<p>AD vs. Controls, Differential Diagnosis of AD v. Other Dementias There is substantial evidence from the last decade to support the safety and efficacy of FDG-PET for use in the diagnosis of AD and other progressive cognitive impairments.</p>
Daniela (2014) ³⁴	FDG-PET	Histopathologic or clinical diagnosis	NR	GRADE Level of Confidence score ⁺⁺ , meta-analysis	<p>Early AD diagnosis <u>Evidence base:</u> 10 cohort studies <u>Outcomes:</u> Diagnostic Accuracy: 93% Sensitivity: 96% Specificity: 90% Sensitivity effect measures: 0.86</p> <p>Differential Diagnosis of AD vs. Other Dementias <u>Evidence base:</u></p>	<p>Early AD diagnosis, Differential Diagnosis of AD vs. Other Dementias There is moderate quality evidence available to support the ability of FDG-PET to diagnose early AD and to differentiate among dementia subtypes.</p>

Assessment (Year)	Functional Imaging	Reference Standard	Lit Search Dates	Critical Appraisal	Evidence Base And Outcomes	Conclusion
					4 cohort studies <u>Outcomes:</u> Diagnostic Accuracy: 85% Sensitivity: 87% Specificity: 81% Sensitivity effect measures: 0.90	
Gill (2003) ⁶⁰	FDG-PET	Clinical diagnosis	1975 – January 2001	Classification Categories [†]	AD vs. normal aging, AD vs. non-AD dementia <u>Evidence base:</u> 7 HTAs, 16 original articles (study design NR) <u>Outcomes:</u> NR	AD vs. normal aging, AD vs. non-AD dementia Little evidence for use of FDG-PET in routine use of dementia diagnosis.
Knopman (2001) ⁸²	FDG-PET	Histopathologic diagnosis	January 1985 – November 1999	Classification of Evidence ^{§§}	AD vs. non-AD dementia <u>Evidence base:</u> NR <u>Outcomes:</u> Diagnostic Accuracy: 87%	AD vs. non-AD dementia FDG-PET scans have promise for diagnosis of dementia, but more prospective studies are needed to establish true value over clinical diagnosis.
Patwardhan (2004) ¹³⁶	FDG-PET	Histopathologic or clinical diagnosis	1989 - 2003	Rating Scale ^{***}	AD vs. non-AD dementia <u>Evidence base:</u> 15 studies (study design NR) <u>Outcomes:</u> Sensitivity: 86% (95% CI, 76%, 93%) Specificity: 86% (95% CI, 72%, 83%)	AD vs. non-AD dementia Specificity and sensitivity are limited by study design and patient population characteristics; there is not enough evidence to make a suggestion.
Sinha (2012) ¹⁶⁵	FDG-PET	Clinical diagnosis	2000 – October 2010	NR	AD vs. DLB <u>Evidence base:</u> 1 multicenter study, 2 study (study	AD vs. DLB, DLB vs. PDD, DLB vs. NC Diagnostic value of PET

Assessment (Year)	Functional Imaging	Reference Standard	Lit Search Dates	Critical Appraisal	Evidence Base And Outcomes	Conclusion
					design type NR) <u>Outcomes:</u> Sensitivity: 77-90% Specificity: 71-80% (reflects only 2/3 studies) DLB vs. PDD <u>Evidence base:</u> 1 study (study design NR) <u>Outcomes:</u> DLB patients showed significant metabolic decrease in anterior cingulate compared to PDD patients. DLB vs. NC <u>Evidence base:</u> 1 study (study design NR) <u>Outcomes:</u> DLB patients had reduced parietal metabolism in comparison to NC.	is uncertain and merits further research.
Wollman (2003) ¹⁸⁹	FDG-PET	Histopathologic or clinical diagnosis	August 1998 – August 2001	NR	AD vs. Normal Healthy Control <u>Evidence base:</u> 2 studies (study design NR) <u>Outcomes:</u> Sensitivity: 93 – 94% Specificity: 63 -73% AD vs. DLB <u>Evidence base:</u> 2 studies (study design NR) <u>Outcomes:</u> Sensitivity: 86 – 92%	AD vs. Normal Healthy Control, AD vs. DLB Neuroimaging has a limited range of variability in AD diagnosis, but until further research is conducted to increase its lower bound of diagnostic accuracy, is best used as an adjunct to clinical diagnosis.
Yuan (2009) ¹⁹³	FDG-PET	Histopathologic or clinical diagnosis	January 1990 – April	NR	MCI conversion to AD <u>Evidence base:</u>	MCI conversion to AD FDG PET is a useful

Assessment (Year)	Functional Imaging	Reference Standard	Lit Search Dates	Critical Appraisal	Evidence Base And Outcomes	Conclusion
			2008		6 longitudinal studies <u>Outcomes:</u> Sensitivity: 88.8% (95% CI, 82.2%, 93.6%) Specificity: 84.9% (95% CI, 78.1%, 90.3%) LR+: 2.610 (95% CI, 3.176%, 6.693%) LR-: 0.147 (95% CI, 0.046%, 0.476) OR: 40.146% (95% CI, 18.532%, 6.971%)	supplement to determine conversion of MCI to AD.
Zhang (2012) ¹⁹⁶	FDG-PET	Histopathologic or clinical diagnosis	January 2000 – July 1, 2011	Quality Assessment of Diagnostic Accuracy (QUADAS)	MCI conversion to AD <u>Evidence Base:</u> 7 studies (study design NR) <u>Outcomes:</u> Sensitivity: 78.7% (95% CI, 68.7%, 86.6%) Specificity: 74.0% (95% CI, 67.0%, 80.3%) LR+: 18.1 (95% CI, 7.3, 45.0) LR-: 0.32 (95% CI, 0.16, 0.61) DOR: 17.3 (95% CI, 5.08, 59.2)	MCI conversion to AD Although some publication bias has been found, FDG-PET is a promising tool for prediction of MCI conversion to AD.

Assessment (Year)	Functional Imaging	Reference Standard	Lit Search Dates	Critical Appraisal	Evidence Base And Outcomes	Conclusion
Dougall (2004) ⁴²	99Tc-HMPAO-SPECT	Clinical diagnosis	January 1985 – December 2002	Internal Validity Checklist ⁺⁺⁺	<p>AD vs. FTD <u>Evidence base:</u> 7 studies (study design NR) <u>Outcomes</u> Sensitivity: 71.5% (95% CI, 66.3%, 76.7%) Specificity: 78.2% (95% CI, 71.2%, 85.2%)</p> <p>AD vs. non-AD Dementia <u>Evidence base:</u> 13 studies (study design NR) <u>Outcomes:</u> Sensitivity: 65.7% (95% CI, 62.2%, 69.3%) Specificity: 79.1% (95% CI, 75.1 %, 83.1%)</p> <p>AD vs. Normal Healthy Control <u>Evidence base:</u> 7 studies (study design NR) <u>Outcomes:</u> Sensitivity: 77.1% (95% CI, 74.5%, 79.7%) Specificity: 89.0% (95% CI, 86.7%, 91.4%)</p>	<p>AD vs. FTD, AD vs. non-AD Dementia, AD vs. Normal Healthy Control SPECT is able to discriminate between AD, VFTD, and normal healthy control groups.</p>
Knopman (2001) ⁸²	SPECT	Histopathologic diagnosis	January 1985 – November 1999	Classification of Evidence ^{§§}	<p>AD vs. non-AD Dementia <u>Evidence base:</u> 2 studies (study design NR) <u>Outcomes:</u> Sensitivity: 86 -95% Specificity: 42 – 73% Diagnostic Accuracy: 62.9%</p>	<p>AD vs. non-AD Dementia SPECT sensitivity and specificity are not consistently better than clinical diagnosis of AD.</p>
Sinha (2012) ¹⁶⁵	SPECT	NR	2000 – October	NR	<p>AD vs. DLB <u>Evidence base:</u></p>	<p>AD vs. DLB DLB diagnosis using</p>

Assessment (Year)	Functional Imaging	Reference Standard	Lit Search Dates	Critical Appraisal	Evidence Base And Outcomes	Conclusion
			2010		3 studies (study design NR) <u>Outcomes:</u> Sensitivity: 65 – 85% Specificity: 85 – 87%	HMPAO and ECD SPECT are of uncertain value but merit further research.
Wollman (2003) ¹⁸⁹	SPECT	Histopathologic or clinical diagnosis	August 1998 – August 2001	NR	AD vs. Normal Healthy Control <u>Evidence base:</u> 6 studies (study design NR) <u>Outcomes:</u> Sensitivity: 0.72 – 0.96 Specificity: 0.73 – 1.00	AD vs. Normal Healthy Control There is a wide variation in SPECT diagnostic accuracy, and as such, it has not been shown to be superior to clinical diagnosis criteria for dementia.
Yeo (2013) ¹⁹²	SPECT	Histopathologic or clinical diagnosis	January 1985 – May 2012	Quality Assessment of Diagnostic Accuracy (QUADAS)	AD vs. FTD <u>Evidence base:</u> 10 studies (study design NR) <u>Outcomes</u> Sensitivity: 79.7% (95% CI, 71.0%, 87.3%) Specificity: 79.9% (95% CI, 74.8%, 85.6%) LR+: 3.35 (95% CI, 2.51, 4.46) LR-: 0.256 (95% CI, 0.166, 0.393) Diagnostic OR: 0.3 (95% CI, 7.66, 26.5) AD vs. DLB <u>Evidence base:</u> 3 studies (study design NR) <u>Outcomes:</u> Sensitivity: 70.2% (95% CI, 60.5 %, 78.7%) Specificity: 76.2% (95% CI, 64.8%, 85.4%) LR+: 2.84 (95% CI, 0.60, 5.05)	AD vs. FTD, DLB, NC SPECT is a specific and sensitive method distinguishing AD from FTD, DLB, and NC. However, it should be utilized as an adjunct to traditional methods of AD diagnosis such as structural neuroimaging and clinical assessment until further quantification methods are developed to help improve SPECT sensitivity and specificity.

Assessment (Year)	Functional Imaging	Reference Standard	Lit Search Dates	Critical Appraisal	Evidence Base And Outcomes	Conclusion
					LR-: 0.391 (95% CI, 0.251, 0.609) Diagnostic OR: 0.14 (95% CI, 2.84, 23.3) AD vs. Normal Controls <u>Evidence base:</u> 16 studies (study design NR) <u>Outcomes:</u> Sensitivity: 76.1% (95% CI, 65.6%, 85.1%) Specificity: 85.4% (95% CI, 78.9%, 90.9%) LR+: 5.63 (95% CI, 3.55, 8.92) LR-: 0.262 (95% CI, 0.181, 0.380) Diagnostic OR: 26.2 (95% CI, 12.3, 56.2)	
Yuan (2009) ¹⁹³	SPECT	Histopathologic or clinical diagnosis	January 1990 – April 2008	NR	MCI conversion to AD <u>Evidence base:</u> 8 longitudinal studies <u>Outcomes:</u> Sensitivity: 83.8% (95% CI, 77.1%, 89.1%) Specificity: 90.4% (95% CI, 62.9%, 77.2%) LR+: 2.589 (95% CI, 1.445, 4.639) LR-: 0.318 (95% CI, 0.207, 0.489) OR: 9.288 (95% CI, 4.477, 19.271)	MCI conversion to AD SPECT is not a useful supplement to determine conversion of MCI to AD.
Papathanasiou (2012) ¹³³	DaTscan (¹²³ I-FP-CIT SPECT)	Histopathologic or clinical diagnosis	Start Date NR - August 2011	NR	DLB vs. non-DLB dementia <u>Evidence base:</u> 1 cross-sectional, single center study, 1 cross-sectional multicenter study, 1 retrospective study, 1 study type NR <u>Outcomes:</u> Sensitivity: 86.5% (95% CI, 72%, 94.1%) Specificity: 93.6% (95% CI, 88.5%, 96.6%) DOR (Diagnostic Odds Ratio): 94.2	DLB vs. non-DLB dementia DaTscan can be a useful adjunct for diagnosing DLB patients.

Assessment (Year)	Functional Imaging	Reference Standard	Lit Search Dates	Critical Appraisal	Evidence Base And Outcomes	Conclusion
					(95% CI, 25.7, 345.0) LR+: 13.6 (95% CI, 7.0, 26.3) LR-: .14 (95% CI, 0.06, 0.32)	
Sinha (2012) ¹⁶⁵	DaTscan (¹²³ I-FP-CIT SPECT)	Histopathologic diagnosis	2000 – October 2010	NR	AD vs. DLB <u>Evidence base:</u> 1 multicenter study, 2 studies (study design NR) <u>Outcomes:</u> Sensitivity: 78 – 88% Specificity: 94 – 100%	AD vs. DLB I-FP-CIT SPECT has a strong evidence base to support its ability to diagnose DLB.

*AHRQ HTA (2001) Quality Score is rated on a scale of 0 – 8, 0 = poor study reliability, 8 = best study reliability

† Adapted from Fryback DG, Thornbury JR. The efficacy of diagnostic imaging. Medical Decision Making. 1991;11(2):88-94.

‡ Used to evaluate each study. Ia: Population-based or consecutive-series prospective studies, diagnosis verified neuropathologically; Ib:

Selected patients and controls, prospective studies, diagnosis verified neuropathologically; IIa: Population-based or consecutive-series retrospective studies, diagnosis verified neuropathologically; IIb:: Selected patients and controls, retrospective studies, diagnosis verified neuropathologically; 1a: Population-based or consecutive-series prospective studies, clinical diagnosis, 1b: Population-based or consecutive-series prospective studies, clinical diagnosis; 2a: Population-based or consecutive-series retrospective studies, clinical diagnosis; IIb:: Selected patients and controls, retrospective studies, clinical diagnosis

§ Used to evaluate each modality. Grade 1: Strong evidence, 2 type 1a or Ia studies, meets all general criteria; Grade 2: Moderately strong evidence, ≥ 2 type 1a, Ia, 2a or IIa OR ≥ 4 type 1b, Ib, 2b, or IIb studies, the majority of studies should meet all the general criteria; Grade 3: Limited evidence, 1 type 1a or Ia study, or ≥ 2 type 2a or IIa studies, or ≥ 3 type 1b, Ib, 2b, or IIb studies, the majority of studies should meet all the general criteria; No Evidence: No type 1a or Ia study, or only 1 type 2a or IIb study, or <3 1b, Ib, 2b, or IIb studies, the majority of studies should meet all the general criteria

** Sensitivity and Specificity reported only for each study

†† Detailed-review quality score as described in Patwardhan MB, McCrory DC, Matchar DB, Samsa GP, Rutschmann OT. Alzheimer disease: operating characteristics of PET--a meta-analysis. Radiology. 2004; 231:73-80. Eight questions rated 0 or 1, total score on a scale of 0 – 8 with a higher score corresponding with higher review quality.

‡‡ GRADE analysis as described in the following papers: J. L. Brozek, E. A. Akl, R. Jaeschke et al., “Grading quality of evidence and strength of recommendations in clinical practice guidelines: part 2 of 3. The GRADE approach to grading quality of evidence about diagnostic tests and strategies,” Allergy, vol. 64, no. 8, pp. 1109–1116, 2009. J.Hsu, J. L. Brozek, L. Terracciano et al., “Application of GRADE: making evidence-based recommendations about diagnostic tests in clinical practice guidelines,” Implementation Science, vol. 6, no. 1, article 62, 2011. G. H. Guyatt, A. D. Oxman, R. Kunz et al., “GRADE guidelines: Rating the quality of evidence-inconsistency,” Chinese Journal of Evidence-Based Medicine, vol. 11, no. 12, pp. 1444–1451, 2011. H. J. Schunemann, A. D. Oxman, J. Brozek et al., “GRADE: grading quality of evidence and strength of recommendations

§§ Classification of Evidence ratings are as follows: I- Evidence provided by a well-designed prospective study in a broad spectrum of persons with the suspected condition, using a “gold standard” for case definition, in which test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy. II - Evidence provided by a well-designed prospective study of a narrow spectrum of persons with the suspected condition, or

a well-designed retrospective study of a broad spectrum of persons with an established condition (by “gold standard”) compared with a broad spectrum of controls, in which test is applied in blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy. III- Evidence provided by a retrospective study in which either persons with the established condition or controls are of a narrow spectrum, and in which test is applied in a blinded evaluation. IV- Any design in which test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls).

*** Eight different criteria scored as either 0 or 1, total score from 0-8; the higher the score, the better the quality of the study.

††† IVC is based on the Scottish Intercollegiate Guidelines Network (SIGN) Methodology Checklist of Diagnostic Studies (Harbour R, Miller J. A. New System for Grading Recommendations in Evidence Based Guidelines. MJ 2001; 323: 334-336 (<http://www.show.scot.nhs.uk/sign/guidelines/fulltext/50/index.html>))

2.11. Medicare and Representative Private Insurer Coverage Policies

Payer websites were searched for coverage decisions on the use of functional neuroimaging in the diagnosis of dementia. Eleven policies were identified for selected bell-weather payers and coverage policies are consistent for non-coverage of functional neuroimaging. Generally speaking, the payers will not provide coverage for any of the diagnostic functional neuroimaging modalities, with the exception of two policies:

- Centers for Medicare and Medicaid Services (CMS) will provide coverage for FDG-PET scans for either the differential diagnosis of FTD and AD under specific requirements; OR, the use of FDG-PET in a CMS-approved practical clinical trial focused on its utility in the diagnosis or treatment of dementing neurodegenerative diseases.
- Cigna covers SPECT as medically necessary for Alzheimer's disease when other imaging studies are inconclusive or contraindicated; however, results should be considered supportive and not diagnostic.

Coverage decisions are summarized briefly below and policy details are provided in Table 5.

Centers for Medicare and Medicaid Services (CMS) National Coverage Determinations *National Coverage Determination (NCD) for FDG PET for Dementia and Neurodegenerative Diseases (220.6.13)*

Medicare covers FDG Positron Emission Tomography (FDG-PET) scans for either the differential diagnosis of FTD and AD under specific requirements (see Table 5); OR, for use in a CMS-approved practical clinical trial focused on the utility of FDG-PET in the diagnosis or treatment of dementing neurodegenerative diseases. All other uses of FDG-PET for patients with a presumptive diagnosis of dementia-causing neurodegenerative disease (e.g., possible or probable AD, clinically typical FTD, dementia of Lewy bodies) for which CMS has not specifically indicated coverage continue to be noncovered.

National Coverage Determination (NCD) for Single Photon Emission Computed Tomography (SPECT) (220.12)

Medicare does not include MCI, dementia, AD, FTD, DLB etc. in the list of conditions for which SPECT is covered.

Oregon Health Evidence Review Commission (HERC) Coverage Guidance *Functional neuroimaging (PET, SPECT, or fMRI)*

Oregon HERC states that functional neuroimaging (PET, SPECT, or fMRI) should not be covered for screening, diagnosis, or monitoring of dementia. Furthermore, in patients with mild cognitive impairment, imaging should not be used to predict progression of the risk of developing dementia (note: the evidence review evaluates use of SPECT and PET for these purposes).

Aetna

Functional Magnetic Resonance Imaging (fMRI)

Aetna considers functional magnetic resonance imaging (fMRI) experimental and investigational for the diagnosis, monitoring, prognosis, or surgical management of all other indications for Alzheimer's disease. Further validation of the use of fMRI is warranted.

Positron Emission Tomography (PET)

Aetna considers PET scans experimental and investigational for Alzheimer disease, dementia, Parkinson's disease, or for other neurologic indications not listed as medically necessary in this policy because of insufficient evidence of its effectiveness.

Single Photon Emission Computed Tomography (SPECT)

Aetna considers SPECT experimental and investigational for the differential diagnosis of Parkinson's disease from other Parkinsonian syndromes. SPECT is also considered experimental and investigational for initial or differential diagnosis of members with suspected dementia (e.g., Alzheimer's disease, dementia with Lewy bodies, frontotemporal dementia). The diagnostic value of SPECT has not been established in the peer-reviewed medical literature.

Cigna***Single Photon Emission Computed Tomography (SPECT)***

Cigna covers SPECT as medically necessary for Alzheimer's disease (AD) when other imaging studies are inconclusive or contraindicated. Characteristic patterns have been described in AD but have not been fully substantiated with clinicopathologic correlations. At this stage, results should be considered supportive but not diagnostic.

Functional Magnetic Resonance Imaging (fMRI)

Cigna considers fMRI for the diagnosis of dementia and Alzheimer's disease to be investigational, citing that fMRI does not have an established clinical role for these indications.

Positron Emission Tomography (PET)

Cigna considers PET for the diagnosis of Parkinson's, Alzheimer's, and dementia to be medically unnecessary. Cigna cites the demonstrated specificity and sensitivity in current PET studies is limited by study design issues, and as such, the clinical value for PET is unclear.

Premera Blue Cross Blue Shield***Dopamine Transporter Imaging with Single -Photon Emission Computed Tomography (DAT-SPECT)***

Dopamine transporter imaging with DAT-SPECT is investigational for all indications, including but not limited to: aiding in the diagnosis of patients with clinically uncertain parkinsonian syndromes, dementia with Lewy bodies, or monitoring of disease progression. The gold standard for the diagnosis of Parkinsonian syndromes and dementia is post-mortem neuropathological examination. In the absence of comparisons with the gold standard, long-term clinical follow-up may be used as a surrogate standard to evaluate the ability of DAT-SPECT to discriminate degenerative Parkinsonian syndromes from normality or from non-degenerative disorders that present with similar symptoms, and to discriminate DLB from Alzheimer's disease.

Functional Magnetic Resonance Imaging (fMRI)

fMRI is considered investigational for all indications other than for preoperative investigation for neurosurgery candidates.

Table 5. Overview of payer technology assessments and policies for functional neuroimaging

Payer (Year)	Lit Search Dates	Evidence Base Available	Policy	Rationale/ Comments
<p>Center for Medicare & Medicaid Services (CMS) (2009)</p> <p><i>National Coverage Determination (NCD) for FDG PET for Dementia and Neurodegenerative Diseases</i></p> <p>Manual Section #: 220.6.13</p> <p>Effective Date: 04/03/2009 Implementation Date: 10/30/2009</p>	<p>NR</p>	<p>NR</p>	<p>Medicare covers FDG-PET scans for either the differential diagnosis of FTD and AD under specific requirements; OR, its use in a CMS-approved practical clinical trial focused on the utility of FDG-PET in the diagnosis or treatment of dementing neurodegenerative diseases. Specific requirements for each indication are clarified below:</p> <p>FDG-PET Requirements for Coverage in the Differential Diagnosis of AD and FTD:</p> <ol style="list-style-type: none"> 1. In patients with a recent diagnosis of dementia and documented cognitive decline of at least 6 months, who meet diagnostic criteria for both AD and FTD. These patients have been evaluated for specific alternate neurodegenerative diseases or other causative factors, but the cause of the clinical symptoms remains uncertain, and: <ul style="list-style-type: none"> • The patient’s onset, clinical presentation, or course of cognitive impairment is such that FTD is suspected as an alternative neurodegenerative cause of the cognitive decline • The patient has had a comprehensive clinical evaluation (as defined by AAN), physical and mental status examination aided by cognitive scales or neuropsychological testing, laboratory tests, and structural imaging • The evaluation of the patient has been conducted by a physician experienced in the diagnosis and assessment of dementia • The evaluation of the patient did not clearly determine a specific neurodegenerative disease or other cause for the clinical symptoms, and 	<p>NR</p>

Payer (Year)	Lit Search Dates	Evidence Base Available	Policy	Rationale/ Comments
			<p>information available through FDG-PET is reasonably expected to help clarify the diagnosis between FTD and AD and help guide future treatment</p> <ul style="list-style-type: none"> • The FDG-PET scan is performed in a facility that has all the accreditation necessary to operate nuclear medicine equipment. The reading of the scan should be done by an expert in nuclear medicine, radiology, neurology, or psychiatry, with experience interpreting such scans in the presence of dementia • A brain SPECT or FDG-PET scan has not been obtained for the same indication • The referring and billing provider(s) have documented the appropriate evaluation of the Medicare beneficiary <p>2. FDG-PET Requirements for Coverage in the Context of a CMS-approved Practical Clinical Trial Utilizing a Specific Protocol to Demonstrate the Utility of FDG-PET in the Diagnosis, and Treatment of Neurodegenerative Dementing Diseases:</p> <ul style="list-style-type: none"> • Only in the context of an approved clinical trial that contains patient safeguards and protections to ensure proper administration, use and evaluation of the FDG-PET scan <p>All other uses of FDG-PET for patients with a presumptive diagnosis of dementia-causing neurodegenerative disease (e.g., possible or probable AD, clinically typical FTD, DLB) for which CMS has not specifically indicated coverage continue to be non-covered.</p>	

Payer (Year)	Lit Search Dates	Evidence Base Available	Policy	Rationale/ Comments
<p>Center for Medicare & Medicaid Services (2002)</p> <p><i>National Coverage Determination for Single Photon Emission Computed Tomography (SPECT)</i></p> <p>Manual Section #: 220.12</p> <p>Effective Date: 10/01/2002 Implementation Date: 10/01/2002</p>	NR	NR	<p>Medicare does not include MCI, dementia, AD, FTD, DLB etc. in the list of conditions for which SPECT is covered. There is no specific indication of non-coverage.</p>	NR
Oregon HERC (2012)	NR	<p>1 meta-analysis, 6 case series. Complete evidence base NR.</p>	<p>Functional neuroimaging (PET, SPECT or fMRI) should not be covered for screening, diagnosis, or monitoring of dementia.</p> <p>In patients with mild cognitive impairment, imaging should not be used to predict progression of the risk of developing dementia.</p>	<p>No evidence for improved outcomes from any functional neuroimaging intervention.</p>
<p>Aetna (2013)</p> <p><i>Clinical Policy Bulletin: Functional Magnetic Resonance Imaging</i></p> <p>POLICY #: 0739</p> <p>Effective Date: 11/09/2007 Last Review Date: 11/21/2013 Next Review Date: 09/04/2014</p>	NR	<p>This policy is based on 1 RCT.</p>	<p>Aetna considers fMRI experimental and investigational for the diagnosis, monitoring, or prognosis of AD and PD.</p>	<p>Further validation of the use of fMRI is warranted.</p>

Payer (Year)	Lit Search Dates	Evidence Base Available	Policy	Rationale/ Comments
<p>Aetna (2014)</p> <p><i>Clinical Policy Bulletin: Positron Emission Tomography (PET)*</i></p> <p>POLICY #: 0071</p> <p>Effective Date: 10/23/1995 Last Review Date: 03/28/2014 Next Review Date: 01/22/2015</p>	<p>NR</p>	<p>NR for neurologic indications.</p>	<p>Aetna considers PET scans experimental and investigational for AD (including the use of florbetapir-PET for imaging beta-amyloid), dementia, Parkinson's disease, or for other neurologic indications not listed as medically necessary in this policy because of insufficient evidence of its effectiveness.</p>	<p>There is insufficient evidence of effectiveness for PET scanning.</p>
<p>Aetna (2013)</p> <p><i>Clinical Policy Bulletin: Single Photon Emission Computed Tomography (SPECT)</i></p> <p>POLICY #: 0376</p> <p>Effective Date: 03/08/2000 Last Review Date: 07/12/2013 Next Review Date: 04/24/2014</p>	<p>NR</p>	<p>NR</p>	<p>Aetna considers SPECT experimental and investigational the following in these situations:</p> <ul style="list-style-type: none"> • Initial or differential diagnosis of members with suspected dementia (e.g., AD, DLB, FTD). 	<p>The diagnostic value of SPECT has not been established in the peer-reviewed medical literature.</p>

Payer (Year)	Lit Search Dates	Evidence Base Available	Policy	Rationale/ Comments
Cigna (2006) <i>Nuclear Imaging including Single-Photon Emission Computed Tomography (SPECT)</i> POLICY #: 0169 Effective Date: 09/15/2004 Revised Date: 10/15/2006	NR	This policy is based on 14 reports examining neuroimaging in the brain, as well as information from multiple professional societies/ organizations.	Cigna covers SPECT as medically necessary for dementia (including AD) when other imaging studies are inconclusive or contraindicated.	Characteristic patterns have been described in AD but have not been fully substantiated with clinicopathologic correlations. At this stage, results should be considered supportive but not diagnostic.
Cigna (2012) <i>Functional Magnetic Resonance Imaging (fMRI)</i> POLICY #: 0478 Effective Date: 07/15/2012 Next Review Date: 07/15/2013	NR	NR	Cigna considers fMRI for the diagnosis of dementia, AD, and PD to be investigational.	fMRI is not routinely employed in clinical practice for diagnosis of dementia, AD, and PD.
Cigna (2006) <i>Positron Emission Tomography (PET)*</i> POLICY #: 0091 Effective Date: 06/15/2006 Original Effective Date:	NR	This policy is based on 13 reports, including one systematic review, a 2001 AHRQ HTA, a CMS NCD, and information from multiple professional societies/organizations.	Cigna considers PET-based diagnosis of dementia, PD, and AD to be experimental.	Cigna cites a lack of demonstrated diagnostic specificity and sensitivity in the current literature.

Payer (Year)	Lit Search Dates	Evidence Base Available	Policy	Rationale/ Comments
06/15/2004				
Premera Blue Cross Blue Shield (2013) <i>Dopamine Transporter Imaging with Single -Photon Emission Computed Tomography (DAT-SPECT)</i> POLICY #: 6.01.54 Effective Date: 9/27/2013 Last Review Date: 5/28/2013	Through 5/28/2013	"Published peer-reviewed literature"	Dopamine transporter imaging with DAT-SPECT is investigational for all indications, including but not limited to: <ul style="list-style-type: none"> • Aiding in the diagnosis of patients with clinically uncertain parkinsonian syndromes • DLB • Monitoring of disease progression 	<ul style="list-style-type: none"> • In the absence of comparisons with the gold standard (neuropathological exam), long-term clinical follow-up may be used as a surrogate standard to evaluate the ability of DAT-SPECT to discriminate degenerative PS from normality or from non-degenerative disorders that present with similar symptoms, and to discriminate DLB from AD.

Payer (Year)	Lit Search Dates	Evidence Base Available	Policy	Rationale/ Comments
Premera Blue Cross Blue Shield (2013) <i>Functional Magnetic Resonance Imaging (fMRI)</i> POLICY #: 6.01.47 Effective Date: 08/16/2013 Last Review Date: 08/12/2013	NR	NR	fMRI is considered investigational for all indications other than for preoperative investigation for neurosurgery candidates.	NR

AAN: American Academy of Neurology; AD: Alzheimer’s disease; AHRQ: Agency for Healthcare and Research Quality; CMS: Center for Medicare and Medicaid Services; CPB: Clinical policy bulletin; DAT-SPECT: Dopamine Transporter Imaging with Single -Photon Emission Computed Tomography; DLB: dementia with Lewy bodies; EEG: Electroencephalogram; FTD: frontotemporal dementia; NCD; National Coverage Determination; NMR: Nuclear magnetic resonance; PET: Positron Emission Tomography; PD: Parkinson’s disease; PS: Parkinsonian syndromes; SPECT: Single-Photon Emission Computed Tomography.
 *It is unclear if this policy includes both 18F-FDG-PET and beta-amyloid PET.

2.12. Ongoing Clinical Trials

A search of clinicaltrials.gov indicated that there are a number of relevant ongoing clinical trials. While some of the trials are focused on reporting on the diagnostic accuracy functional neuroimaging, most are aimed at using diagnostic functional neuroimaging to predict disease progression and clinical outcomes. Functional neuroimaging modalities being studied included FDG-PET, DaTscan, and fMRI; these are being compared to amyloid imaging (PIB-PET) and structural neuroimaging by many of the studies. Of the identified relevant trials, estimated completion dates range from March 2015 to December 2021. Additional details are available in the Appendix.

3. The Evidence

3.1. Methods of the Systematic Literature Review

3.1.1. Objectives

The objective of this Health Technology Assessment was to systematically review, critically appraise, analyze and synthesize research evidence evaluating the ability of neuroimaging to differentially diagnose, predict progression and outcomes, and influence therapeutic decisions and clinical management for patients with primary neurodegenerative dementia or mild cognitive impairment. The differential effectiveness and safety of diagnostic neuroimaging for subpopulations was evaluated, as was the cost effectiveness of diagnostic neuroimaging. To that end, the Key Questions below were posed:

Contextual Questions:

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 DLB and 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).

Research Key Questions:

In patients with mild cognitive impairment or clinically diagnosed dementia who have completed a comprehensive initial diagnostic work-up (that included structural neuroimaging):

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)?
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?
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?
4. What are the short and long term harms of diagnostic functional neuroimaging?

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

3.1.2. Inclusion/exclusion

The inclusion and exclusion criteria are summarized in Table 6 and further discussed below.

Table 6. Summary of inclusion and exclusion criteria

Study Component	Inclusion	Exclusion
Population	<p>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:</p> <ul style="list-style-type: none"> • 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) 	<ul style="list-style-type: none"> • 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	<p>Diagnostic functional neuroimaging modalities of interest:</p> <ul style="list-style-type: none"> • 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) 	<ul style="list-style-type: none"> • 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),

Study Component	Inclusion	Exclusion
		deformation-based morphometry (DBM), tensor-based morphometry (TBM) <ul style="list-style-type: none"> • 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	<p><u>KQ1</u>: Gold standard (histopathological confirmation or genetic confirmation if applicable)</p> <p><u>KQ2</u> (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)</p> <p><u>KQ2</u> (first part), <u>KQ3</u>, <u>KQ5</u>, <u>KQ6</u>: Comprehensive initial diagnostic work-up (to include structural neuroimaging</p>	<p><u>KQ1</u>: Clinical diagnosis (based on standardized comprehensive exam that may include patient history, cognitive testing, neurological exam, structural neuroimaging, and blood work)</p> <p><u>KQ2</u> (i.e., portion of question that compares functional neuroimaging modalities): Indirect comparisons of functional neuroimaging methods</p>
Outcomes	<p><u>Primary outcomes of interest:</u></p> <ul style="list-style-type: none"> • <u>KQ 2, KQ5:</u> <ul style="list-style-type: none"> • Patient progression (e.g., functional and/or cognitive decline, as discussed below) • Patient health outcomes, including: <ul style="list-style-type: none"> • 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)) • <u>KQ 4, KQ 5:</u> Harms (e.g., radiation exposure; magnetic field exposure; pain, redness, swelling at injection site; allergic reaction to tracer) • <u>KQ 6:</u> 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 	<ul style="list-style-type: none"> • 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) <p><u>Context questions:</u></p> <ul style="list-style-type: none"> • <u>First context question:</u> inter-method reliability

Study Component	Inclusion	Exclusion
	<p><u>Intermediate or secondary outcomes:</u></p> <ul style="list-style-type: none"> • <u>KQ 1:</u> diagnostic accuracy measures (e.g., sensitivity, specificity, likelihood ratios, predictive values, receiver operating characteristics (ROC)) • <u>KQ 2, KQ5:</u> <ul style="list-style-type: none"> • 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)) • <u>KQ 3:</u> impact on therapeutic decisions or clinical management (e.g., treatments planned, treatments given) <p><u>Context questions:</u></p> <ul style="list-style-type: none"> • <u>First context question:</u> intra-method reliability: inter-rater reliability and intra-rater (test-retest) reliability measures (kappa, percent agreement) • <u>Second context question</u> diagnostic accuracy measures (e.g., sensitivity, specificity, likelihood ratios, predictive values, receiver operating characteristics (ROC)) 	
<p>Study Design</p>	<p>Focus will be on studies with the least potential for bias.</p> <ul style="list-style-type: none"> • <u>KQ 1-5:</u> Prospective studies will be sought. Retrospective studies will be considered only if there are insufficient prospective studies • <u>KQ 1-5:</u> Studies must make a diagnosis/prediction based on functional neuroimaging scans using criteria specified <i>a priori</i>. • <u>KQ 1-5:</u> High quality systematic reviews will be considered if available • <u>KQ 1, context question on accuracy:</u> Studies directly comparing functional neuroimaging with the gold standard (e.g., histopathological or genetic confirmation) • <u>KQ 2 (first part), KQ 5:</u> Longitudinal studies designed specifically to evaluate progression that provide 	<ul style="list-style-type: none"> • <u>KQ 1 and second context question:</u> Studies comparing functional neuroimaging to clinical diagnosis • <u>KQ2, 3, 5:</u> Prediction model generated in the same population it is then tested in. • <u>KQ 2, KQ 5:</u> Longitudinal studies with less than 80% follow-up (excluding death) or less than 1 year follow-up • <u>KQ 2 (second part):</u> indirect comparisons of functional imaging modalities • <u>KQ 6:</u> Incomplete economic evaluations such as costing studies • Studies with fewer than 10 patients

Study Component	Inclusion	Exclusion
	<p>sufficient information on baseline status and measurements, have sufficient follow-up time to evaluate progression, and clearly articulate changes from baseline</p> <ul style="list-style-type: none"> • <u>KQ 2</u> (second part): Longitudinal studies directly comparing functional imaging modalities • <u>KQ4-5</u>: Studies that report on adverse events from functional neuroimaging in this patient population • <u>KQ5</u>: Studies from KQ2/5 which stratify on patient or other characteristics and formally evaluate statistical interaction (effect modification) • <u>KQ 6</u>: Only full, formal economic studies (i.e., cost-effectiveness, cost-utility, cost-minimization, and cost-benefit studies) will be considered. 	<ul style="list-style-type: none"> • Case reports • Case control studies
Publication	<ul style="list-style-type: none"> • Studies published in English in peer reviewed journals or publically available FDA reports 	<ul style="list-style-type: none"> • 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

3.1.2.1. Population

For inclusion, the study population must consist of at least 80% of patients with diagnoses of interest. 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)

Studies that used functional neuroimaging on asymptomatic patients were excluded if these patients consisted of more than 20% of the population or if the results for these patients were not presented separately from those of patients with diagnoses of interest.

3.1.2.2. Index and comparator tests

Diagnostic functional neuroimaging modalities of interest include:

- 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., ^{99m}Tc-HMPAO-SPECT) and dopamine transporter uptake (e.g., ¹²³I-FP-CIT-SPECT, ¹²³I-ioflupane-SPECT, Dat-SCAN)

- fMRI (functional MRI)

For inclusion, studies were required to make a diagnosis/prediction using functional neuroimaging; studies that utilized functional neuroimaging but did not use the scans to make a diagnosis/prediction were excluded. For interpretation of functional neuroimaging tests, studies must have used a previously developed cut-off value (i.e., threshold) or use generally accepted methods for interpreting scans (see section 2.5 and EFNS guidelines⁵¹). Other imaging modalities that were excluded include PET to assess the presence of beta-amyloid protein (e.g., PIB-PET, beta-amyloid-PET, Flortetapir PET), structural neuroimaging (e.g., CT, MRI), electroencephalography, magnetoencephalography, magnetic resonance spectroscopy, and near-infrared spectroscopy.

For Key Question 2, comparator tests of interest included functional neuroimaging methods (i.e., two different modalities of interest directly compared with each other (e.g., FDG-PET vs HMPAO-SPECT)). Indirect comparisons will be excluded. For Key Questions 2, 3, 5, and 6, comparators of interest also included the comprehensive initial diagnostic work-up (including structural imaging).

3.1.2.3. Outcomes

The greatest emphasis was placed on outcomes that are directly related to the health outcomes of patients. This approach is consistent with that suggested by the AHRQ Methods Guide for Medical Test Reviews.⁷ Thus to the extent possible, less focus was placed on test performance characteristics such as reliability, sensitivity, and specificity. The *a priori* defined primary outcomes of interest included patient progression, function, quality of life, behavior, psychological status, safety/harms of the test, and cost-effectiveness. Secondary outcomes included cognition, depression, caregiver burden, global outcomes, impact on therapeutic decisions, and impact on clinical management. Diagnostic test performance measures were considered intermediate outcomes. Results of the context questions on diagnostic reliability and accuracy (sensitivity, specificity) were summarized briefly. Outcome measures used in the studies included in the report are summarized in Table 1. Because positive and negative predictive values are highly dependent on disease prevalence (higher prevalence leads to higher predictive values) and can be misleading and inaccurate if the disease prevalence in the population being studied is different than that expected in the population in which the test is being used, emphasis was not placed on these values, though they were included in the detailed appendix tables (Appendix G). Technical efficacy (i.e., the ability of the diagnostic test to conform to technical specifications) outcomes were excluded.

3.1.2.4. Study design

The focus for all key questions was placed on studies with the least potential for bias. Because relatively few prospective studies were identified, retrospective studies were included. For inclusion, studies must have made a diagnosis/prediction based on functional neuroimaging scans using criteria specified *a priori*. For inclusion in the accuracy context question and Key Question 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 Key Question 2, longitudinal studies with at least one year follow-up and designed specifically to evaluate progression were considered. Focus was placed first on studies with the least potential for bias; that is, CoE I and CoE II studies. For CoE III studies, greater focus was placed on those conducted retrospectively. The following study types were excluded: case control studies, studies with less than 10 patients (including case reports). For Key Question 3, studies that reported on changes in therapeutic decisions or clinical management following functional neuroimaging compared with those made for patients who did not receive functional neuroimaging were sought. For Key Question 4, studies that reported on adverse

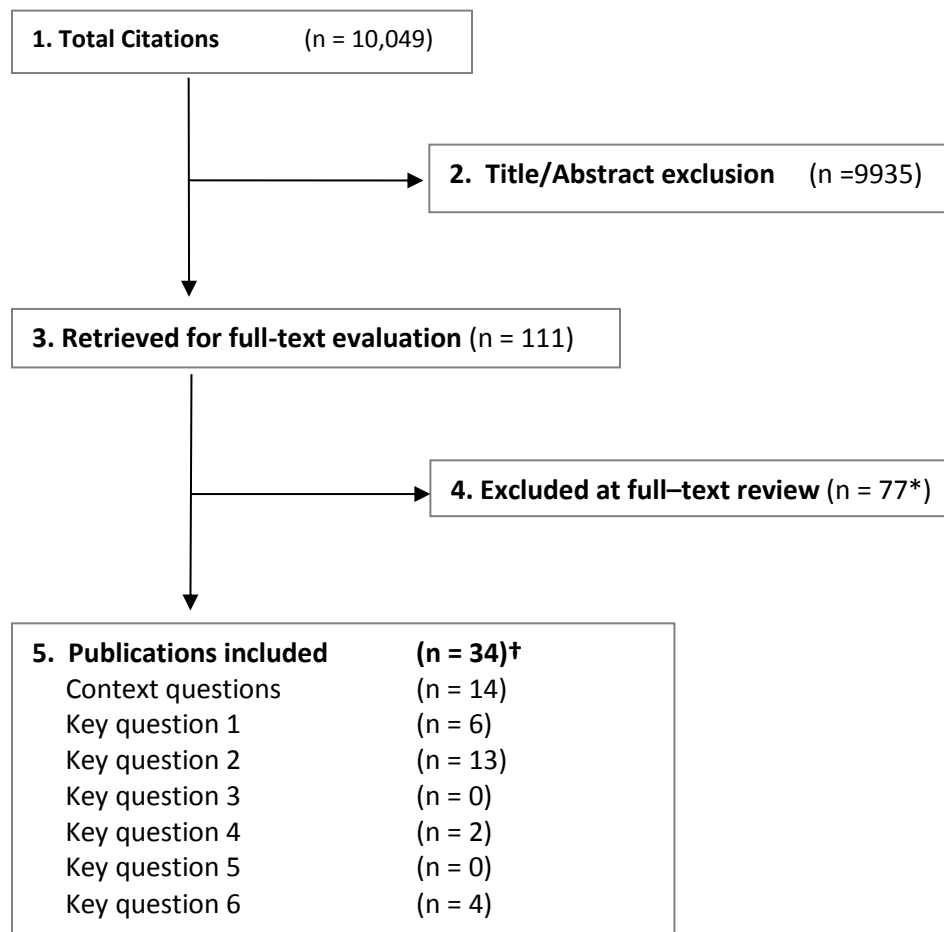
events/harms from the neuroimaging procedure in the patient population of interest were sought. For Key Question 5, all studies that reported on the use of functional neuroimaging to predict progression and/or clinical outcomes (i.e., studies included in Key Question 2) and which stratified on patient or other characteristics and formally evaluated effect modification were sought. For Key question 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.

3.1.3. Data sources and search strategy

The clinical studies included in this report were identified using the algorithm shown in Appendix A. The search took place in four stages. The first stage of the study selection process consisted of a comprehensive literature search using electronic means and hand searching. We then screened all possible relevant articles using titles and abstracts in stage two. This was done by one to two individuals independently. Those articles that met a set of *a priori* retrieval criteria based on the criteria above were included. Any disagreement between screeners that were unresolved resulted in the article being included for the next stage. Stage three involved retrieval of the full text articles remaining. The final stage of the study selection algorithm consisted of the selection of those studies using a set of *a priori* inclusion criteria, again, by two independent investigators. Those articles selected form the evidence base for this report.

We searched electronic databases from their inception through June 25, 2014 to determine new publications since our original report. Electronic databases searched included PubMed, *The Cochrane Library*, FDA, and AHRQ for eligible studies, including health technology assessments (HTAs), systematic reviews, primary studies and FDA reports. The search strategies used for PubMed are shown in Appendix B. Figure 2 shows a flow chart of the results of all searches for included primary studies. Articles excluded at full-text review are listed in Appendix C.

Figure 2. Flow chart of literature search results



*Six studies (in addition to these 77) were excluded from addressing one key (or context) question but included to address other questions in the report. All excluded studies are listed in Appendix C.

† Five studies were included in more than one key (or context) question.

3.1.4. Data extraction

Reviewers extracted the following data from the studies included to address Key Questions 1-5: inclusion/ exclusion criteria, number of raters (if applicable), imaging modality/tracer, diagnosis, demographics and disease severity, gold standard (if applicable), interval between imaging and outcome, method for interpreting test, and results. For Key Question 6, data related to sources used, economic parameters and perspectives, results, and sensitivity analyses were abstracted. An attempt was made to reconcile conflicting information among multiple reports presenting the same data. Detailed data abstraction tables are available in Appendices F and G.

3.1.5. Study quality assessment: Class of evidence (CoE) and QHES evaluation

The method used by Spectrum Research, Inc. (SRI) for assessing the quality of evidence of individual studies as well as the overall quality of evidence incorporates aspects of the rating scheme developed by the Oxford Centre for Evidence-based Medicine,¹³⁶ precepts outlined by the Grades of Recommendation Assessment, Development and Evaluation (GRADE) Working Group,⁶ and recommendations made by the Agency for Healthcare Research and Quality (AHRQ).¹⁸² Economic studies were evaluated according to The Quality of Health Economic Studies (QHES) instrument developed by Ofman et al.¹²⁷ Details of the CoE and QHES methodology are available in Appendix D. Based on these quality criteria, each study chosen for inclusion for a Key Question was given a CoE (or QHES) rating; details of each rating are available in Appendix E. Standardized abstraction guidelines were used to determine the CoE (or QHES) rating for each study included in this assessment. Studies were considered to have been conducted retrospectively unless clearly stated otherwise.

3.1.6. Analysis

For Key Questions 1 to 5, an attempt was made to pool results when there were three or more studies of similar quality and that employed similar imaging and outcome interpretation. However, because of differences in study quality (i.e., CoE I/II studies were not pooled with CoE III studies), methodology between studies, including differences in imaging interpretation and cut-off values, clinical interpretation, and/or length of follow-up, none of the outcomes were pooled. For studies reporting on diagnostic accuracy, true positive (TP), false positive (FP), false negative (FN), and true negative (TN) values were abstracted or calculated from studies whenever possible. When studies did not report the prevalence, sensitivity and/or specificity, values were calculated either manually or using an online calculator (http://www.medcalc.org/calc/diagnostic_test.php).

3.1.7. Assessment of the Overall Strength of Evidence

The strength of evidence for the overall body of evidence for all primary health outcomes was assessed by one researcher following the principles for adapting GRADE (Grades of Recommendation Assessment, Development and Evaluation) as outlined by the Agency for Healthcare Research and Quality (AHRQ) in the Methods Guide for Medical Tests⁷. In determining the strength of body of evidence regarding a given outcome, the following domains were considered:

- Risk of bias: the extent to which the included studies have protection against bias
- Consistency: the degree to which the included studies report results that are similar in terms of range and variability.
- Directness: describes whether the evidence is directly related to patient health outcomes.
- Precision: describes the level of certainty surrounding the effect estimates.

- Publication bias: is considered when there is concern of selective publishing.

Bodies of evidence consisting of studies that are CoE I/II were initially considered as High strength of evidence, while those made of CoE III/IV studies began as Low strength of evidence. The strength of evidence could be downgraded based on the limitations described above. There are also situations where the CoE III/IVs studies could be upgraded, including the presence of plausible unmeasured confounding and bias that would decrease an observed effect or increase an effect if none was observed, and large magnitude of effect (strength of association). The final strength of evidence was assigned an overall grade of high, moderate, low, or insufficient, which are defined as follows:

- **High** - Very confident that effect size estimates lie close to the true effect for this outcome; there are few or no deficiencies in the body of evidence; we believe the findings are stable.
- **Moderate** – Moderately confident that effect size estimates lie close to the true effect for this outcome; some deficiencies in the body of evidence; we believe the findings are likely to be stable but some doubt remains.
- **Low** – Limited confidence that effect size estimates lie close to the true effect for this outcome; 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.
- **Insufficient** – We have no evidence, are unable to estimate an effect or have no confidence in the effect estimate for this outcome; OR no available evidence or the body of evidence has unacceptable deficiencies precluding judgment.

Similar methods for determining the overall quality (strength) of evidence related to economic studies have not been reported, thus the overall strength of evidence for outcomes reported in Key Question 6 was not assessed.

3.1.8. Quality of studies available

The quality of evidence available is presented at the beginning of each results section.

4. Results

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

4.1.1. Summary

- **FDG-PET:**
 - Evidence base: 7 studies (5 CoE I, 1 CoE II, 1 CoE III); N = 45-132.^{54,57,67,146,163,190,191}
 - Visual assessments of FDG-PET blinded to clinical information.
 - Inter-rater reliability for discriminating AD vs. FTD :
 - Kappa ranged from 0.72-0.81 (i.e., substantial to almost perfect agreement) (3 studies (2 CoE I & 1 CoE II), 2-6 raters, N = 45-132)^{54,57,146}
 - Agreement between all raters: 76% of cases (1 study (CoE 1), 12 raters, N = 45)¹⁹⁰
 - Inter-rater reliability for distinguishing AD from other dementias:
 - Kappa ranged from 0.52-0.67 (i.e., moderate to substantial agreement) (2 studies (1 CoE I, 1 CoE III), 3 raters, N = 67-110)^{67,191}
 - Agreement between raters: 94% cases (1 study (CoE 1), 2 raters, N = 100)¹⁶³
 - Intra-rater reliability for diagnosing AD demonstrated moderate agreement: mean kappa from 3 raters of 0.52 (range, 0.50, 0.94) (1 study, CoE II, N = 110).⁶⁷
- **¹¹C-DTBZ-PET:**
 - Evidence base: 1 study (CoE II); N = 27.⁸⁴
 - Inter-rater reliability for discriminating AD, FTD, and DLB demonstrated almost perfect agreement: Kappa: 0.85 (3 raters).
 - Intra-rater reliability for discriminating AD, FTD, and DLB was not reported.
- **HMPAO-SPECT:**
 - Evidence base: 2 studies (CoE III); N = 16-57.^{41,100}
 - Inter-rater reliability for discriminating AD vs. FTD:
 - Kappa: 0.48 (i.e., moderate agreement) (1 study, 2 raters, N = 16).¹⁰⁰
 - Agreement between all raters: 35% cases. (1 study, 5 raters, N = 57)⁴¹
 - Intra-rater reliability for discriminating AD vs. FTD: not reported.
- **¹²³I-FT-CIT-SPECT:**
 - Evidence base: 2 studies (CoE I); N = 20-288.^{94,182}
 - Inter-rater reliability for differentiating between DLB and non-DLB dementias:
 - Kappa: 0.87 (95% CI, 0.79-0.94) (i.e., almost perfect agreement) (1 study, 3 raters, N = 288).⁹⁴
 - Agreement between all raters: 75% cases (1 study, 3 raters, N = 20).¹⁸²
 - Intra-rater reliability for differentiating between DLB and non-DLB dementias: not reported.
- **fMRI, ASL:** No studies identified.

4.1.2. Number of studies retained

Studies that evaluated the diagnostic inter- or intra-rater reliability of functional neuroimaging to diagnose MCI and/or dementia patients were sought. For inclusion, the same method must have been used by each rater or at each test/re-test. From a list of 44 studies that explicitly included wording related to reliability, 12 studies met our inclusion criteria.^{41,54,57,67,84,94,100,146,163,182,190,191} Specific reasons for excluding each of 32 studies at full-text review are documented in Appendix C; the majority of these studies did not evaluate the reliability of using functional neuroimaging to make a diagnosis.

Functional neuroimaging modalities for which inter- or intra-rater diagnostic reliability studies were identified include FDG PET (seven studies), DTBZ-PET (1 study), HMAPO-SPECT (2 studies), and ¹²³I-FP-CIT-SPECT (2 studies). No studies were identified for fMRI or ASL.

4.1.3. Critical appraisal of included studies

Of the 12 studies that met our inclusion criteria, seven were considered to be at low risk of bias (CoE I), meeting all the requirements for a good-quality reliability study.^{54,57,94,163,182,190,191} One was considered to be at moderately low risk of bias (CoE II): the study did not provide details as to whether the second interpretation of the test was performed independently of the first.¹⁴⁶ Four studies were found to be at moderately high risk of bias (CoE III): none indicated whether the second test was assessed independently of the first, two did not provide adequate descriptions of the population to judge whether a broad spectrum of patients with the expected condition(s) were included,^{41,67} one study did not provide information to determine whether the tests were evaluated in a manner such that they were blinded to clinical information,⁸⁴ and one did not provide adequate description of the methodology used for replication.¹⁰⁰

Two studies (Gabel 2010⁵⁷; Womack 2011¹⁹⁰) reported reliability data from the same patient set used in Foster 2007⁵⁴. It was unclear how much overlap there was between the raters across these studies. While Foster et al. utilized six experienced neurologists who were either experts or novices in evaluating FDG-PET images,⁵⁴ Gabel et al. employed six expert raters.⁵⁷ Womack et al. reported reliability data from 12 raters and the data includes that from the 6 raters used in Foster 2007.¹⁹⁰

Specific information regarding the CoE rating for each study is detailed in Appendix E.

4.1.4. Detailed results

FDG-PET (Table 7)

Seven studies evaluated the inter-rater reliability of FDG-PET, of which five were considered to be at low risk of bias (CoE I),^{54,57,163,190,191} one was to be at moderately low risk of bias (CoE II),¹⁴⁶ and one to be at moderately high risk of bias (CoE III).⁶⁷ In general, AD was distinguished from other types of dementia on the basis of bilateral temporoparietal hypometabolism, and in some studies, hypometabolism in the posterior cingulate cortices as well. In each study, the raters were blinded to clinical diagnosis. Overall, there was moderate to almost perfect agreement between raters in making a diagnosis using FDG-PET images, with mean or median kappa ranging from 0.52 to 0.81.

In terms of the reliability of using FDG-PET to discriminate between AD and FTD, four studies reported substantial to almost perfect agreement between 2 and 12 raters with kappa ranging from 0.72 to 0.81 as reported by three studies (2 of which, Foster and Gabel, used the same patient population but not all of the same raters),^{54,57,146} and agreement between all 12 raters in 76% of scans as reported by one study (which used the same patient population as the Foster study).¹⁹⁰

Three studies evaluated the reliability to distinguish AD from other dementias, either progressive or non-progressive patterns.^{67,163,191} Two studies reported moderate to substantial agreement among three raters, with kappa ranging from 0.52 to 0.67.^{67,191} One study reported 94% agreement between two raters in distinguishing AD from non-AD progressive dementia versus non-progressive patterns in 100 patients presenting with dementia.¹⁶³

Test-retest reliability was reported by one study (Hoffman 1996) to have moderate reliability (median kappa: 0.55 (range, 0.50-0.64)) as measured by three different raters on two separate occasions by one study.⁶⁷

¹¹C-DTBZ-PET (Table 8)

One study evaluated the inter-rater reliability of distinguishing AD, FTD, DLB, and normal controls using ¹¹C-DTBZ-PET.⁸⁴ The study was considered to be at moderately high risk of bias (CoE III). ¹¹C-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 ¹¹C-DTBZ. 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 ¹¹C-DTBZ DV deficits in the striatum. Overall, there was almost perfect agreement between three raters blinded to the clinical diagnosis of 27 patients in terms of the ability to distinguish AD, FTD, DLB, and normal controls using composite images of ¹¹C-DTBZ K_1 and DV, with a kappa of 0.85.⁸⁴ Test-retest reliability was not assessed.

HMPAO-SPECT (Table 9)

Two studies assessed the inter-rater reliability of distinguishing between AD and FTD and other diagnoses using HMPAO-SPECT, both of which were found to be at moderately high risk of bias (CoE III).^{41,100} HMPAO-SPECT allows readers to visualize regional cerebral blood flow; however, neither study detailed the specific regions of interest for which hypoperfusion was associated with a diagnosis of AD versus FTD. McNeill et al. reported moderate agreement between two blinded raters who used visual assessment of SPECT images to diagnose 56 patients with either FTD, AD, or “non-specific”, with a kappa of 0.48.¹⁰⁰ In terms of diagnosing patients with either AD, FTD, vascular dementia, or normal, Doran et al. reported relatively poor agreement amongst five blinded raters (35% agreement) who assessed the scans of 57 patients with cognitive impairment for whom the clinical diagnosis was unclear.⁴¹ Interestingly, the percent agreement was even lower (35%) when the raters had access to patient information (i.e., symptoms, history). The same study reported 63% agreement in terms of making a general assessment of normal versus abnormal.⁴¹ Test-retest reliability was not evaluated in either study.

¹²³I-FP-CIT-SPECT (Table 10)

Two studies assessed the inter-rater reliability of differentiating between DLB and non-DLB dementias (primarily AD) using ¹²³I-FP-CIT-SPECT.^{94,182} Both studies were considered to be at low risk of bias (CoE I). ¹²³I-FP-CIT is a ligand for the dopamine transporter (DAT); DAT loss is a consequence of the nigrostriatal degeneration that occurs with DLB but not AD. Both studies reported good inter-rater reliability for distinguishing DLB from non-AD dementias. McKeith et al. reported an overall kappa of 0.87 (95% CI, 0.79, 0.94) for the inter-rater reliability between three raters who blindly evaluated 288 scans,⁹⁴ while Walker et al. reported agreement between three blinded raters in 75% of 19 scans.¹⁸² Intra-rater (test-retest) reliability was not assessed.

Table 7. Overview of primary findings for reliability studies on FDG-PET

Study (CoE)	Clinical Diagnosis	FDG-PET Diagnosis	Raters	Inter-Rater Reliability	Intra-Rater (Test-Retest) Reliability	Blinded To Clinical Diagnosis?	FDG-PET Diagnostic Criteria
Foster 2007 ⁵⁴ (CoE I)	N = 45: AD (n = 31) FTD (n = 14)	AD vs. FTD	6 (individual raters, mix of experts & novices)	<u>Kappa (mean):</u> Transaxial: 0.73 3D-SSP: 0.78	NR	yes	AD: greater hypometabolism in the posterior association cortex and posterior cingulate gyrus (vs. the anterior regions) FTD: greater hypometabolism in the frontal association cortex, anterior temporal cortex, and anterior cingulate gyrus (vs. posterior regions)
Gabel 2010 ⁵⁷ (CoE I)			6 (experts)	<u>Kappa (mean):</u> 3D-SSP: 0.81	NR	yes	
Womack 2011 ¹⁹⁰ (CoE I)			12*	Agreement in 76% cases (12/12 raters)	NR	yes	The presence of hypometabolism in each individual region (frontal, temporoparietal, anterior temporal, anterior cingulate, posterior cingulate) was correlated with pathology of FTD vs. AD, however no clear description of how a final diagnosis of FTD vs. AD using SPECT images was provided.
Rabinovici 2011 ¹⁴⁶ (CoE II)	N = 132: AD (n=62) FTD (n=45) Normal controls (n=25)†	AD vs. FTD	2	<u>Kappa:</u> 0.72 (95% CI, 0.56, 0.84)	NR	yes	AD: hypometabolism greatest in the temporoparietal cortex FTD: hypometabolism most severe in the frontal or anterior temporal cortex
Hoffman 1996 ⁶⁷ (CoE III)	N = 110: Probable AD (n=18) Possible AD (n=33) Dementia (n=26)	AD vs. other	3	<u>Kappa (median)§:</u> 0.52 (range, 0.46-0.56)	<u>Kappa (median)**:</u> 0.55 (range, 0.50-0.64)	yes	AD: bilateral temporoparietal hypometabolism

Study (CoE)	Clinical Diagnosis	FDG-PET Diagnosis	Raters	Inter-Rater Reliability	Intra-Rater (Test-Retest) Reliability	Blinded To Clinical Diagnosis?	FDG-PET Diagnostic Criteria
	MMI (n=17) Other (n=16)‡						
Yamane 2014 ¹⁹¹ (CoE I)	N = 67: Mild AD (n = 100) MCI (n = 67)	AD vs. non-progressive patterns	3	<u>Kappa (mean) §:</u> FDG-7 (7 categories for diagnosis): 0.57 FDG (2 categories for diagnosis): 0.67	NR	yes	AD: For FDG with 7 categories for diagnosis, AD in scans with focal cortical hypometabolism in parietal, temporal, and/or frontal lobes (as Silverman 2001) <u>or</u> AD: For FDG with 2 categories for diagnosis, AD in scans with posterior-predominate hypometabolism patterns
Silverman 2001 ¹⁶³ (CoE I)	N = 100: Dementia (n=100)	AD vs. progressive dementia (not AD) vs. non-progressive patterns	2	Agreement in 94% cases (2/2 raters)	NR	yes	AD: focal cortical hypometabolism in parietal, temporal, and/or frontal lobes

NR: not reported

* Womack 2001: uses same patient population and data from 6 raters reported in Foster 2007.

† Rabinovici 2011: Because this population of normal controls consisted of less than 20% of the total patient population evaluated, the study was included.

‡ Hoffman 1996: Other diagnoses with 1-3 patients each included Pick’s disease, Huntington’s disease, subcortical dementia, vascular dementia, tumor, encephalitis, toxic encephalopathy, anxiety disorder, and healthy controls. Because this population of many excluded conditions consisted of less than 20% of the total patient population evaluated, the study was included.

§ Hoffman 1996, Yamane 2014: 2 raters per kappa value

** Hoffman 1996: median test-retest for each of the 3 raters

Table 8. Overview of primary findings for reliability studies on ¹¹C-DTBZ-PET

Study (CoE)	Clinical Diagnosis	¹¹ C-DTBZ-PET Diagnosis	Raters	Inter-Rater Reliability	Intra-rater (Test-Retest) Reliability	Blinded To Clinical Diagnosis?	¹¹ C-DTBZ-PET Diagnostic Criteria
Koeppel 2005 ⁸⁴ (CoE III)	N = 27: FTD (n=6) AD (n=8) DLB (n=8) NC (n=5)*	AD vs. FTD vs. DLB vs. normal	3 raters	Kappa (mean): ¹¹ C-DTBZ K ₁ and DV: 0.85	NR	yes	AD: ligand (K ₁) binding deficits in the posterior cingulate, superior parietal, and inferior tempoparietal cortex, sometimes with frontal deficits, but with relative sparing of the sensorimotor cortex DLB: AD criteria with the presence of ¹¹ C-DTBZ DV deficits in the striatum FTD: presence of primary K ₁ deficits in frontal or temporal cortex, with frontal deficits being greater than posterior deficits

DTBZ: dihydrotetrabenazine (binds to nigrostriatal terminal); DV: distribution volume (of nigrostriatal terminal); K1: measure of transport (of ¹¹C-DTBZ to nigrostriatal terminal); NR: not reported

* Koeppel: Because the population of normal controls consisted of less than 20% of the total patient population evaluated, the study was included.

Table 9. Overview of primary findings for reliability studies on HMPAO-SPECT

Study (CoE)	Clinical Diagnosis	HMPAO-SPECT Diagnosis	Raters	Inter-Rater Reliability	Intra-Rater (Test-Retest) Reliability	Blinded To Clinical Diagnosis?	HMPAO-SPECT Diagnostic Criteria
Doran 2005 ⁴¹ (CoE III)	N = 57: Cognitively impaired, diagnosis uncertain (n=57) Note: young patient population (59 ± 11 years)	Normal vs. abnormal AD vs. FTD/focal syndrome vs. VaD vs. normal	5 raters	Agreement in 63% cases (5/5 raters) Agreement in 35% cases (5/5 raters)	NR	yes	Diagnosis based on the presence of perfusion deficits and if so, whether they were focal or multifocal, symmetrical or asymmetrical, and anterior or posterior. However, no clear description of how a final diagnosis using SPECT images was provided.
McNeill 2007 ¹⁰⁰ (CoE III)	N = 16: 16 scans from: FTD (n=25) AD (n=31)	AD vs. FTD vs. "non-specific"	2 raters	<u>Kappa:</u> 0.48	NR	yes	The presence of hypoperfusion in each individual region (frontal, parietal, temporal and occipital) was correlated with pathology of FTD vs. AD, however no clear description of how a final diagnosis of FTD vs. AD using SPECT images was provided.

NR: not reported

Table 10. Overview of primary findings for reliability studies on ¹²³I-FP-CIT-SPECT

Study (CoE)	Clinical Diagnosis	¹²³ I-FP-CIT-SPECT Diagnosis	Raters	Inter-Rater Reliability	Intra-Rater (Test-Retest) Reliability	Blinded To Clinical Diagnosis?	¹²³ I-FP-CIT-SPECT diagnostic criteria
McKeith 2007 ⁹⁴ (CoE I)	N = 288: Probable DLB (n=88) Possible DLB (n=56) Probable AD (n=90) Possible AD (n=34) Probable VaD (n=1) Possible VaD (n=8) Dementia, diagnosis unclear (n=11)	Abnormal (DLB) vs. normal (non-DLB)	3 raters	Kappa: 0.87 (95% CI, 0.79, 0.94)	NR	yes	DLB ("abnormal"): asymmetric uptake with normal or almost normal putamen activity in one hemisphere and a more marked change on the other side, greatly reduced uptake in the putamen in both sides, or virtually absent uptake.
Walker 2007 ¹⁸² (CoE I)	N = 20: DLB (n=13) AD (n=6) Corticobasal degeneration (n=1)	DLB vs. non-DLB	3 raters	Agreement in 75% cases (3/3 raters)	NR	yes	DLB ("abnormal"): significantly reduced uptake in any of the following regions: right caudate, left caudate, right putamen, left putamen

NR: not reported

4.2. Context question: Provide a summary of the sensitivity and specificity of diagnostic functional neuroimaging based on an appropriate gold standard (e.g., autopsy)

4.2.1. Summary

- **FDG-PET:**
 - Evidence base: 2 retrospective studies (one CoE II, one CoE IV); N = 55-138.^{68,163}
 - Gold standard: autopsy.
 - Visual assessments of FDG-PET to diagnose AD: 93-95% sensitivity; 63-73% specificity (2 studies, N = 55-138).^{68,163}
 - Combination of FDG-PET + clinical diagnosis: not reported.
 - Clinical diagnosis of probable or possible AD (according to NINCDS-ADRDA criteria): 79% sensitivity; 88% specificity (1 CoE IV study, N = 55).⁶⁸
- **HMPAO-SPECT:**
 - Evidence base: 1 retrospective study (CoE IV); N = 73.²³
 - Gold standard: autopsy.
 - Visual assessments of HMPAO-SPECT to diagnose AD: 93% (95% CI, 81-98%) sensitivity; 85% (95% CI, 64-95%) specificity.²³
 - Diagnostic accuracy of clinical diagnosis alone or the combination of FDG-PET and clinical diagnosis was not reported.
- **¹²³I-FT-CIT-SPECT:**
 - Evidence base: 1 prospective study (CoE I); N = 20.¹⁸²
 - Gold standard: autopsy.
 - Visual assessments of FP-CIT-SPECT to diagnose DLB: 88% sensitivity; 83% specificity.¹⁸²
 - Semi-quantitative interpretations of FP-CIT-SPECT to diagnose DLB: 88% sensitivity; 100% specificity.¹⁸²
 - Diagnostic accuracy of the combination of SPECT and clinical diagnosis was not reported.
 - Clinical diagnosis of DLB (Consensus DLB criteria): 75% sensitivity; 42% specificity.¹⁸²
- **¹¹C-DTBZ-PET, fMRI, ASL:** No studies identified.

4.2.2. Number studies retained

Studies that evaluated the diagnostic accuracy of functional neuroimaging to diagnose MCI and/or dementia were sought. For inclusion, an appropriate gold standard must have been used; in nearly all cases, this was autopsy. Of 25 studies that explicitly included wording related to diagnostic accuracy (i.e., sensitivity, specificity), four studies met the inclusion criteria for this context question^{23,68,163,182} (and six studies met the inclusion criteria for Key Question 1). Specific reasons for excluding each of the 15 studies at full-text review are documented in Appendix C; several studies were excluded on the basis of including more than 20% of patients without dementia or with excludable clinical diagnoses in the diagnostic accuracy estimates.

Functional neuroimaging modalities for which diagnostic accuracy studies were identified include FDG-PET (2 studies), HMPAO-SPECT (1 study), and FP-CIT-SPECT (1 study). No studies were identified for fMRI or ASL.

4.2.3. Critical appraisal of included studies

One of the four studies that met our inclusion criteria was prospectively conducted and were considered to be at low risk of bias (CoE I),¹⁸² meeting all the requirements for a good-quality diagnostic accuracy study. The remaining three studies were conducted retrospectively. One was considered to be at moderately low risk of bias (CoE II)¹⁶³ and met all the criteria of a good quality retrospective diagnostic test study. The remaining two studies were considered to be at high risk of bias (CoE IV): neither provided sufficient detail to determine whether they included a broad spectrum of patients with the expected condition or whether autopsy was performed blinded to diagnostic test.^{23,68} Further, Bonte et al. did not provide sufficient details regarding how the autopsy results were interpreted to allow for replication.²³ Specific information regarding the CoE rating for each study is detailed in Appendix E.

4.2.4. Detailed results

FDG-PET (Table 11)

Two studies assessed the diagnostic accuracy of correctly identifying AD with FDG-PET based on autopsy.^{68,163} In both studies, scan results were classified after visual assessment; all raters were blinded to the clinical diagnosis. Both diagnosed AD based on the presence of tempoparietal hypometabolism. On average, there was 2.1 to 2.9 years (range of means) between FDG-PET scans and autopsy. Overall, AD was diagnosed with a sensitivity ranging from 93-95% and a specificity ranging from 63-73%.

In a good quality retrospective study (CoE II), Silverman et al.¹⁶³ evaluated sensitivity and specificity of FDG-PET obtained at the initial evaluation for diagnosing AD in 138 patients who presented with dementia. Dementia severity ratings were available for 79 of the 138 patients, and included patients with questionable (22%), mild (48%), moderate (16%), and severe (14%) dementia. Patients had a mean age of 67 ± 10 years, and 59% were male. Autopsy revealed that the prevalence of AD was 70%. The authors reported FDG-PET to have a sensitivity of 94% (95% CI, 89-99%) and a specificity of 73% (95% CI, 60-87%). Results were similar in a subset of 55 patients with mild or questionable AD (sensitivity: 95%; specificity: 71%); the prevalence of AD in this subset was 75%. No comparison to the accuracy of clinical diagnosis in this population was made.

In a poor quality retrospective study (CoE IV) Hoffman et al.⁶⁸ evaluated 22 patients who presented with memory loss or dementia that was difficult to diagnose clinically. The mean age at FDG-PET was 65.5 ± 9.4 years and 68% were male. A diagnosis of AD was made by autopsy (or biopsy in two cases) in 68% of patients. Diagnosis of AD with FDG-PET scans alone yielded a sensitivity of 93% and a specificity of 63%. In contrast, a clinical diagnosis of probable or possible AD (according to NINCDS-ADRDA criteria) had lower sensitivity (79%) but higher specificity (88%).

HMPAO-SPECT (Table 12)

One poor-quality retrospective study (CoE IV) by Bonte et al. evaluated the diagnostic accuracy of Tc-99m HMPAO-SPECT based on the gold standard of autopsy in 73 dementia patients.²³ There was a mean of 5.9 years between SPECT and autopsy. Diagnosis at autopsy was AD (with or without Lewy bodies) in 64% of patients. No demographic details about this series of patients were presented. A physician blinded to the clinical diagnosis visually assessed the scans and diagnosed patients for the presence or absence of AD, which was classified based on the presence regional hypoperfusion in the hippocampus,

temporal lobes, parietal lobes, posterior cingulate cortex, left caudate nucleus, or inferior occipital cortex (as compared to the control group); however no clear definition of what constituted an AD pattern was reported. The authors reported high sensitivity (93% (95% CI, 81%, 98%)) and specificity (85% (95% CI, 64%, 95%)) for diagnosing AD in a series of dementia patients using HMPAO-SPECT.

¹²³I-FP-CIT-SPECT (Table 13)

In a good quality prospective study (CoE I), Walker et al. evaluated the diagnostic accuracy of ¹²³I-FP-CIT-SPECT compared with autopsy for identifying the presence of DLB in 20 dementia patients.¹⁸² At the time of SPECT, patients had a mean age of 77 years, and 30% of patients were male. SPECT scans were obtained a mean of 4 years after the onset of dementia, and autopsy was performed after death a mean of 2.8 years later. DLB was identified at autopsy either alone or in conjunction with AD or vascular dementia in 40% of patients. Both visual and semi-quantitative assessments of the SPECT scans were performed, with raters blinded to the clinical diagnosis. Scans visually interpreted to have significantly reduced ligand uptake in any of the four regions of interest (right and left caudate, right and left putamen) were classified as DLB. For semi-quantitative analysis of the scans, binding levels were calculated, and scans in which binding in the posterior putamen was at least two standard deviations below the mean of that in control scans were considered to have DLB. Both visual and semi-quantitative interpretations of FP-CIT-SPECT scans yielded high sensitivity (88%) based on autopsy results. While the visual rating method had good specificity (83%), the semi-quantitative rating had perfect specificity (100%). In comparison, clinical diagnosis of DLB in accordance with the Consensus DLB criteria achieved 75% sensitivity and 42% specificity.

Table 11. Overview of primary findings for diagnostic accuracy studies on FDG-PET

Study	CoE	Diagnosis At Autopsy	Interval: Imaging To Autopsy	FDG-PET Diagnostic Criteria	Diagnostic Test	Sensitivity	Specificity
Silverman 2001 ¹⁶³	II	N = 138: AD (70.3%) Neurodegenerative disease (not AD) (16.7%) No neurodegenerative dementia (13.0%)	2.9 yrs. (range, 1.0-9.4) yrs.	AD: Focal cortical hypometabolism in parietal, temporal, and/or frontal lobes	FDG-PET	94% (95% CI, 89-99%)	73% (95% CI, 60-87%)
					FDG-PET + clinical diagnosis	NR	NR
					Clinical diagnosis	NR	NR
		FDG-PET			95% (95% CI, 89-100%)	71% (95% CI, 48-95%)	
		FDG-PET + clinical diagnosis			NR	NR	
		Clinical diagnosis			NR	NR	
Hoffman 2000 ^{*68}	IV	N = 22 AD (63.6%) AD + LBD (4.5%) AD + PSP (4.5%) LBD (4.5%) Other (22.7%) [†]	2.1 ± 2.3 yrs.	AD: Classic bilateral temporoparietal hypometabolism <u>or</u> abnormal with varying degree of bilateral temporo-parietal hypometabolism.	FDG-PET	93%	63%
					FDG-PET + clinical diagnosis	NR	NR
					Clinical diagnosis	79%	88%

NR: not reported

*Hoffman: gold standard was autopsy alone in all but 2 patients, for whom gold standard was biopsy (n=2).

†Hoffman: “other” includes the following: neuronal degeneration (n=1), pre-amyloid (n=1), mesio-limbo cortical dementia (n=1), progressive supranuclear palsy (n=1), Creutzfeldt-Jacob disease (n=1)

Table 12. Overview of primary findings for diagnostic accuracy studies on HMPAO-SPECT

Study	CoE	Diagnosis At Autopsy	Interval: Imaging to Autopsy	HMPAO-SPECT diagnostic criteria	Diagnostic Test	Sensitivity	Specificity
Bonte 2011 ²³	IV	N = 73: AD (with or without Lewy bodies): (64%) Non-AD dementia (36%)	5.9 yrs.	AD: Significantly lower regional cerebral blood flow in the hippocampus, temporal lobes, parietal lobes, posterior cingulate cortex, left caudate nucleus, or inferior occipital cortex (as compared to the control group).	SPECT	93% (95% CI, 81-98%)	85% (95% CI, 64-95%)
					SPECT + clinical diagnosis	NR	NR
					Clinical diagnosis	NR	NR

NR: not reported

*Diagnosis at autopsy. See Appendix G for clinical diagnosis.

Table 13. Overview of primary findings for diagnostic accuracy studies on ¹²³I-FP-CIT-SPECT

Study (CoE)	CoE	Diagnosis At Autopsy	Interval: imaging to autopsy	FP-CIT-SPECT Diagnostic Criteria	Diagnostic Test	Sensitivity	Specificity
Walker 2007 ¹⁸²	I	N = 20: DLB (20%) DLB + AD (15%) DLB + VaD (5%) AD (15%) AD + VaD (30%) FTLD (5%) CBD (5%) Unspecified (5%)	2.8 yrs.	DLB: visual rating, significantly reduced uptake in any of the following regions: right caudate, left caudate, right putamen, left putamen	SPECT (visual)	88%	83%
					SPECT + clinical diagnosis	NR	NR
					Clinical diagnosis	75%	42%
				DLB: Semi-quantitative rating: hypo-metabolism defined as ≥ 2 SD	SPECT (semi-quantitative)	88%	100%
					SPECT + clinical diagnosis	NR	NR
					Clinical diagnosis	75%	42%

SD: standard deviation

4.3. Key question 1: What is the diagnostic accuracy of functional neuroimaging for the differential diagnosis of AD, FTD, and Lewy body dementia based on an appropriate gold standard (e.g., autopsy)?

4.3.1. Summary

- **FDG-PET: AD vs. FTD**
 - Evidence base: 3 retrospective studies (two CoE II, one CoE III); N = 10-45.^{54,57,146}
 - Prevalence of AD: 30-68%
 - Gold standard: autopsy.
 - Diagnosis of AD with FDG-PET alone:
 - Visual assessments using SPM or SSP images only: 94-98% sensitivity; 73-76% specificity (2 CoE II studies, N = 90 total).^{54,57}
 - One additional CoE III study reported 67% sensitivity and 93% specificity (N = 10).¹⁴⁶
 - Automated classification: 67% sensitivity, 100% specificity (1 study (CoE III), N = 10).¹⁴⁶
 - Additional information for context:
 - Combination of FDG-PET (visual classification) + clinical diagnosis: 90% sensitivity, 86% specificity (1 study (CoE II), N = 45).⁵⁷
 - Clinical diagnosis of AD (methods varied): 63-100% sensitivity, 79-100% specificity (3 studies, N = 10-45).^{54,57,146}
 - Note that sensitivity of an AD diagnosis is the same as the specificity of an FTD diagnosis (and vice versa).

- **HMPAO-SPECT: AD vs. FTD**
 - Evidence base: 1 retrospective study (CoE IV); N = 56.¹⁰⁰
 - Prevalence of AD: 55%
 - Gold standard: autopsy.
 - Diagnosis of AD with HMPAO-SPECT using visual classification: 65% sensitivity, 72% specificity.¹⁰⁰
 - Additional information for context:
 - Combination of SPECT + clinical diagnosis: 84% sensitivity & specificity.¹⁰⁰
 - Clinical diagnosis of AD after comprehensive work-up: 77% sensitivity, 88% specificity.¹⁰⁰
 - Note that sensitivity of an AD diagnosis is the same as the specificity of an FTD diagnosis (and vice versa).

- **FDG-PET: AD vs. DLB**
 - Evidence base: 2 retrospective studies (CoE III); N = 11-21.^{104,174}
 - Prevalence of DLB: 45-52%
 - Gold standard: autopsy.
 - Diagnosis of DLB (alone or in combination with AD) (versus AD alone): 80-90% sensitivity, 80-100% specificity (2 studies).^{104,174}
 - Additional information for context:
 - Diagnostic accuracy of clinical diagnosis either alone or in combination with SPECT was not reported.

- Note that sensitivity of a DLB diagnosis is the same as the specificity of an AD diagnosis (and vice versa).
- ¹²³I-FP-CIT-SPECT, ¹¹C-DTBZ-PET, fMRI, ASL: No studies identified.

4.3.2. Number of studies retained

Studies that evaluated the diagnostic accuracy of functional neuroimaging to differentially diagnose two different types of dementia were sought. For inclusion, an appropriate gold standard must have been used, which was autopsy in all studies. Six studies^{54,57,100,104,146,174} met our inclusion criteria for this key question; see section 4.2.1 and/or Appendix C for more information on studies excluded after full-text review.

Functional neuroimaging modalities for which differential diagnostic accuracy studies were identified include FDG-PET (5 studies) and HMPAO-SPECT (1 study). No studies were identified for FP-CIT-SPECT, fMRI, or ASL.

4.3.3. Critical appraisal of included studies

All six studies were conducted retrospectively. Two (Foster and Gabel) were considered to be good quality retrospective studies and at moderately low risk of bias (CoE II)^{54,57} and met the requirements for a good-quality diagnostic accuracy study. Three studies were found to be moderate quality retrospective studies and at moderately high risk of bias (CoE III)^{104,146,174}: each failed to meet one criteria for a good quality retrospective study: none indicated that the reference standard (autopsy) was conducted blinded to the functional neuroimaging test results. One study was found to be at high risk of bias (CoE IV), not meeting two criteria for a good quality retrospective study¹⁰⁰: it was not clear that the reference standard (autopsy) was conducted blinded to the functional neuroimaging test results, and an adequate description of the way in which an overall diagnosis was made using SPECT was not provided. Specific information regarding the CoE rating for each study is detailed in Appendix E.

4.3.4. Detailed results

Intermediate outcomes: Diagnostic accuracy measures

FDG-PET (Tables 14-15): AD vs. FTD

Three studies evaluated the diagnostic accuracy of FDG-PET for differentiating between AD and FTD.^{54,57,146} Two of these studies used the same patient population but at least some of the raters were different between the studies: while Foster et al.⁵⁴ utilized six experienced neurologists as raters, some of whom were considered novice and others experienced at interpreting FDG-PET scans, Gabel et al.⁵⁷ reported on the findings of a consensus panel of six expert raters. These two studies were considered to be at moderately low risk of bias (CoE II), while the third study (Rabinovici et al.) was considered to be at moderately high risk of bias. Autopsy served as the reference standard in all three studies, and was performed 4.7 ± 2.7 years after FDG-PET scans in the Foster/Gabel studies and 2.5 years post-scan in the Rabinovici study. The prevalence of AD was 68% in the Foster/Gabel studies and 30% in the Rabinovici study (and the remaining patients in each had FTD). All three studies classified scans after visual assessment in a manner blinded to clinical and autopsy information; SSP images were used by the Foster and Gabel studies,^{54,57} SPM-processed images were used by Rabinovici et al.,¹⁴⁶ and transaxial images additionally used by Foster et al.⁵⁴ In addition, Rabinovici et al. also employed automated classification. See Table 14 for additional details regarding image processing as well as patient demographics. Foster and Gabel classified scans as AD-positive on the basis of greater hypometabolism in the posterior cingulate cortex and posterior cingulate gyrus,^{54,57} while Rabinovici scored scans as positive for AD when

hypometabolism was greater in the lateral and medial temporoparietal cortex.¹⁴⁶ Foster and Gabel classified scans as FTD if hypometabolism was greater in the frontal association cortex, anterior temporal cortex, and anterior cingulate gyrus,⁵⁷ while Rabinovici looked for greater hypometabolism in two regions of interest: the frontal cortex anterior to the precentral gyrus as well as in the temporal pole and amygdala.¹⁴⁶ Overall, visual classification of AD (versus FTD) using FDG-PET scans had a sensitivity that ranged from 67% to 98% and a specificity that ranged from 59% to 93%.^{54,57,146} Note that the sensitivity of an AD diagnosis is equivalent to the specificity of an FTD diagnosis, and vice versa.

CoE I/II studies

The Foster and Gabel studies reported that the sensitivity of an AD diagnosis was similar regardless of whether transaxial or SSP images were used; the sensitivity in these two studies ranged from 94% to 98%. Use of SSP images resulted in a higher specificity (73% to 76%) than that obtained with transaxial images (59%).^{54,57}

Foster and Gabel also reported the diagnostic accuracy when only the “clinical scenario” was used.^{54,57} How this was defined was not clear, though the neurologists had access to medical records, neuropsychological data, and structural neuroimaging (MRI or CT). While Foster et al. reported that the clinical scenario yielded a diagnosis of AD with 63% sensitivity,⁵⁴ Gabel et al. reported a sensitivity of 89%.⁵⁷ Specificity of the AD diagnosis was more consistent between the studies, ranging from 79% to 86%. Gabel et al. also reported that using both the FDG-PET scans and the clinical scenario resulted in a sensitivity (90%) that was similar to and a specificity (86%) that was higher than that obtained with either modality on its own (see Table 15).⁵⁷

CoE III/IV studies

In contrast, Rabinovici et al. reported that visual classification of SPM images as AD (versus FTD) yielded a sensitivity of 67% and a specificity of 93%. Rabinovici et al. found similar results when automated classification of FDG-PET scans were used (Table 15).¹⁴⁶ Caution should be used when interpreting the results from the Rabinovici study; in addition to being at moderately high risk of bias, only ten patients were included in this portion of the study.

Rabinovici et al. reported that the clinical diagnosis alone, which was made using the NINCDS-ADRDA criteria (AD) and the FTD consensus criteria, yielded perfect sensitivity and specificity (100%).¹⁴⁶

SPECT (Tables 16-17): AD vs. FTD

CoE III/IV studies

The ability of HMPAO-SPECT to discriminate between AD and FTD was evaluated by one retrospective study that was considered to be at high risk of bias (CoE IV).¹⁰⁰ McNeill et al. included 56 patients who had been diagnosed with either AD or FTD and had SPECT scanning within one month of the first clinical evaluation; patients were followed until death, at which point autopsy was performed. The mean interval between imaging and autopsy was not reported. Scans were classified visually by one nuclear medicine specialist, however it was unclear what criteria were needed to constitute a diagnosis of AD versus AD. Visual classification of AD using SPECT scans yielded 65% sensitivity and 72% specificity (and vice versa for FTD). When both SPECT and the clinical diagnosis were used, the sensitivity and specificity both increased to 84%. The clinical diagnosis alone had a sensitivity of 77% and a specificity of 88%.

Clinical diagnoses were made through a comprehensive work-up, though no specific criteria were delineated.

FDG-PET (Tables 18-19): AD vs. AD/DLB or DLB alone***CoE III/IV studies***

Two retrospective studies evaluated the utility of FDG-PET to detect the presence of DLB in dementia patients.^{104,174} Both studies were found to be at moderately high risk of bias (CoE III) and were small, including 11 and 21 patients. Minoshima et al. included patients with a final diagnosis at autopsy of AD (n = 10), AD with Lewy body disease (n = 7), or pure DLB; Toledo et al. evaluated patients with a pathological diagnosis of AD (n = 6) or AD with coincident DLB (n = 5). Both studies used automated methods to classify patients as having DLB: hypometabolism in the occipital lobe beyond a defined threshold was considered indicative of the disease. Overall, the studies found that FDG-PET was able to detect the presence of DLB (either alone or in addition to AD) with 80-90% sensitivity and 80-100% specificity. The accuracy of the clinical diagnosis was not reported. Overall, the prevalence of DLB ranged from 45-52% of patients.

Table 14. FDG-PET study characteristics, differential diagnostic accuracy based on autopsy: AD vs. FTD

Study (CoE)	Interval: imaging to autopsy	Demographics (mean ± SD)	Image processing	Imaging reference standard	Criteria for positive image	Image interpretation	Clinical diagnosis	Blinded interpretation?
CoE I/II studies								
Foster 2007 ⁵⁴ Retrospective study (CoE II)	4.7 ± 2.3 yrs.	N = 45 Age at scan: 65.6 ± 9.6 yrs. Male: 60% MMSE at scan: 14.4 ± 8.8 Symptom duration (at scan): 5.0 (range, 1-19.1) yrs.	Transaxial images: manual SSP	NR Pons for metabolic map image; normal control for statistical map image	Greater hypometabolism in: AD: posterior cingulate cortex and posterior cingulate gyrus (vs. anterior regions). FTD: frontal association cortex, anterior temporal cortex, and anterior cingulate gyrus (vs. posterior regions).	Visual interpretation (6 raters)	Clinical scenario (based on medical records including neuropsychological data and MRI or CT)	Image: yes Clinical scenario: yes Autopsy: yes
Gabel 2010 ⁵⁷ ‡ Retrospective study (CoE II)	See Foster 2007	See Foster 2007	See Foster 2007	See Foster 2007	See Foster 2007	Visual interpretation (consensus panel of 6 raters)	See Foster 2007	Image: yes Clinical scenario: yes Autopsy: yes
CoE III/IV studies								
Rabinovici 2011 ¹⁴⁶ Retrospective study	2.5 yrs.	N = 10 Age at scan: 68.0 (range, 58.1-89.9) yrs.	SPM	Pons	ROI with the greater hypometabolism (visual) or lower z-scores (automated): AD: lateral and medial	Visual interpretation (2 raters)	AD: NINCDS-ADRDA FTD: FTD consensus criteria ¹²¹	Image: yes Clinical diagnosis: yes Autopsy: NR

Study (CoE)	Interval: imaging to autopsy	Demographics (mean ± SD)	Image processing	Imaging reference standard	Criteria for positive image	Image interpretation	Clinical diagnosis	Blinded interpretation?
(CoE III)		Male: 90% MMSE at scan: NR Symptom duration: NR			temporoparietal cortex FTD: 2 ROIs- the frontal cortex anterior to precentral gyrus; & the temporal pole and amygdala	Automated (quantitative)		

Table 15. FDG-PET results for differential diagnostic accuracy based on autopsy: AD vs. FTD

Study (CoE)	CoE	N: AD* (%)	N: FTD* (%)	Diagnosis	Diagnostic method	TP†	FP†	FN†	TN†	AD Sensitivity (FTD Specificity)	AD Specificity (FTD Specificity)
CoE I/II studies											
Foster 2007 ⁵⁴ (6 neurologists: mix of experts % novices) Retrospective	II	31 (68%)	14 (32%)	AD (vs. FTD)	FDG-PET <i>Visual classification (transaxial images)</i>	NR	NR	NR	NR	Mean of 6 raters: 96% (range, 92-100%)	Mean of 6 raters: 59% (range, 43-71%)
					FDG-PET <i>Visual classification (SSP images)</i>	NR	NR	NR	NR	Mean of 6 raters: 98% (range, 94-100%)	Mean of 6 raters: 73% (range, 57-82%)
					FDG-PET + Clinical scenario‡	NR	NR	NR	NR	NR	NR
					Clinical scenario‡	NR	NR	NR	NR	Mean of 6 raters: 63% (range, 36-79)	Mean of 6 raters: 86% (range, 74-100)
Gabel 2010 ⁵⁷ (consensus panel of 6 expert raters) Retrospective	II	31 (68%)	14 (32%)	AD (vs. FTD)	FDG-PET <i>Visual classification (SSP images)</i>	NR	NR	NR	NR	94%	76%
					FDG-PET (SSP images) + Clinical scenario‡	NR	NR	NR	NR	90%	86%
					Clinical scenario‡	NR	NR	NR	NR	89%	79%

Study (CoE)	CoE	N: AD* (%)	N: FTD* (%)	Diagnosis	Diagnostic method	TP†	FP†	FN†	TN†	AD Sensitivity (FTD Specificity)	AD Specificity (FTD Specificity)
CoE III/IV studies											
Rabinovici 2011 ¹⁴⁶ (2 raters) Retrospective	III	3 (30%)	7 (70%)	AD (vs. FTD)	FDG-PET <i>Visual classification (SPM processed images)</i>	2/2	0/1	1/1	7/6	67% <i>(both raters)</i>	<i>Mean of 2 raters: 93%</i> <i>(range, 86-100%)</i>
					FDG-PET <i>(Automated classification)</i>	2	0	1	7	67%	100%
					FDG-PET+ Clinical diagnosis§	NR	NR	NR	NR	NR	NR
					Clinical diagnosis§	3	0	0	7	100%	100%

NR: not reported

*Diagnosis at autopsy. See Appendix G for clinical diagnosis.

†In terms of TP, FP, FN, and TN, results are presented for AD (vs. FTD) and were interpreted as follows (diagnosis by imaging or clinical exam / diagnosis at autopsy): TP: AD/AD; FP: AD/FTD; FN: FTD/AD; TN: FTD/FTD.

‡Foster 2007, Gabel 2010: Clinical scenario based on medical records including neuropsychological data and MRI or CT.

§Rabinovici 2011: Clinical diagnosis made using standard criteria: NINCDS-ADRDA for AD⁴⁴ and FTD consensus criteria for FTD¹²¹

Table 16. SPECT study characteristics, differential diagnostic accuracy based on autopsy: AD vs. FTD

Study (CoE)	Interval: imaging to autopsy	Demographics (mean ± SD)	Image processing	Imaging reference standard	Criteria for positive image	Image interpretation	Clinical diagnosis	Blinded interpretation?
CoE III/IV studies								
McNeill 2007 ¹⁰⁰ Retrospective study (CoE IV)	NR	N = 56 Age at scan: 60.0 yrs. Male: 68% MMSE at scan: 17.8 Symptom duration (at scan): 4.0 yrs.	Manual	NR	Scans rated for normal or abnormal cerebral blood flow, and the rating was performed regionally for frontal, parietal, temporal, and occipital regions on both sides. Blood flow was assessed using a colored magenta heat scale; areas were considered	Visual interpretation	Clinical diagnosis made through comprehensive work-up. No specific diagnostic criteria reported.	Image: yes Clinical diagnosis: yes Autopsy: yes*

Study (CoE)	Interval: imaging to autopsy	Demographics (mean ± SD)	Image processing	Imaging reference standard	Criteria for positive image	Image interpretation	Clinical diagnosis	Blinded interpretation?
					abnormal if they were below the halfway point of this scale on more than two sections. A diagnosis of AD, FTD, or “non-specific” was made (details NR).			

NR: not reported

*McNeill 2007: autopsy performed before diagnosis using SPECT scans.

Table 17. SPECT results for differential diagnostic accuracy based on autopsy: AD vs. FTD

Study (CoE)	CoE	N: AD* (%)	N: FTD* (%)	Diagnosis	Diagnostic method	TP†	FP†	FN†	TN†	AD Sensitivity (FTD Specificity)	AD Specificity (FTD Specificity)
CoE III/IV studies											
McNeill 2007 ¹⁰⁰	IV	31	25	AD (vs. FTD)	SPECT	NR	NR	NR	NR	65%	72%
Retrospective		(55%)	(45%)		<i>Visual classification</i>						
					SPECT + Clinical diagnosis†	NR	NR	NR	NR	84%	84%
					Clinical diagnosis†	NR	NR	NR	NR	77%	88%

NR: not reported

*Diagnosis at autopsy. See Appendix G for clinical diagnosis.

†Clinical diagnosis made through comprehensive diagnostic work-up.

Table 18. FDG-PET study characteristics, differential diagnostic accuracy based on autopsy: AD vs. DLB

Study (CoE)	Interval: imaging to autopsy	Demographics (mean ± SD)	Image processing	Imaging reference standard	Criteria for positive image	Image interpretation	Clinical diagnosis	Blinded interpretation?
CoE III/IV studies								
Minoshima 2001 Retrospective study (CoE III)	3 yrs.	N = 21 Age at scan: 70.4 yrs. Male: 71% MMSE at scan: 13.8 Symptom duration (at scan): 3.4 yrs.	3D-SSP	Pons	Hypometabolism in occipital lobe was indicative of DLB (either alone or with AD). Threshold: z = -2.4	Automated interpretation	NR	Image: yes Autopsy: NR
Toledo 2013 ¹⁷⁴ Retrospective study (CoE III)	3.8 yrs.	N = 11 Age at scan: NR Male: NR MMSE at scan: NR Symptom duration (at scan): NR	SPM-5	Whole brain	Occipital lobe hypometabolism was indicative of DLB. Threshold: t = 1.8	Automated interpretation	NR	Image: yes Autopsy: NR

NR: not reported

Table 19. Characteristics of studies evaluating differential diagnostic accuracy using autopsy as gold standard: FDG-PET for AD vs. DLB

Study	CoE	N: AD* (%)	N: DLB or AD/DLB* (%)	Diagnosis	Diagnostic method	TP†	FP†	FN†	TN†	DLB or AD/DLB Sensitivity (AD Specificity)	DLB or AD/DLB Specificity (AD Sensitivity)
CoE III/IV studies											
Minoshima 2001 ¹⁰⁴ Retrospective	III	10 (48%)	DLB: 4 AD/DLB: 7 (52%)	DLB or AD/DLB (vs. AD)	FDG-PET Automated classification	NR	NR	NR	NR	90%	80%
					FDG-PET + Clinical diagnosis	NR	NR	NR	NR	NR	NR
					Clinical diagnosis	NR	NR	NR	NR	NR	NR
Toledo 2013 ¹⁷⁴ Retrospective	III	6 (55%)	AD/DLB: 5 (45%)	DLB or AD/DLB (vs. AD)	FDG-PET Automated classification	NR	NR	NR	NR	80%	100%
					FDG-PET + Clinical diagnosis	NR	NR	NR	NR	NR	NR
					Clinical diagnosis	NR	NR	NR	NR	NR	NR

NR: not reported

*Diagnosis at autopsy. See Appendix G for clinical diagnosis.

4.4. Key question 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?

4.4.1. Summary

Ability of functional neuroimaging to predict progression and clinical outcomes:

- **FDG-PET**

Outcome: Patient progression (MCI to AD/dementia conversion)

- Evidence base: 10 studies (2 CoE I, 8 CoE III); N = 12 – 128.^{39,43,48,65,80,85,134,144,164,175}
- Baseline diagnosis: MCI or aMCI
- CoE I/II studies (2 studies (CoE I); N = 17 – 30):^{43,48}
 - Length of follow-up: 1.3 – 1.6 years
 - Prediction of AD/dementia with FDG-PET using visual assessment (2 studies)^{43,48}
 - 25 – 40% progressed to AD/dementia
 - Prediction of AD or dementia with FDG-PET alone had 92-100% sensitivity and 75-89% specificity
 - Prediction of progressive cognitive decline with FDG-PET (1 study, N = 17):⁴⁸
 - 50% had cognitive decline
 - Prediction of decline with FDG-PET alone had 75% sensitivity and 88% specificity
- CoE III/IV studies (8 studies (CoE III); N = 12 – 128):^{39,65,80,85,134,144,164,175}
 - Length of follow-up: 1.3 – 3 years
 - Prediction of AD/dementia using automated assessment of FDG-PET scans (3 studies, N = 24 – 93):^{80,85,144}
 - 42 – 68% progressed to AD/dementia
 - Prediction of AD or dementia with FDG-PET alone: 33-45% sensitivity and 43-93% specificity
 - Prediction of AD/dementia using visual assessment of FDG-PET images (5 studies):^{39,65,134,164,175}
 - 11 – 68% progressed to AD/dementia
 - Prediction of AD or dementia with FDG-PET alone had 25-100% sensitivity and 24-83% specificity

Outcome: Cognition (MMSE scores)

- Evidence base: 1 study (CoE III); N = 167 (MMSE data available for subset of 95 patients)¹⁶⁴
- Baseline diagnosis: MCI
- Length of follow-up: 3.5 ± 1.0 years
- MMSE scores:
 - Baseline: 24 ± 6.4 (n=95)
 - Prediction of progressive (n=67) vs. nonprogressive (n=28) dementia with FDG-PET using visual assessment: ~18 vs. ~25.5 (P < 0.05)

Outcomes related to function, quality of life, behavior, psychological status, depression, caregiver burden, and global health: No evidence identified.

- **SPECT (perfusion)**

- **Outcome: Patient progression (MCI to AD/dementia conversion)**

- Evidence base: 3 studies (CoE III); N = 12 – 316.^{36,39,74}
 - Ligands used: ⁹⁹Tc-HMPAO (2 studies), ¹²³I-IMP (1 study) (all measured cerebral blood flow)
 - Baseline diagnosis: MCI or aMCI
 - Length of follow-up: 1.3 – 4 years
 - Prediction of AD using automated assessment of SPECT scans (1 study, N = 316):⁷⁴
 - 46.7% progressed to AD
 - Prediction of AD with SPECT alone: 58% sensitivity and 81% specificity
 - Prediction of AD/dementia using visual assessment of SPECT images (3 studies):^{36,39,74}
 - 24.4 – 50% progressed to AD/dementia
 - Prediction of AD or dementia with SPECT alone had 36-76% sensitivity and 39-82% specificity

Outcomes related to function, quality of life, behavior, cognition psychological status, depression, caregiver burden, and global health: No evidence identified.

- **fMRI**

- **Outcome: Patient progression (MCI to AD/dementia conversion)**

- Evidence base: 1 study (CoE III); N = 33¹⁴⁰
 - Memory tasks given during scan
 - Baseline diagnosis: MCI
 - Length of follow-up: 2.5 ± 0.8 years
 - Prediction of dementia using assessment of PMC activation as seen in fMRI scans:
 - 33% progressed to AD
 - Prediction of dementia with fMRI alone: 55% sensitivity and 73% specificity

Outcomes related to function, quality of life, behavior, cognition psychological status, depression, caregiver burden, and global health: No evidence identified.

- ¹²³I-FP-CIT-SPECT, ¹¹C-DTBZ-PET, ASL: No studies identified.

Ability of one type versus another type functional neuroimaging to predict progression and clinical outcomes: no evidence found.

4.4.2. Number of studies retained

Studies that evaluated disease progression and/or clinical outcomes in patients who had been diagnosed with functional neuroimaging were sought. For inclusion, studies must have been longitudinal and designed specifically to evaluate progression, with sufficient information on baseline status and measures, sufficient follow-up time to evaluate progression, and clear articulation of changes from baseline. Further, studies must have used criteria developed *a priori* to diagnose patients with functional neuroimaging. From a total of 40 references identified after title and abstract review, 13 studies^{36,39,43,48,65,74,80,85,134,140,144,164,175} were identified that met the inclusion criteria and addressed the key question. The remaining 29 studies were excluded after full-text review; a list of these studies and reasons for exclusion are documented in Appendix C. The most common reasons for exclusion included

retrospective application of predictive criteria to the same population in which the predictive criteria were developed, and studies that explored proof of concept by identify features of functional neuroimaging at baseline that were exhibited in patients who progressed/declined/converted but not in those who did not progress/decline/convert; these features are then used in regression models to test for associations with progression/decline/conversion.

The 13 included studies evaluated use of FDG-PET (10 studies), HMPAO-SPECT (3 studies (1 of which also evaluated FDG-PET)), and fMRI (1 study) for predicting progression.

The second part of the key question asks whether one type of functional neuroimaging is better at predicting progression than other. For this question, studies comparing the ability of two different functional neuroimaging modalities of interest in predicting progression or clinical outcomes were sought; however no studies were identified.

4.4.3. Critical appraisal of included studies

Seven studies were conducted prospectively; the remaining six three were considered to be retrospective in nature. Two of the prospective studies were considered good quality and at low risk of bias (CoE I); both evaluated FDG-PET.^{43,48} The remaining 11 studies were all found to be at moderately high risk of bias (CoE III) and included five prospective studies (FDG-PET, SPECT, and fMRI)^{36,74,140,164,175} and six retrospective studies (FDG-PET and SPECT)^{39,65,80,85,134,144}. All 11 of these studies failed to meet two or more criteria of a good quality study, including: insufficient documentation of follow-up to assess whether there was complete follow-up of $\geq 80\%$ of patients (8 studies), failure to provide information as to whether the clinical outcome was evaluated independently of the functional neuroimaging test results (6 studies), inadequate description of the functional neuroimaging test and/or the outcome (i.e., clinical standard) (4 studies), failure to provide information regarding blinding of the neuroimaging test to the outcome (4 studies), and insufficient detail to determine whether a broad spectrum of patients with the expected condition were included (3 studies). Specific information regarding the CoE rating for each study is detailed in Appendix E.

4.4.4. Detailed results

FDG-PET: Primary outcomes

Study characteristics are presented alphabetically in Table 20 and results stratified by CoE in Table 21.

FDG-PET (Tables 20-21): Patient progression (MCI to AD/dementia conversion)

Ten studies evaluated the ability of FDG-PET to predict conversion from MCI to AD or dementia.^{39,43,48,65,80,85,134,144,164,175} Two prospective studies were found to be at low risk of bias (CoE I)^{43,48}; the remaining two prospective and six retrospective studies were all considered to be at moderately high risk of bias (CoE III).

CoE I/II studies

Two prospective studies were considered to be at low risk of bias (CoE I)^{43,48}; as these studies were considered to be of the highest quality, their results will be presented separately from the CoE III studies. Both Drezzga and Fellgiebel enrolled MCI patients from a university clinic setting. Drezzga et al. enrolled MCI patients and monitored progression to AD, which was diagnosed according to the NINCDS-ADRA criteria. Fellgiebel et al. followed amnesic MCI patients and assessed for conversion to dementia, which was defined by a global clinical dementia rating (CDR) of ≥ 1.0 . Both studies were small, enrolling 17 and 30 patients. Mean age ranged from 69 to 70 years, and 47% to 56% of patients were

male. Mean baseline MMSE scores ranged from 25.7 to 26.9. Drezzga et al. reported that 57% of patients were positive for the ApoE ϵ 4 allele, which increases a patient's risk for developing AD. All patients received FDG-PET scans at baseline. Images produced through automated processes were interpreted visually; patients with hypometabolism in regions that have been implicated in AD were considered to be likely to progress to AD. Details of the hypometabolism and thresholds are available in Table 20. Scans were interpreted in a manner blinded to clinical diagnosis and clinical outcome, while clinical outcomes were evaluated blinded to FDG-PET results. Patients were followed for 1.3 to 1.6 years.

Drezzga et al. found that during the 1.3 years of follow-up, 40% of the 30 enrolled patients progressed from MCI to AD.⁴³ Visual interpretation of automated FDG-PET scans correctly predicted conversion from MCI to AD in this population with a sensitivity of 92% (95% CI, 62-99%) and a specificity of 89% (95% CI, 65-98%). Similarly, Fellgiebel et al. reported that visual interpretation of automated FDG-PET scans had 100% sensitivity and 75% specificity; in this population of aMCI patients, 25% converted to dementia during the mean 1.6 years of follow-up.⁴⁸ Fellgiebel et al. also assessed the ability of FDG-PET to predict progressive cognitive decline, which was defined as a reduction in MMSE scores by two or more points along with clinical deterioration from a clinician's perspective. Half of the aMCI patients met these criteria and were considered to have progressive cognitive decline. Evaluation of baseline FDG-PET scans had a sensitivity of 75% and a specificity of 88% for correctly predicting decline.

Fellgiebel et al. performed Kaplan-Meier survival analysis and found that FDG-PET positive images were predictive of conversion to dementia ($P = 0.033$) but not to progressive cognitive impairment ($P = 0.20$).

CoE III studies

Eight additional studies evaluated the ability of FDG-PET to predict progression from MCI to AD or dementia; however, these studies were considered to be at moderately high risk of bias (CoE III).^{39,65,80,85,134,144,164,175} Two of the eight studies were conducted in a prospective manner. Briefly, 12 to 167 MCI patients per study were followed for 1.3 to 3 years (range of means). Most studies evaluated patients from memory clinics, though two studies^{85,144} included patients from the ADNI (Alzheimer's Disease Neuroimaging Initiative) and/or TOMC (Translational Outpatient Memory Clinic) databases. At (or near) baseline, patients underwent FDG-PET scans, which were interpreted either visually (5 studies) or in an automated fashion (3 studies). Conversion to AD was defined as hypometabolism in regions shown to be affected by AD (i.e., the temporoparietal region); though some studies evaluated hypometabolism in whole cortical regions. Studies that performed automated scan interpretation considered images as positive when the degree of hypometabolism in predefined regions of interest met a specific threshold. Seven studies interpreted the scans in a manner blinded to clinical information and clinical outcome. At the end of the follow-up period, patients were assessed for conversion to AD or dementia. Six of the eight studies considered a patient to have progressed to AD if they met the NINCDS-ADRDA criteria.^{39,65,80,85,144,175} Silverman et al. defined progression to dementia as "memory, language, or functional abilities progressively diminished at a pace faster than would be expected as a consequence of the normal aging process",¹⁶⁴ while Pardo et al. did not specify the criteria used to diagnose patients with AD, FTD, or DLB at follow-up.¹³⁴ Four studies stated that clinical progression was assessed blinded to FDG-PET scans.^{39,85,144,164} See Table 20 for additional details on scan interpretation and clinical diagnostic criteria used.

Silverman et al. conducted a longitudinal prospective study and assessed progression from MCI to dementia.¹⁶⁴ The authors reported that visual interpretation of 128 FDG-PET scans was associated with a sensitivity of 91.5% and a specificity of 73.9% in terms of accurately predicting conversion to

progressive dementia. Further, comparisons between clinical diagnosis and diagnosis using FDG-PET were provided: in a subset of 102 patients with a working baseline diagnosis of progressive neurodegenerative disease or a non-progressive condition, 64% progressed to dementia. FDG-PET had a sensitivity of 95% (95% CI, 90-100%) and a specificity of 79% (95% CI, 66-92%) for correctly predicting progression, while in comparison, the clinical prediction had a lower sensitivity (77% (95% CI, 66-87%)) and a similar specificity (76% (95% CI, 63-90%)).

The remaining studies evaluated progression from MCI to AD.^{39,65,80,85,134,144,175} Overall, positive FDG-PET scans were associated with a sensitivity that ranged from 50% to 100% and a specificity that ranged from 24 to 93%; between 11% and 45% of patients progressed from MCI to AD. More specifically, one prospective study (Tripathi) of 35 patients reported that visual interpretation of automated images had 100% sensitivity and 77% specificity; the prevalence of AD was 11%.¹⁷⁵ Two retrospective studies (Kakimoto and Prestia) that employed automated FDG-PET scan interpretations had 50% to 80% sensitivity and 43% to 93% specificity for predicting conversion to AD; the prevalence of AD ranged from 42% to 45% in these studies.^{80,144} Prestia et al. also reported that hippocampal volume on MRI had a lower sensitivity than FDG-PET (47% versus 50-67% depending on the method of FDG-PET image interpretation) and a comparable specificity (65% versus 59-69%).¹⁴⁴ The remaining two retrospective studies (Dobert and Hatashita) that used visual interpretation of scans reported a sensitivity of 93% to 100% and a specificity of 24% to 83% for accurately predicting conversion to AD.^{39,65}

Landau et al.⁸⁵ also used automated scan interpretation, but did not report enough information to allow for the calculation of sensitivity and specificity. Rather, the authors reported that in a population with an AD prevalence of 33% at follow-up, FDG-PET had a positive predictive value of 41% and a negative predictive value of 79%. The authors also reported that detection of hippocampal atrophy via MRI had similar positive and negative predictive values (41% and 78%, respectively) to those with FDG-PET. Note that the appropriateness of positive and negative predictive values is dependent on the prevalence reflecting real-world values, so caution should be used when interpreting these results. According to univariate analysis, a positive FDG-PET or MRI image was significantly associated with conversion to AD (FDG-PET: hazard ratio 2.94 (95% CI, 1.23, 7.04), $P = 0.02$; MRI: hazard ratio 2.49 (95% CI, 1.02, 5.96), $P = 0.04$) or cognitive decline (hazard ratios not reported; $P = 0.003$, $P = 0.03$, respectively), which was assessed using the ADAS-Cog outcome measure but not clearly defined.

In a retrospective study, Pardo et al. reported that visual interpretation of automated images resulted in 25% sensitivity and 43% specificity in terms of predicting progression to AD, FTD, or DLB.¹³⁴

FDG-PET: Function, quality of life, behavioral and psychological outcomes

No evidence was found.

FDG-PET: Secondary outcomes

FDG-PET: Cognition (MMSE scores)

Silverman et al. conducted a prospective longitudinal study that was considered to be at moderately high risk of bias (CoE III).¹⁶⁴ The authors enrolled 167 MCI patients who had FDG-PET scans at baseline. Patients were followed for a mean of 3 years (range, 2-10) years and then assessed for progression as measured by MMSE scores. As described in Table 1, MMSE is a clinician-reported outcome measure that measures several components of cognitive impairment. The score ranges from 0 to 30, and lower scores indicate greater cognitive impairment. Baseline FDG-PET scans were interpreted visually: scans with focal or diffuse cortical hypometabolism in parietal, temporal, and/or frontal lobes were considered

positive. Both scans and clinical progression were interpreted in a blinded manner; see Table 20 for additional demographic and scan information.

At baseline, the mean MMSE score was 24 ± 6.4 , which falls into the MMSE classification of mild cognitive impairment. At 3.5 ± 1.0 years follow-up, MMSE scores in a subset of 95 patients were significantly lower in patients who had FDG-PET positive scans ($n=67$) versus those with normal scans ($n=28$) (~ 18 versus ~ 25.5 , $P < 0.05$). Scores ranging from 10 to 18 correlate with an MMSE classification of moderate cognitive impairment while those ranging from 19 to 24 correlate with mild cognitive impairment.

FDG-PET: Depression, caregiver burden, global outcomes

No evidence was found.

SPECT: Primary outcomes

Study characteristics are presented in Table 22 and results in Table 23.

SPECT (Tables 22-23): Patient progression (MCI to AD/dementia conversion)

Three studies were identified that assessed the ability of ^{99}Tc -HMPAO- or ^{123}I -IMP-SPECT, both of which assess blood flow, to predict patient progression.^{36,39,74} Two of these studies were conducted prospectively^{36,74} and one retrospectively³⁹; because of methodological limitations all three were considered to be at moderately high risk of bias (CoE III).

Both prospective studies evaluated conversion of MCI to AD.^{36,74} Between 127 and 316 MCI (or amnesic MCI) patients were enrolled from specialty clinics and followed for 3 to 4 years. Note that while Ito et al. enrolled 316 patients, attrition was high and only 68% ($n=216$) of patients completed follow-up.⁷⁴ Patients had a mean age of 66.5 to 73.7, and 31.9% to 43.3% of patients were male. Mean baseline MMSE scores ranged from 26.4 to 27.6. A diagnosis of AD was made according to the NINCDS-ADRDA criteria in both studies; Ito et al. also required a global CDR score of at least 1. While Devanand et al. evaluated progression to AD in a manner blinded to SPECT data, Ito et al. did not provide this information. SPECT scans were taken at or within three months of baseline. Both studies evaluated scans visually; Ito et al. additionally employed automated image analysis, requiring the z-scores measuring hypometabolism to be at least two standard deviations greater than that in the same region of normal control patients. Scans were considered indicative of AD if there was hypometabolism in the temporoparietal regions (see Table 22 for details). Devanand et al. did not interpret SPECT images in a manner completely independent of the clinical work-up: the authors stated that raters had access to brief clinical history (but were blinded to clinical follow-up information).³⁶ Ito et al. assessed SPECT scans in a blinded manner.⁷⁴ Additional information on patient demographics and scan interpretation is provided in Table 22. Between 24% and 47% of patients progressed to AD during the follow-up period. Visual analysis of SPECT images taken at or near baseline had a sensitivity that ranged from 42% to 76% and a specificity that ranged from 39% to 82%.^{36,74} Results from the automated image analysis were in the same range, with 58% sensitivity and 81% specificity.⁷⁴

One retrospective study (Dobert) evaluated progression from MCI to AD or FTD. This small study followed 11 patients for 1.3 ± 1.0 years. Visual interpretation of the SPECT scans resulted in a sensitivity of 36% and a specificity of 50%. Half of the patients progressed to either AD or FTD. See Tables 22-23 for additional details.³⁹

SPECT: Function, quality of life, behavioral and psychological outcomes

No evidence was found.

SPECT: Secondary outcomes**SPECT: Cognition, depression, caregiver burden, global outcomes**

No evidence was found.

fMRI: Primary outcomes

Study characteristics are presented in Table 24 and results in Table 25.

fMRI (Tables 24-25): Patient progression (MCI to dementia conversion)

One prospective study evaluated the prognostic value of functional MRI in terms of predicting conversion from MCI to dementia.¹⁴⁰ This study was considered to be at moderately high risk of bias (CoE III). Petrella et al. assessed 33 MCI patients with a mean age of 73.6 ± 8.5 years. Patients underwent fMRI, during which they were challenged with a series of novel and familiar face-name pairs. In normal patients, cognitive tasks such as this would result in deactivation of the “default network” in the posteromedial cortex (PMC), however, it has been suggested that task-related deactivation of this region is inhibited in AD and MCI patients. The authors tested whether activation of the PMC during cognitive challenges was predictive of conversion from MCI to AD at the end of 2.5 ± 0.8 years follow-up, and found that it had a sensitivity of 55% and a specificity of 73%. A total of 33% of patients progressed to AD during this time period.

fMRI: Function, quality of life, behavioral and psychological outcomes

No evidence was found.

fMRI: Secondary outcomes**fMRI: Cognition, depression, caregiver burden, global outcomes**

No evidence was found.

Table 20. FDG-PET: diagnostic prediction study characteristics

Study (CoE)	Demographics (mean ± SD)	Images obtained	Image processing	Reference standard	Criteria for positive image (Cut-off value)	Image interpretation	Diagnostic criteria used for progression	Blinded interpretation?
CoE I/II studies								
Drezezga 2005 Longitudinal prospective CoE I	N = 30 Diagnosis: MCI Age: 70 ± 8 Male: 47% Duration of symptoms: 2.6 ± 2 yrs. MMSE: 26.9 ± 1.9 ADAS-Cog: NR Global CDR: NR ApoE genotype (ε4 positive): 57%	Baseline	NEUROSTAT	Normal database of 22 age-matched healthy controls	Hypometabolism in posterior cingulate cortex plus cortical hypometabolism in at least unilateral temporoparietal areas. (Cut-off value: z-score > 1.64 (vs. reference))	Visual interpretation of automated image	AD: NINCDS-ADRDA criteria (diagnosed by physician at research memory clinic)	Image: yes Progression: yes
Fellgiebel 2007 Longitudinal prospective CoE I	N = 17 For the 16 patients with completed f/u: Diagnosis: aMCI Age: 68.6 ± 7.9 Male: 56% Duration of symptoms: NR MMSE: 25.7 ± 2.7 ADAS-Cog: NR Global CDR: NR ApoE genotype: NR	Baseline	NEUROSTAT	Normal database of 25 healthy controls of similar age	Cerebral hypometabolism in at least one of the brain regions that have been shown to be typically involved in early AD: parietal mesial or posterior cingulate and temporal region. (Cut-off value: z-score > 2.0 in more than 50 adjacent pixels (vs. reference))	Visual interpretation of automated image (2 raters)	Dementia: CDR ≥ 1 (diagnosed by physician at research memory clinic)	Image: yes Progression: yes

Study (CoE)	Demographics (mean ± SD)	Images obtained	Image processing	Reference standard	Criteria for positive image (Cut-off value)	Image interpretation	Diagnostic criteria used for progression	Blinded interpretation?
CoE III/IV studies								
Doberst 2005 Longitudinal retrospective CoE III	N = 12 Diagnosis: MCI (The following demographics are for 24 patients (12 of which are not applicable to this KQ) Age: 69 ± 7 Male: 46% Duration of symptoms: NR MMSE: NR (≥ 24) ADAS-Cog: NR Global CDR: 0.5 ApoE genotype: NR	Baseline	Iterative reconstruction algorithm	NR	Bilaterally reduced tracer uptake in AD affected areas: parietal, parietotemporal, temporal cortex. (Cut-off value NR)	Visual interpretation (2 raters)	AD: NINCDS-ADRDA criteria (diagnosed by multi-professional team)	Image: yes Progression: yes
Hatashita 2013 Longitudinal retrospective CoE III	N = 68 Diagnosis: MCI Age: NR (range, 50-89 years) Male: NR Duration of symptoms: NR MMSE: 26.9 ADAS-Cog: NR Global CDR: 0.5 ApoE genotype (ε4/4, ε3/4 positive): 41%	Baseline	NR; ROIs manually drawn	Cerebellar cortex	Hypometabolism in whole cortical regions. (Cut-off value: SUVR ≤ 0.99 (vs. reference))	Visual interpretation (2 raters)	AD: NINCDS-ADRDA criteria (diagnosed by physician at memory clinic)	Image: NR Progression: NR

Study (CoE)	Demographics (mean ± SD)	Images obtained	Image processing	Reference standard	Criteria for positive image (Cut-off value)	Image interpretation	Diagnostic criteria used for progression	Blinded interpretation?
Kakimoto 2012 Longitudinal retrospective CoE III	N = 24 Diagnosis: aMCI Age: 69.2 ± 9.9 years Male: 37.5% Duration of symptoms: NR MMSE: 25.4 ADAS-Cog: NR Global CDR: NR ApoE genotype: NR	Baseline	3D-SSP	Whole brain from set of normal patients	Hypometabolism in cerebral cortex (Cut-off value: z-score ≤ 1.9 (vs. reference))	Automated interpretation	AD: NINCDS-ADRDA & DSM-IV criteria (diagnosed by physician at memory clinic)	Image: not applicable (automated) Progression: NR
Landau 2010 Longitudinal retrospective CoE III	N = 85 Diagnosis: MCI Age: 78.1 years Male: 65.8% Duration of symptoms: NR MMSE: 27.0 ADAS-Cog: 11.3 Global CDR: NR ApoE genotype (ε4 positive): 30%	Baseline	SPM-5	Cerebellar vermis and pons	Hypometabolism in cerebral cortex (Cut-off value: z-score ≤ 1.21 (vs. reference))	Automated interpretation	AD: NINCDS-ADRDA criteria (diagnosed by physician at memory clinic followed by central review)	Image: not applicable (automated) Progression: yes
Pardo 2010 Longitudinal retrospective CoE III	N = 19 Diagnosis: MCI Age: 80 (range, 54-85) years Male: 95% Duration of symptoms: NR MMSE: NR ADAS-Cog: NR Global CDR: NR ApoE genotype: NR	Baseline	NEUROSTAT	Healthy persons (normative database)	AD: hypometabolism in the medial parietal cortex and lateral parietal regions; FTD: hypometabolism in anterior/superior temporal cortex and mesial/lateral	Visual interpretation of automated image (2 raters: one viewed transverse images, other viewed all perspectives (coronal,	NR (diagnostician NR)	Image: yes Progression: NR

Study (CoE)	Demographics (mean ± SD)	Images obtained	Image processing	Reference standard	Criteria for positive image (Cut-off value)	Image interpretation	Diagnostic criteria used for progression	Blinded interpretation?
					prefrontal cortex, especially with greater involvement in the left than in the right sides; DLB: occipital hypometabolism. (Cut-off value: $t \leq -2$ (minimum hypometabolism, colored purple on image) to $t \leq -6$ (maximum hypometabolism, colored white on image))	sagittal, and transverse) using iiv software		
Prestia 2013 Longitudinal retrospective CoE III	N = 93 Diagnosis: MCI Age: 73.6 (range, 51-89) years Male: 53% Duration of symptoms: NR MMSE: 27 (range, 24-30) ADAS-Cog: NR Global CDR: NR ApoE genotype: NR	Baseline	PALZ software (from PMOD)	Normal elderly persons	AD pattern mask (not defined). (Cut-off value: $t \geq 13,481$)	Automated	AD: NINCDS-ADRDA criteria (diagnostician NR)	Image: yes (automated) Progression: yes
			SPM	Healthy persons (normative database)	AD pattern mask (not defined) (Cut-off value: HcL ≥ 1055)			
			NR	Control subjects	5 ROIs: left and right angular lobe, posterior cingulate gyrus, and right and left temporal lobe. (Cut-off value: $w \geq -2.60$)			

Study (CoE)	Demographics (mean ± SD)	Images obtained	Image processing	Reference standard	Criteria for positive image (Cut-off value)	Image interpretation	Diagnostic criteria used for progression	Blinded interpretation?
Silverman 2003 Longitudinal prospective CoE III	N = 167 Diagnosis: cognitive deficit (89.8%), altered personality or behavior (2.4%), unspecified (1.2%) (all patients presented with symptoms of dementia) Age: 66 ± 13 years Male: 49.1% Duration of symptoms: NR MMSE: 24 ± 6.4 ADAS-Cog: NR Global CDR: NR ApoE genotype: NR <u>NOTE.</u> Data reported on the 128 (of 167) patients with a working clinical diagnosis before PET: Diagnosis: <ul style="list-style-type: none"> • Non-progressive: 34% (44/128) • Indeterminate: 20% (26/128) • Progressive neurodegenerative process: 45% (58/128) 	Baseline	NR	NR	Focal cortical hypometabolism in parietal, temporal, and/or frontal lobes, or diffuse cortical hypometabolism with sparing of sensorimotor ± visual cortex*. (Cut-off value: NR)	Visual interpretation	Memory, language or functional abilities progressively diminished at a pace faster than would be expected as a consequence of normal aging processes*	Image: yes Progression: yes

Study (CoE)	Demographics (mean ± SD)	Images obtained	Image processing	Reference standard	Criteria for positive image (Cut-off value)	Image interpretation	Diagnostic criteria used for progression	Blinded interpretation?
Tripathi 2013 Longitudinal prospective CoE III	N = 35 Diagnosis: aMCI Age: 67.9 ± 8.7 years Male: 77% Duration of symptoms: NR MMSE: ≥ 24 ADAS-Cog: NR Global CDR: NR ApoE genotype: NR	Baseline	SPM-5	Normal database of 20 healthy controls	Hypometabolism in unilateral or bilateral parietal, temporal, posterior cingulate, and precuneus (high likelihood of AD) or in any isolated region pertaining to the Alzheimer's territory (intermediate likelihood of AD). (Cut-off value: Decreased glucose metabolism in each patient compared to the control group below the statistical threshold of P<0.05.)	Visual interpretation of automated image	AD: NINCDS-ADRDA criteria (memory clinic)	Image: yes Progression: NR

SUVR: standardized uptake value ratio

*Silverman 2003: and changes could not be attributed to CT/MRI-documented cerebrovascular disease

Table 21. FDG-PET: diagnostic prediction study results

Study (CoE)	CoE	N	Patient source	F/U (% patients)	Image interpretation	Progression assessed	TP	FP	FN	TN	Progressed (%)	Sensitivity (%)	Specificity (%)
CoE I/II studies													
Drezezga 2005 Prospective	I	30	University research unit	1.3 yrs. (100%)	Visual interpretation of automated image	MCI to AD	11	2	1	16	40%	92% (95% CI, 62-99%)	89% (95% CI, 65-98%)
Fellgiebel 2007 Prospective	I	17	University memory clinic	1.6 yrs. (100%)	Visual interpretation of automated image	aMCI to dementia	4	3	0	9	25%	100%	75%
						aMCI to progressive cognitive decline	6	1	2	7	50%	75%	88%
CoE III/IV studies													
Dobert 2005 Retrospective	III	11	University memory clinic	1.3 ± 1.0 yrs. (% f/u NR)	Visual	MCI to AD	5	1	0	5	45%	100%	83%
Hatashita 2005 Retrospective	III	68	Memory clinic	1.6 ± 0.6 yrs. (% f/u NR)	Visual	MCI to AD	28	29	2	9	44%	93%	24%
Kakimoto 2012 Retrospective	III	24	NR	(% f/u NR)	Automated	aMCI to AD	8	1	2	13	42%	80%	93%
Landau 2010 Retrospective	III	85	ADNI database	1.9 ± 0.4 yrs. (% f/u NR)	Automated	MCI to AD	NR	NR	NR	NR	33%	NR	NR

Study (CoE)	CoE	N	Patient source	F/U (% patients)	Image interpretation	Progression assessed	TP	FP	FN	TN	Progressed (%)	Sensitivity (%)	Specificity (%)
				NR)									
Pardo 2010 Retrospective	III	19	Memory clinic	3 yrs. (% f/u NR)	Visual interpretation of automated image	MCI to AD, FTD, or DLB	3	4	9	3	68%	25%	43%
Prestia 2013 Retrospective	III	93	ADNI & TOMC databases	2.7 (1-4) yrs. (% f/u NR)	Automated: PALZ	MCI to AD	NR	NR	NR	NR	45%	50%	69%
					Automated: Hcl							67%	59%
					Automated: ROI							50%	67%
Silverman 2003 Prospective	III	1 2 8	University nuclear medicine clinic	3 (2-10) yrs. (% f/u NR)	Visual	MCI to progressive dementia	75	12	7	34	64%	91.5%	73.9%
Tripathi 2013 Prospective	III	35	Memory clinics of neurology centers	2 yrs. (100%)	Visual interpretation of automated image	aMCI to AD	4	7	0	24	11%	100%	77%

Table 22. SPECT: diagnostic prediction study characteristics

Study (CoE)	Demographics (mean ± SD)	Images obtained	Image processing	Reference standard	Criteria for positive image	Image interpretation	Diagnostic criteria used for progression	Blinded interpretation?
CoE III/IV								
Devanand 2010 Longitudinal prospective CoE III	N = 127 Diagnosis: MCI Age: 66.5 years Male: 43.3% Duration of symptoms: NR MMSE: 27.6 ADAS-Cog: NR Global CDR: NR ApoE genotype (ε4 positive): 27.6%	≤3 months of baseline	NeuroFocus	NR	Diagnosis made by taking into account the consensus regional hypometabolism ratings (0=normal, 1=mild, 2=moderate, 3=severe flow reduction) for the medial temporal, lateral temporal, medial parietal, and lateral parietal regions. (Cut-off value: NR)	Visual interpretation of ⁹⁹ Tc-HMPAO-SPECT images	AD: NINCDS-ADRDA criteria (diagnosed by 2 “expert raters”)	Image: no Progression: yes
Dobert 2005 Longitudinal retrospective CoE III	N = 12 Diagnosis: MCI (The following demographics are for 24 patients (12 of which are not applicable to this KQ) Age: 69 ± 7 Male: 46% Duration of symptoms: NR MMSE: NR (≥ 24)	Baseline	Backprojection method	NR	AD: Bilaterally reduced tracer uptake in AD affected areas (parietal, parietotemporal, temporal cortex) FTD: Frontotemporal reduced tracer accumulation (Cut-off value: NR)	Visual interpretation of ⁹⁹ Tc-HMPAO-SPECT images (2 raters)	AD: NINCDS-ADRDA criteria (diagnosed by multi-professional team)	Image: yes Progression: yes

Study (CoE)	Demographics (mean ± SD)	Images obtained	Image processing	Reference standard	Criteria for positive image	Image interpretation	Diagnostic criteria used for progression	Blinded interpretation?
	ADAS-Cog: NR Global CDR: 0.5 ApoE genotype: NR							
Ito 2013 Longitudinal prospective CoE III	<p><u>Patients included</u> N = 316 Age: 73.6 ± 6.6 Male: 32.6% Duration of symptoms: NR MMSE: 26.4 (all ≥24) Diagnosis: amnesic MCI (aMCI) (100%) ApoE genotype (ε4 positive): NR</p> <p><u>Patients with complete f/u who were included in the analysis</u> N = 216 Age: 73.7 ± 6.3 Male: 31.9% Duration of symptoms: NR MMSE: 26.4 ± 1.8 (all ≥24)</p>	Baseline	3D-SSP	Database of healthy subjects	<p>3D-SSP z-score map used to classify the images: AD/DLB pattern based on hypometabolism in the following regions: precuneus and posterior cingulate gyrus, temporo-parietal cortex, frontal cortex, and visual cortex. (Cut-off value: NR)</p> <p>≥2 areas in the bilateral parietal association areas and posterior cingulate cortices, where the summed z-scores exceeded the thresholds (Cut-off value: +2 SD (vs. reference) (based on z-score</p>	<p>Visual interpretation of ¹²³I-IMP-SPECT images (consensus of 4 raters)</p> <p>Automated</p>	<p>NINCDS-ADRDA criteria for probable AD <u>and</u> CDR global score ≥ 1</p> <p>(diagnosis reviewed by multispecialty committee)</p>	<p>Image: yes</p> <p>Progression: NR</p>

Study (CoE)	Demographics (mean ± SD)	Images obtained	Image processing	Reference standard	Criteria for positive image	Image interpretation	Diagnostic criteria used for progression	Blinded interpretation?
	Diagnosis: amnesic MCI (100%) ApoE genotype (ε4 positive): NR				map))			

SUVr: standardized uptake value ratio

*Silverman 2003: and changes could not be attributed to CT/MRI-documented cerebrovascular disease

Table 23. SPECT: diagnostic prediction study results

Study (CoE)	CoE	N	Patient source	F/U (% patients)	Progression assessed	Image interpretation	TP	FP	FN	TN	Progressed (%)	Sensitivity (%)	Specificity (%)
CoE III/IV													
Devanand 2010 Prospective	III	127	University memory clinic	4.1 (range, 1-9) yrs. (100% f/u)	MCI to AD	Visual	13	17	18	79	24.4%	42%	82%
Dobert 2005 Retrospective	III	11	University memory clinic	1.3 ± 1.0 yrs. (% f/u NR)	MCI to AD or FTD	Visual	2	5	2	2	50%	36%	50%
Ito 2013 Prospective	III	316	41 AD and dementia centers	3 yrs. (68% f/u)	aMCI to AD	Visual	75	69	24	44	46.7%	76%	39%
						Automated	80	71	19	42		58%	81%

Table 24. Functional MRI: diagnostic prediction study characteristics

Study (CoE)	Demographics (mean ± SD)	Images obtained	Task(s) given during scan	Image process.	Reference standard	Criteria for positive image	Image interpretation	Diagnostic criteria used for progression	Blinded interpretation?
CoE III/IV									
Petrella 2007 Longitudinal prospective CoE III	N = 33 Age at scan: 73.6 ± 8.5. Male: 45% MMSE at scan: 26.8 ± 1.7 Symptom duration (at scan): ≥ 1 yr.	Baseline	Memory tasks (60 novel and 2 familiar face-name pairs presented in 3 runs, for 6 minutes (50 seconds per run)).	SPM-2	NR	“Activation” in the posteromedial cortex (PMC) (precuneus, posterior cingulate, and retrosplenial cortices): activation magnitude of blood oxygen levels ≥ 0.	NR	Dementia: CDR ≥ 1.0; diagnosis confirmed by physician evaluations and neuropsychological tests	Image: NR Progression: NR

SUVR: standardized uptake value ratio

*Silverman 2003: and changes could not be attributed to CT/MRI-documented cerebrovascular disease

Table 25. fMRI: diagnostic prediction study results

Study (CoE)	CoE	N	Patient source	F/U (% patients)	Progression assessed	Criteria for positive image	TP	FP	FN	TN	Progressed (%)	Sensitivity (%)	Specificity (%)
CoE III/IV													
Petrella 2007 Prospective	III	33	University research center	2.5 ± 0.8 yrs. (94% f/u)	MCI to Dementia	Activation magnitude ≥ 0 in the PMC	6	6	5	16	33%	55%	73%

4.5. Key question 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?

4.5.1. Number of studies retained

Studies that reported on the impact of therapeutic decisions or clinical management (e.g., treatments planned or given) following diagnosis using functional neuroimaging compared with one made without functional neuroimaging. Of the eight studies that explicitly included wording related to clinical management or therapeutic decisions, no studies met our inclusion criteria. Specific reasons for excluding each of the eight studies at full-text review are documented in Appendix C; several studies were excluded on the basis of including more than 20% of patients without dementia or with excludable clinical diagnoses.

4.6. Key question 4: What are the short and long term harms of diagnostic functional neuroimaging?

4.6.1. Summary

- **FDG-PET**
 - One study was identified (N = 36 dementia/MCI patients) and reported short-term harms as identified by patients on a follow-up telephone call.⁸⁹ No adverse events assessed were reported to occur, including injection site pain, tenderness, redness, or swelling; or new fever, rash, breathing difficulties, diarrhea, headache, or muscle pain.
- **¹²³I-FP-CIT-SPECT (DaTscan)**
 - One study was identified (N = 326 dementia patients) and reported procedural and postprocedural harms only.⁹⁴ Adverse events attributed to the ¹²³I-FP-CIT injection occurred in 9 patients (10 events), including nausea (3 events), injection site hemorrhage (2 events), injection site erythema (2 events), dry mouth (1 event), vomiting (1 event), and headache (1 event).
- **HMPAO-SPECT, ¹¹C-DTBZ-PET, fMRI, ASL:**
 - No evidence identified.

4.6.2. Number of studies retained

Of three studies identified for possible inclusion after title-abstract review, one was excluded at full-text. Thus only two studies were identified for inclusion, both of which evaluated short-term harms resulting directly from diagnostic functional neuroimaging and/or the injections associated with the process.^{89,94} The two studies identified reported minimal data. Both were designed to evaluate the diagnostic accuracy of functional neuroimaging compared with the clinical diagnosis and both reported on short-term harms only.

The reference library was also searched for studies that reported on the harms or health impacts of missed diagnoses, false negative diagnoses, or false positive diagnoses, and no studies were identified. In addition, no studies were identified which reported on the long-term harms of functional neuroimaging, including effects of radiation exposure following PET or SPECT.

4.6.3. Detailed results

FDG-PET

Lowe et al. conducted a study to evaluate the diagnostic accuracy of FDG-PET for diagnosing the type of cognitive impairment compared to reference standard.⁸⁹ A total of 36 dementia or MCI patients as well as 20 healthy controls underwent FDG-PET; the mean patient age was 77 years and the percentage of males was not reported. Injection doses averaged 540 MBq and ranged from 366 to 399 MBq. Image acquisition consisted of four two-minute frames. The authors conducted a follow-up call to assess for adverse events. None of the patients reported any adverse event inquired about, including injection site pain, tenderness, redness, or swelling; or new fever, rash, breathing difficulties, diarrhea, headache, or muscle pain.

One recent systematic review by Bohnen et al. (2012) designed to evaluate the safety of FDG-PET in the diagnosis of dementia reported that “no safety issues have been raised in the multitude of papers that have studied the application of 18F-FDG-PET in AD, AD-related dementias, or other neurodegenerative disorders...”²¹ This systematic review was described in more detail in Table 4.

¹²³I-FP-CIT-SPECT (DaTscan)

McKeith et al. reported safety outcomes from a phase III study in which the diagnostic accuracy of ¹²³I-FP-CIT-SPECT (DaTscan) for DLB was evaluated.⁹⁴ A total of 326 patients received SPECT; mean patient age was 74.3 years and 68% were male. Patients had a clinical diagnosis of DLB (44%), AD (38%), vascular dementia (3%), or dementia with an unclear diagnosis (3%). Patients were injected with ¹²³I-FP-CIT at doses ranging from 111 to 185 MBq. Images were obtained for approximately 40 to 60 minutes. In addition, patients were given a “thyroid-blocking preparation” to inhibit local uptake of the tracer. Overall, 2.8% (9/326) of patients experienced at least one adverse event considered related to the injection of the ligand. There were 10 adverse events total in 9 patients, including nausea (3 events), injection site hemorrhage (2 events), injection site erythema (2 events), dry mouth (1 event), vomiting (1 event), and headache (1 event). No other details were reported.

4.7. Key question 5: What is the evidence that functional neuroimaging may perform differently in subpopulations? Consider the impact on disease progression, clinical outcomes, and harms.

4.7.1. Number of studies retained

All studies included to address Key Questions 2 and 4 were evaluated for inclusion. However, none of the studies stratified results on patient or other characteristics in order to evaluate effect modification.

4.8. Key question 6: What is the cost-effectiveness of incorporating diagnostic functional neuroimaging into the comprehensive initial diagnostic work-up?

4.8.1. Summary

Studies

Two cost utility analyses^{98,99} and two cost effectiveness studies^{109,162} comparing functional neuroimaging modalities to a conventional clinical work-up for the diagnosis of dementia (and dementia-related diseases) were included. After evaluation using methodological questions from the Quality of Health Economic Studies (QHES), all studies were moderately well done, with scores ranging from 66 to 77 (mean score of 73)^{98,99,109,162}. Three studies^{98,99,162} were conducted in the United States and one study¹⁰⁹ used a European perspective (Belgium with a sensitivity analysis including other European nations). All studies were published in or after the year 2000. Only one study¹⁶² disclosed their funding source and two publications^{98,99} (one study group) reported authors' conflicts of interest, which included relations to industry.

Summary

- **FDG-PET:**

- One cost-utility study⁹⁹ and two cost effectiveness studies^{109,162} explored the addition of FDG-PET to the conventional clinical work-up for the diagnosis of AD.
- Cost utility study:
 - Simulated cohort of hypothetical patients presenting with mild or moderate dementia.
 - A decision tree analysis and Markov modeling were used to estimate the long-term costs and QALYs gained (due to diagnosis and drug treatment).
 - Time horizon: 18 months.
 - The associated costs of care and drug treatment costs for the entire time horizon were included.
- Cost effectiveness studies:
 - Simulated cohort of hypothetical patients.
 - Decision tree analysis used to estimate the costs per accurate diagnosis.
 - One cost effectiveness study¹⁶² used a 6 month time horizon for patients with early cognitive symptoms.
 - The other cost effectiveness study¹⁰⁹ did not report a time horizon; the cohort represented patients with probable AD.
 - The costs of care were not included unless the patient was placed into the simulated group who received a false negative diagnosis (these costs were still less than those included in the cost utility study).
 - Similarly, the costs of medical treatment were not included unless the patient was placed into the group who received a false positive diagnosis.
- The costs of FDG-PET as well as other costs included in the conventional clinical work-up (lab tests, structural imaging, and physician consultations) were similar across all three studies.
- The cost utility study concluded that FDG-PET was more costly (imaging costs, additional travel days, caregiver time and consultation fees) and provided no benefit in QALYs, thus FDG-PET was not cost effective as an add-on in the diagnosis of AD.
- Conversely, the cost effectiveness studies^{109,162} found that the use of FDG-PET, when deemed appropriate, in addition to a conventional clinical evaluation, to be cost-effective for the diagnosis of AD, particularly because it was less costly and had increased accuracy over the conventional work-up.

- **SPECT (visual and computed)**

- Two cost-utility studies^{98,99} examine the use of SPECT as an add-on functional imaging modality to a conventional clinical work-up, compared with the conventional work-up alone.
 - Simulated; used hypothetical patients presenting with mild or moderate dementia, referred to a specialized AD clinic.
 - The same decision tree analysis with Markov modeling was used by both studies to estimate the costs and QALYs associated with diagnosis and drug treatment.
 - Time horizon: 18 months.
 - Drug treatment duration: 18 months for both diagnostic groups.
 - The costs associated with SPECT were slightly higher than those accrued for the conventional work-up alone due to the cost of the imaging (\$699-\$2,175, depending on the Medicare reimbursement schedule used and computed vs. visual SPECT).
 - The QALYs gained after diagnosis with SPECT were no higher than those associated with the conventional diagnostic approach.
 - Conclusion: SPECT was not cost-effective as an add-on to the conventional clinical evaluation in the diagnosis of AD.
- **fMRI:** No studies identified.

4.8.2. Number of studies retained

This review focused on economic studies that evaluated, synthesized and compared costs and treatment effects for at least two treatment alternatives. Four studies met the inclusion criteria, and three studies were excluded after full-text review: one did not report any data, and two were narrative reviews (see Appendix C).

4.8.3. Critical appraisal of included studies

The quality of included studies varied. All studies selected pertinent articles as literature data sources. All studies used governmental data for the prevalence of AD and/or economic details, as well as transition probabilities and other factors of their analyses. Three studies used institutional data to supplement the literature and governmental values^{98,99,109}. A MEDLINE search was completed in two studies^{109,162}. The studies included did not state the type of studies (retrospective, prospective or administrative database) they used for literature values. Auxiliary details on economic modeling, including justification for the economic model chosen were rarely described. Rationale for the study perspective and time horizon were not apparent in all studies. All studies provided at least minimal information on data sources, including detailed tables of the included costs. Detailed information on study outcomes of interest were not described. Follow-up periods for clinical studies and time horizons ranged six to 18 months (not reported in one study¹⁰⁹) and may not adequately represent the longer-term costs and clinical consequences associated with diagnosing the degenerative disease of Alzheimer's. The two cost effectiveness studies^{109,162} also adjusted their models to include the negative effects of false diagnoses. A majority of studies account for some indirect costs to the patient or society^{98,99,109}. All studies conducted sensitivity analyses, though the number of interactions made with the variables were rarely explained. Scores on the QHES ranged from 64 to 77, indicating variation in the extent to which studies met quality reporting standards and suggesting most were of moderate quality (QHES table). The Cost-Effectiveness Analysis Registry created by the Center for Evaluation of Value and Risk in Health (Tufts Medical Center, Institute for Clinical Research and Health Policy Studies) was also reviewed for their audit score of the articles included. This audit was only available for the McMahon

studies^{98,99} (QHEs table). Two studies were conducted by the same author group^{98,99} and the other two studies used very similar models^{109,162} (one adapted the model from the earlier study). The generalizability of included studies to broader populations needs to be considered before applying the results found in this review. Specific information regarding the QHEs rating for each study is detailed in Appendix E, and detailed data abstraction tables are available in Appendix G.

4.8.4. Detailed results

McMahon et al. 2000: Dementia patients referred to a specialized AD clinic: diagnosis made with conventional clinical work-up with or without visual SPECT or computed SPECT

Overview:

McMahon et al. (2000)⁹⁸ investigated the cost utility of a diagnostic work-up consisting of functional neuroimaging with a conventional clinical evaluation compared to the conventional clinical evaluation only. The authors evaluated two different functional imaging techniques (visual and computed SPECT) as add-ons performed after the clinical work-up. The conventional clinical work-up included a detailed history, cognitive and functional assessment, lab testing, and non-enhanced computed tomography (CT) for a structural brain imaging component. The study was conducted from a societal perspective.

The primary source of data for this cost-utility analysis was literature reviews. Additionally, retrospective data from their institution were included. The estimated costs and quality adjusted life years (QALY) associated with each treatment arm were evaluated using the incremental cost-effectiveness ratio (ICER) relative to the conventional clinical evaluation to form the conclusions of this study.

This study was specific to healthcare in the United States, using costing sources from 1998. Funding for the study was not reported. A discount rate of 3% was applied to future costs and QALYs annually over the 18 month time horizon.

A decision tree model using Markov cycles was constructed to simulate stable estimates of economic costs and clinical benefits for each treatment arm. Each scenario (disease state and care setting) was calculated with a constructed trial population of 32,000 simulated individuals (results were averaged). In each six week cycle, patients were classified into one of five disease states (no AD or other, mild AD, moderate AD, severe AD, or dead) and one of two health care settings (community or nursing home). All patients began in the community setting and depending on disease severity at the beginning of each new cycle, may transition to nursing home care. Transition probabilities between states were adopted from another analysis¹²⁴ in conjunction with data from the National Center for Health Statistics. The necessary long-term data were not available to the authors' knowledge at the time of the study, therefore the model did not include a long-term analysis beyond 18 months.

Assumptions:

A hypothetical population comprised of patients with symptoms of dementia presenting to specialized AD clinics were used for this study. For the base case analysis, it was assumed that 56% of presenting patients would have either mild or moderate AD (i.e., this diagnosis would be expected at autopsy). A ratio of mild to moderate AD patients was assumed to be 1.5 to 1. It was assumed that all patients who receive a diagnosis of probable Alzheimer disease (AD) will receive treatment with the acetylcholinesterase inhibitor donepezil and that the treatment would be continued until the patient has progressed to severe AD. The model assumed that the beneficial effects of donepezil reduced the probability of transitioning from mild to moderate AD by 50% and a 2.36-fold increase in the progression from moderate to mild AD. These effects were assumed constant over the 18 month time horizon and

there were assumed to be no lingering effects after discontinuation upon progression to severe AD (time to progression is not reported). The time horizon was equal to the drug treatment duration, thus patients received care at the start of the 18 month time horizon.

It was assumed that the annual transition probability from mild to moderate AD was 0.322, mild to severe AD was 0.042, and moderate to severe AD was 0.339. It was also assumed that the probability of transition from community to nursing home occurred was 0.038 in mild AD patients, 0.110 in moderate AD patients, and 0.259 in severe AD patients.

The authors estimated the sensitivity and specificity of the conventional clinical work-up to be 0.75 and 0.90, respectively. These values were used for both mild and moderate AD. The sensitivity and specificity of the functional imaging modalities (visual SPECT and computed SPECT) were based on one study, which reported the sensitivity and specificity for discriminating between AD and normal healthy patients using clinical diagnosis as a reference standard.⁶³ Visual SPECT was assumed to have sensitivity of 0.50 for mild AD and 0.74 for moderate AD, and a specificity was assumed to be 1.00 for AD. The sensitivity of computed SPECT was assumed to be 0.90 for mild and moderate AD, and the specificity assumed to be 0.87 for AD.

Literature sources were used to create the majority of probabilities and assumptions in the model. Massachusetts General Hospital data was reviewed retrospectively to provide resource utilization data, data to extrapolate the prevalence of AD and the cost of follow-up visits based on the frequency of follow-up at the institution.

Costs were derived from literature, 1998 Medicare reimbursement rates and institutional data alike. The conventional clinical work-up included costs associated with two consultations (internal medicine and neurology), laboratory tests, and structural imaging (CT or structural MRI). Travel expenses were also included in the analysis, with an additional travel day necessary for the SPECT imaging arms (assumed to be scheduled after the conventional work-up). The costs of patient care, including donepezil prescription costs and caregiver/patient time were also summed, based on the care setting (home care or nursing home). For the home care setting, the cost was assumed to reflect the cost of care in addition to the yearly cost of living (based on the mean of an age-matched individual). Utility values were taken from the literature; utility ranges from 0 to 1, with 0 corresponding to death and 1 corresponding to perfect health. Quality of life weights for patients without AD was estimated at 0.826, whereas a range of 0.310 – 0.710 estimated the quality of life for patients. Depending on care setting, patients with mild AD were assumed to have QoL weights between 0.68-0.71, moderate AD between 0.48-0.54 and severe AD ranging from 0.31-0.37.

Results:

The base-case analysis showed that the cumulative 18-month cost of diagnosis, treatment, and care using the conventional clinical work-up (\$54,762) were less than any of the treatment arms with functional imaging included (visual SPECT: \$55,362; computed SPECT: \$55,549). The model predicted a QALY of 0.9889 for the conventional arm, 0.9851 for visual SPECT, and 0.9888 for computed SPECT. Thus, in comparison to the conventional work-up, both SPECT imaging arms were dominated by the conventional work-up because they had both higher associated costs and lower estimated QALYs; thus SPECT was less cost-effective in this model than the conventional clinical work-up.

The authors completed a number of one-way sensitivity analyses in which different variables were altered to test the range of costs and QALYs related to each treatment arm, including the raising and

lowering the cost of the imaging procedures, lowering the sensitivity and specificity of the conventional work-up (0.50 and 0.80 respectively), lowering the sensitivity of computed SPECT in the mild AD group (0.88) and increasing it for the moderate AD group (0.92), the effect of a hypothetical “perfect” diagnostic test that has a sensitivity and specificity of 1.0, the effect of using hypothetical drugs with varied effectiveness (assumed to incur the same costs, treatment duration and duration of effectiveness as donepezil), varying the duration of drug effectiveness from 6 to 48 months, and altering the disease progression probabilities (e.g., lowering the rate of no-AD (other dementia) patients in the population and producing different ratios of mild to moderate AD (2:11, 1:1, and 1:1.5)). In addition, costs were adjusted regarding patient time costs, caretaker costs or travel costs in different analyses. Finally, quality of life weights were modified ± 0.1 in the estimates for each disease state and corresponding care setting.

In all sensitivity analyses, visual SPECT remained dominated by the conventional clinical work-up. Computed SPECT reached an ICER of \$180,200 for the low end of the sensitivity analyses, (assuming very low sensitivity and specificity for the conventional work-up with all patients undergoing CT and computed SPECT) to \$816,700 (if the ratio of mild to moderate AD was 1:1), and at the highest end, an ICER of \$1.9 million, when it was assumed that patients without AD had lower quality-of-life weights. Otherwise, computed SPECT remained dominated by the conventional work-up.

Conclusions and limitations:

McMahon et al.⁹⁸ concluded that the addition of a functional imaging test for the diagnosis of AD is not cost-effective compared with the conventional clinical work-up for any modality included in their analysis (visual or computed SPECT). From a societal perspective in the United States, the effectiveness of currently available pharmaceuticals and the accuracy of imaging modalities are not conducive to including functional imaging in the diagnosis of AD.

However, the authors discuss several limitations within their study. The clinical data available only reflect a short-term time horizon. To fully evaluate the role of functional imaging in diagnosing AD, a larger scope and longer follow-up is required, since AD is a progressive disease. In addition, the benefits of accurately diagnosing a patient was not quantified in this study. Literature data may not represent all patient populations, particularly those receiving a diagnosis outside of a specialized center. Additionally, consideration should be taken when generalizing these results outside of the United States health care system, since the analysis was designed specifically for this setting. In relation to their methodology, the authors explicitly state the costs associated with each piece of the diagnosis, but the study lacks information about the clinical assumptions and quality-of-life components. Lastly, consideration should be taken when generalizing these results outside of the United States health care system, as well as a specialized AD center, since the analysis was designed for this setting.

Notes:

- No direct funding was disclosed.
- At least one author has served in a position associated with the pharmaceutical company that produces the drug used in this analysis.
- This was a moderately-well conducted economic study, with a QHES of 77/100.

McMahon et al. 2003: Dementia patients referred to a specialized AD clinic: diagnosis made with conventional clinical work-up with or without computed SPECT or FDG-PET

Overview:

McMahon et al. (2003)⁹⁹ investigated the cost utility of a diagnostic work-up consisting of functional neuroimaging with a conventional clinical evaluation compared to the conventional clinical evaluation only. The authors evaluated two different functional imaging techniques (computed SPECT or FDG-PET) as add-ons performed after the initial clinical work-up. The conventional clinical work-up included a detailed medical history, cognitive and functional assessment, lab testing, and non-enhanced CT for a structural brain imaging component. The study was conducted from a societal perspective.

As was done in the McMahon (2000)⁹⁸ study, the source of data was primarily from literature reviews, though some retrospective data from their institution were also included. The estimated costs and quality adjusted life years associated with each treatment arm were evaluated using the ICER relative to the conventional clinical evaluation to form the conclusions of this study.

This study was specific to healthcare in the United States and used costing sources from 1999, which provided different figures compared to the former study published in 2000⁹⁸. The study may have been supported, at least in part, by grants from the National Cancer Institute, National Library of Medicine and the U.S. Department of the Army. As in the 2000⁹⁸ study, a discount rate of 3% was applied to future costs and QALYs annually over the 18 month time horizon.

The same decision tree model using Markov cycles (detailed in the previous in the 2000 study⁹⁸) was used. However, each scenario (disease state and care setting) was constructed with a much larger sample (100,000 simulated individuals, results were averaged). As in the previous study, all patients began in the community setting and could transition into the nursing home setting. Transition probabilities between states were adopted from another analysis¹²⁴ in conjunction with data from the National Center for Health Statistics. As in the 2000⁹⁸ study the necessary long-term data were not available to the authors' knowledge at the time of the study; therefore the model did not include a long-term analysis beyond 18 months.

Assumptions:

A hypothetical population comprised of dementia patients presenting to specialized AD clinics were used for this study. For the base case analysis, AD prevalence at diagnosis was the same as the base case in McMahon et al. published in 2000⁹⁸. It was assumed that all AD patients will receive a diagnosis of probable AD and receive treatment with donepezil. The same effects regarding donepezil were assumed for this study as for the 2000⁹⁸ study. The time horizon was equal to the drug treatment duration, thus patients received care at the start of the 18 month time horizon.

It was assumed that the yearly probability of transitioning from mild to moderate AD was 0.322, mild to severe AD was 0.042, and moderate to severe AD was 0.339. It was also assumed that the probability of transition from community to nursing home occurred was 0.038 in mild AD patients, 0.110 in moderate AD patients, and 0.259 in severe AD patients. (These values are identical to those used in the 2000 study.⁹⁸)

The sensitivity and specificity of computed SPECT were assumed to be the same values described for 2000⁹⁸. These values reflect the ability of each modality to discriminate between AD and normal patients and were based on the reference standard of clinical diagnosis. The sensitivity of FDG-PET was 0.94 for mild and moderate AD, with a specificity of 0.72 for AD; these values were based on the ability of FDG-PET to discriminate AD from other types of dementia and the reference standard of pathological diagnosis.¹⁶³ Values for the sensitivity and specificity of the conventional clinical work-up were also

based on the gold standard of pathologic analysis;¹⁰⁸ the sensitivity of the conventional work-up was 0.70 for mild AD and 0.80 for moderate AD, and the specificity was of 0.73 for AD.

Literature sources were used to create the majority of probabilities and assumptions in the model. Massachusetts General Hospital data was reviewed retrospectively to provide resource utilization data, data to extrapolate the prevalence of AD and the cost of follow-up visits based on the frequency of follow-up at the institution.

Costs were derived from literature, 1999 Medicare reimbursement rates and institutional data alike. The conventional clinical work-up included costs associated with two consultations (internal medicine and neurology), laboratory tests, and structural imaging (non-enhanced CT). At the time of publication, Medicare did not reimburse for FDG-PET in the diagnosis of AD-related dementia, so a resource use estimation from the authors' institution was used. Computed SPECT was calculated using the visual SPECT Medicare reimbursement rate, plus the cost for computer-aided manipulation. Travel expenses were also included in the analysis, with an additional travel day necessary for the SPECT and FDG-PET imaging arms (assumed to be scheduled after the conventional work-up). The costs of patient care, including donepezil prescription costs and caregiver/patient time were also summed, based on the care setting (home care or nursing home).

Utility values reflect patient quality of life and range from 0 (death) to 1 (perfect health). For this study, values were taken from the literature as well as on the Health Utilities Index (HUI) Mark III version (the authors noted that in comparison to the Mark II version used in McMahon et al. 2000⁹⁸, was much more sensitive to severe impairments like AD and may provide more appropriate estimates for these patients). A family member or a caregiver could have been a proxy to complete the HUI score, therefore these QoL weights may be biased. Utility values for patients without AD were estimated at 0.80 (slightly less than the HUI2 values), whereas patients with AD had dramatically lower weights than those presented originally in McMahon et al. 2000.⁹⁸ A range of 0.00 – 0.52 estimated the quality of life for patients with mild to severe AD living in the community or a nursing home. Depending on care setting, patients with mild AD were assumed to have QoL weights between 0.37-0.52, moderate AD between 0.18-0.21 and severe AD ranging from 0.00-0.02.

Results:

The base-case analysis showed that the 18-month cumulative cost of diagnosis, treatment, and care using the conventional clinical work-up (\$56,859 ± 18,569) were less than any of the treatment arms with functional imaging included (computed SPECT: \$58,872 ± 18,736; FDG-PET: 58,590 ± 18,799). The model predicted a QALY of 0.7092 ± 0.4120 for the conventional arm, 0.7093 ± 0.4137 for computed SPECT, and 0.7063 ± 0.4127 for FDG-PET. In comparison to the conventional work-up, the computed SPECT and FDG-PET imaging arms were dominated by the conventional work-up because they had both higher associated costs and lower estimated QALYs: in other words, they were not cost effective.

The authors completed a number of one-way sensitivity analyses in which different variables were altered to test the range of costs and QALYs related to each treatment arm, which are described as follows. The sensitivity of the conventional work-up was increased (0.93) and specificity decreased (0.48) to reflect a more lenient treatment rule (treating both possible and probable AD). The specificity of FDG-PET was altered (0.45, 1.0) in different analyses. In another scenario, FDG-PET was offered to all patients who received a diagnosis of "AD unlikely or excluded." The sensitivity of computed SPECT was lowered in the mild AD group (0.88) and increased for the moderate AD group (0.92). The same hypothetical drugs with varied effectiveness ("Drug X" and "Drug Y") were analyzed in this study, as in

McMahon et al. 2000⁹⁸. Unlike the previous study by these authors, the duration of drug effectiveness was either 6 or 48 months in a sensitivity analysis. In a set of analyses, quality-of-life weights were matched to the HUI2 values in McMahon et al. 2000⁹⁸. New pharmaceuticals have been approved for the treatment of AD since the last study⁹⁸, but estimates of RRs had not been documented extensively in the literature. Therefore, in this study, a sensitivity analysis was performed to address potential side effects of donepezil in false-positive diagnoses (0.05 QALY decrease in no-AD or other dementia patients). A “treat all” analysis was also performed where all patients received donepezil, but the diagnosis was already confirmed and no imaging or lab tests were included.

In all sensitivity analyses, computed SPECT remained dominated by the conventional clinical work-up. FDG-PET reached an ICER of \$334,200 when individuals were treated if they were diagnosed with either possible or probable AD (instead of just probable AD) according to the conventional work-up or FDG-PET scan, but was dominated in the other sensitivity analyses performed with this imaging modality.

Conclusions and limitations:

McMahon et al. (2003)⁹⁹ concluded that the addition of a functional imaging test for the diagnosis of AD is not cost-effective compared with the conventional clinical work-up for either modality included in their analysis (computed SPECT; FDG-PET). From a societal perspective in the United States, the effectiveness of currently available pharmaceuticals and the accuracy of imaging modalities are not conducive to including functional imaging in the diagnosis of AD.

Although the authors concluded that functional neuroimaging was not cost effective compared to the conventional clinical work-up, the authors noted several limitations within their study. As in their previous study⁹⁸, the clinical data available only reflect a short-term time horizon. In addition, the benefits of accurately diagnosing a patient were not quantified in this study. Compared with the study in 2000⁹⁸, the use of the more sensitive HUI3 score and the sensitivity and specificity data from multiple literature and institutional sources support a more accurate conclusion presented in this study. In addition, the large standard deviations for the calculated costs and QALYs may temper any conclusions made from these data.

Notes:

- This study may have received funding from grants, unclear in the publication.
- At least one author has served in a position associated with the pharmaceutical company that produces the drug used in this analysis, based on their previous affiliations⁹⁸.
- This was a moderately-well conducted economic study, with a QHES of 77/100.

Silverman et al. 2002: Patients with early dementia (likely seen by a primary care physician: diagnosis with conventional clinical work-up with or without FDG-PET)

Overview:

Silverman et al.¹⁶² investigated the cost effectiveness of a diagnostic work-up of patients with early dementia consisting of a conventional clinical evaluation compared to the conventional clinical evaluation and the addition of FDG-PET when deemed appropriate. The conventional clinical work-up included a detailed history and physical examination, additional follow-up exams to reassess a previously non-demented patient or review an abnormal test, neuropsychological tests, lab testing, and an MRI (with or without contrast). This study was conducted from a payer perspective.

The source of data for this analysis were from literature reviews and 2001 Medicare outpatient reimbursement rates. The estimated cost savings were obtained by subtracting overall costs of the FDG-PET treatment arm from the costs of the conventional work-up. Overall costs were divided by the accuracy of both methodologies to give the overall cost per accurate diagnosis for each strategy. This study was specific to healthcare in United States, using costing sources from 2001. Funding for this study was received from the Department of Energy, Los Angeles Alzheimer's Association, Turken Family Foundation Award and the National Institutes of Health/National Institute on Aging. The time horizon of the study was six months, thus a discounting rate was not used.

A decision tree model was constructed to simulate stable estimates of economic costs and clinical benefits for each treatment arm. Transition probabilities were taken from the literature and the 1994 AAN guidelines. Probabilities of each branch of the decision tree were calculated using standard Bayesian analytic methods, where applicable. The frequency of structural neuroimaging (MRI) was set at levels determined by the AAN guideline and were always equal in the conventional and FDG-PET treatment arms. The branch probabilities to all outcomes, in addition to the sensitivity and specificity data of each arm, were combined to calculate the expected number of accurate diagnoses.

Assumptions:

A hypothetical population comprised of early dementia patients was used for this study (population size not reported). It was assumed that the prevalence of AD was 51.6% in this population (based on literature values), and that patients would most commonly be presenting to a primary care physician. Based on 1994 AAN guidelines, MRI was recommended in 62.5% of cases (equal for both arms) in the initial evaluation.

The sensitivities and specificities of FDG-PET and the conventional work-up were determined from literature and are based on the accuracy of each using histopathology as the gold standard. The conventional work-up was assumed to have a sensitivity of 0.84 and a specificity of 0.525 for diagnosing AD, while FDG-PET was assumed to have sensitivity of 0.94 and a specificity of 0.73 for diagnosing AD. False-positive diagnoses were assumed to occur in 23.1% of conventional work-up cases and in 12.04% of FDG-PET cases. False-negative rates were 8.25% in conventional evaluation and 3.14% in FDG-PET work-ups.

Costs were derived from literature, 2001 Medicare outpatient reimbursement rates and some estimations calculated by the authors. The conventional clinical work-up included costs associated with detailed history and physical examination, additional follow-up exams, neuropsychological tests, lab testing, and an MRI (with or without contrast). The price of FDG-PET imaging was calculated using the Medicare reimbursement rate for whole-body scans multiplied by a factor of 0.70 to reflect reimbursement from private insurance. In addition, the costs included one year's supply of cholinesterase inhibitors unnecessarily prescribed to a patient without AD as a result of a false positive diagnosis. Finally, the costs considered the financial impact of a false-negative diagnosis: it was assumed that on average, a false-negative diagnosis would result in a nine-month treatment lag and that during that time the patient would decline and need additional care. Otherwise, the cost of care did not appear to be included in the analysis, presumably because patients would otherwise be receiving the treatment they needed and wouldn't significantly decline during the six month time horizon of the analysis.

Results:

The base-case analysis showed that on average, the cost of diagnosis and management under the conventional clinical work-up strategy costs more than that with the additional evaluation with FDG-PET

when medically appropriate. Cost savings with FDG-PET were \$131 per patient. With an overall diagnostic accuracy of 69% and a false-negative rate of 8.25% with the conventional work-up compared with an accuracy of 85% and a false-negative rate of 3.14% when FDG-PET could be added, the model predicted a mean cost savings of \$1,138 per accurate diagnosis, favoring FDG-PET.

The authors completed sensitivity analyses in which different variables were altered to test the range of cost savings per accurate diagnosis by increasing or decreasing each of the following: the sensitivity of FDG-PET, the specificity of FDG-PET, the cost of FDG-PET, and the delay in medical treatment due to false-negative diagnoses. One analysis used the more recent AAN guidelines published in 2001, where MRI without contrast was recommended for 100% of patients.

Based on the sensitivity analyses' estimations, FDG-PET remained cost effective as long as the cost of imaging remains less than \$2,728. FDG-PET remained cost effective if the sensitivity of the test is greater than 0.80. If the specificity is greater than 0.35, then FDG-PET will provide a cost savings compared to the conventional clinical work-up. When 100% of patients receive MRI without contrast, FDG-PET maintains a cost savings of \$1,256 compared with the conventional work-up. Sensitivity analyses assessed the effect of a delay in treatment due to a false-negative diagnosis. If the cost of added care due to a false-negative diagnosis is decreased to a six month delay (\$20,000 cost), FDG-PET maintained a cost savings of greater than \$400. At a 12 month delay, FDG-PET provides a cost savings exceeding \$2,000 per accurate diagnosis. Based on a graphical representation produced in the article, cost savings in the variable analyses were most sensitive to the extra costs of care needed in patients who are not diagnosed in a timely manner (delay in treatment due to false-negative diagnoses).

Conclusions and limitations:

Silverman et al.¹⁶² concluded that patients who present with early cognitive symptoms that have not been explained after conventional diagnostic approaches should undergo FDG-PET imaging. From the payer perspective (Medicare) in the United States, FDG-PET is cost effective in accurately diagnosing patients with AD, when compared to the conventional clinical evaluation.

There are a number of limitations and biases evident in this study. The time horizon for this study is a very short six month period. The authors used literature data for their assumptions, probabilities, and costs. The authors relied heavily on guidelines published by the AAN. This study was pointed towards primary care physicians but the AAN recommendations were originally designed for neurologists. The study is considered from a payer perspective and therefore does not include the many costs that burden society or individuals. Accuracy for the conventional arm was based on a literature value calculated after a clinical evaluation averaging about three years per patient, however the time horizon is significantly shorter in this study. The authors chose to use the low value of a nine month delay in diagnosis for false-negative patients, however the findings were similar when they varied this delay in the sensitivity analyses. In relation to their methodology, the authors explicitly state the costs associated with each piece of the diagnosis, but the study lacks information about the clinical assumptions and does not consider quality-of-life components. Lastly, consideration should be taken when generalizing these results outside of the United States health care system, since the analysis was designed for these settings.

Notes:

- Authors report funding received the Department of Energy, Los Angeles Alzheimer's Association, Turken Family Foundation Award and the National Institutes of Health/National Institute on Aging.

- Authors do not report their conflicts of interest.
- This was a moderately-well conducted economic study, with a QHES of 71/100.

Moulin-Romsee et al. 2005: Dementia patients (likely seen in a specialized memory clinic): diagnosis made with conventional clinical work-up with or without FDG-PET

Overview:

Moulin-Romsee et al.¹⁰⁹ conducted a cost effectiveness analysis using a similar approach described by Silverman et al. (2000).¹⁶² The authors evaluated the cost effectiveness of a diagnostic work-up of patients with dementia consisting of a conventional clinical evaluation compared to the conventional clinical evaluation and the addition of FDG-PET when deemed appropriate. The conventional clinical work-up included a detailed history and physical examination, additional follow-up exams to reassess a previously non-demented patient or review an abnormal test, neuropsychological tests, lab testing, and an MRI (with or without contrast). Funding for the study was not reported. This study was conducted from a payer perspective.

This study was specific to healthcare in Belgium (though extrapolated to other European countries in the sensitivity analyses), using costing sources from the early- to mid- 2000s. As such, costs were reported in Euros (€). Costing sources included the Belgium Health Insurance Institution, local government reimbursement of FDG-PET, the Higher Institute of Employment, as well as costing data from their own institution. A discount rate and time horizon were not reported. The conventional clinical work-up included costs associated with consultations (initial or follow-up) for patient history and physical exams, laboratory tests, neuropsychological tests and structural imaging (MRI with or without contrast). The estimated cost savings were obtained by subtracting overall costs of the FDG-PET treatment arm from the costs of the conventional work-up, and overall costs were divided by the accuracy of each diagnostic modality in order to provide an overall cost per correct diagnosis.

A decision tree model was constructed to simulate stable estimates of economic costs and clinical benefits for each treatment arm. Transition probabilities were taken from the literature. The model was adapted from Silverman et al. 2002¹⁶². Three care scenarios were considered: placement in a retirement home, care-taking at home with minimal costs or care-taking at home with all costs included. Home care with minimal costs only included professional care and material costs, while home care including all costs also accounted for the time invested by family members to care for the patient with AD.

Assumptions:

A hypothetical population comprised of dementia patients was used for this study (population size not reported). Most commonly, these patients present to specialized memory clinics. The prevalence of probable AD was assumed to be 52% in the population and was based on literature values. It was assumed that 100% of patients in both arms would undergo MRI. The authors made the assumption that patients would receive care (in one of the three settings described above) only once the cognitive decline progressed. For patients who received a false-negative diagnosis, a nine month delay in treatment was assumed. Assumptions used in the model by Silverman et al.¹⁶² may be present in this model as well. The time horizon was not clearly reported.

The sensitivities and specificities of FDG-PET and the conventional clinical work-up were determined from literature and are based on the gold standard of histopathology. It was assumed that the

sensitivity and specificity of the conventional work-up for diagnosing AD were 0.84 and 0.525, respectively. FDG-PET was assumed to have sensitivity of 0.94 and a specificity of 0.73.

Costs included those from the initial clinical visit as well as follow-up consultations, MRI with or without contrast, neuropsychological tests, lab tests, and PET as appropriate. In addition, the cost of cholinesterase inhibitors unnecessarily prescribed for a year because of a false-positive diagnosis was included. Further, the costs of extra care for a patient who received a false-negative diagnosis were also included; the authors assumed a nine-month treatment delay and thus nine extra months of care.

Results:

The base-case analysis showed that the complete costs as described above following the conventional clinical work-up were higher than the treatment arm in which FDG-PET was used when medically appropriate. Cost savings favoring FDG were €516 (€1,124 per accurate diagnosis) if it was assumed that patients who had received a false negative diagnosis received care in a retirement home, €205 (€623 per accurate diagnosis) if the patient received home care and minimal costs were assumed, and €3,610 if home care was used and all costs were considered. FDG-PET was most cost effective in the scenario for all home care costs included, with a savings of €6,110 per accurate diagnosis.

The authors completed a number of one-way sensitivity analyses in which different variables were altered to test the range of cost savings per accurate diagnosis. The following variables were increased or decreased in separate analyses: the sensitivity and specificity of FDG-PET, the cost of FDG-PET, as well as the time delay in medical treatment due to false-negative diagnoses. The authors also explored how the country of focus may adjust the cost savings. All necessary data were available from Finland, Greece, Ireland and Spain. Additional countries were analyzed (The Netherlands, France, Germany and England), though full estimations could not be made because some data were not available. One two-way sensitivity analysis was also performed, in which a worst-case scenario model was adopted and assumed the sensitivity and specificity of FDG-PET to be 86% and 67%, respectively, and the price of FDG-PET increased by 35%.

Based on the sensitivity analyses' estimations, FDG-PET remains cost effective if the cost of imaging remains less than €1,000 with patients remaining in the home care setting with minimal costs accrued. When extra care is received in the retirement home setting, FDG-PET remains cost effective if the cost of imaging is less than €1,500. When patients remain in the home care setting but all costs are included, the cost of FDG-PET must remain less than about €5,500 to be cost effective. FDG-PET remains cost effective if the sensitivity of the test is greater than 0.85, under all care settings. If the specificity is greater than 0.30 (in both home care settings) and greater than 0.20 (in the retirement home scenario), then FDG-PET will provide a cost savings, when compared to the conventional clinical work-up. When the effect of a delay in treatment due to a false-negative diagnosis was assessed, FDG-PET remained cost effective in the retirement home and minimal cost home care setting if the delay in treatment was greater than or equal to one month. FDG-PET remained cost effective for the home care setting with all costs included for any delay in treatment (one week to 12 months considered). Applying on the data used from different European nations, FDG-PET remained more cost effective than the conventional work-up in all countries. Based on a graphical representation produced in the article, cost savings in the variable analyses were most sensitive to the price of FDG-PET as well as the sensitivity of FDG-PET. The worst-case scenario evaluated with two-way sensitivity analysis, FDG-PET remained cost effective in both the retirement home and home care setting with all costs considered, but was no longer cost effective in the home care setting with minimal costs considered (-€188).

Conclusions and limitations:

Moulin-Romsee et al.¹⁰⁹ concluded that including FDG-PET into the clinical diagnostic work-up for patients with probable AD provides cost savings (as well as more accurate diagnoses), when compared with the conventional clinical work-up (without FDG-PET). From a societal perspective in Belgium (and extrapolated to other European nations in sensitivity analyses), FDG-PET is cost effective in accurately diagnosing patients with AD, when compared to the conventional clinical evaluation.

There are a number of limitations and biases evident in this study. The authors primarily used literature data for their assumptions, probabilities and costs. Institutional data was only used for one measure of cost. The authors relied heavily on guidelines published in 2001 by the AAN, as well as the study by Silverman et al.¹⁶² for their model. The study is considered from a societal approach based on the costs included in the home care scenario with all costs included (time invested by family members to provide care), however this perspective is not explicitly stated by the authors. The follow-up and time horizon for this study can be inferred as a very short six month period, though this is also not indicated. The authors do discuss conservative biases towards the conventional clinical work-up. Accuracy for the conventional arm was based on a study that calculated the sensitivity and specificity rates after a clinical evaluation averaging about three years per patient. However the period of evaluation was only considered to be six months in this study. The authors chose to use the low value of a nine month delay in diagnosis for false-negative patients, however the findings were similar when they varied this in the sensitivity analyses. In relation to their methodology, the authors explicitly state the costs associated with each piece of the diagnosis, but the study lacks information about the clinical assumptions and does not consider quality-of-life components. Lastly, consideration should be taken when generalizing these results outside of the European health care system, as well as a specialized memory center, since the analysis was designed for these settings.

Notes:

- Authors do not report funding received for the study.
- Authors do not report their conflicts of interest.

This was an adequately conducted economic study, with a QHES of 64/100.

5. Summary by Key Question

The following summaries of evidence have been based on the highest quality of studies available. Additional information on lower quality studies is available in the report.

A summary of the primary results for each key question are provided in the tables that follow the text summaries below with a focus on the primary outcomes described above. Details of these and other outcomes are available in the full report. RCTs and comparative nonrandomized controlled trials are the focus for this summary.

Context Question:

Provide a summary of the inter-rater and intra-rater diagnostic reliability (reproducibility) of functional neuroimaging to diagnose AD, FTD, and Lewy body dementia in symptomatic dementia patients based on an appropriate gold standard (e.g., autopsy, genetic confirmation).

- **FDG-PET:**
 - Evidence base: 7 studies (5 CoE I, 1 CoE II, 1 CoE III); N = 45-132.^{54,57,67,146,163,190,191}
 - Visual assessments of FDG-PET blinded to clinical information.
 - Inter-rater reliability for discriminating AD vs. FTD:
 - Kappa ranged from 0.72-0.81 (3 studies (2 CoE I & 1 CoE II), 2-6 raters, N = 45-132)^{54,57,146}
 - Agreement between all raters: 76% of cases (1 study (CoE 1), 12 raters, N = 45)¹⁹⁰
 - Inter-rater reliability for distinguishing AD from other dementias:
 - Kappa ranged from 0.52-0.67 (2 studies (1 CoE I, 1 CoE III), 3 raters, N = 67-110)^{67,191}
 - Agreement between raters: 94% cases (1 study (CoE 1), 2 raters, N = 100)¹⁶³
 - Intra-rater reliability for diagnosing AD: mean kappa from 3 raters of 0.52 (range, 0.50, 0.94) (1 study, CoE II, N = 110).⁶⁷
- **¹¹C-DTBZ-PET:**
 - Evidence base: 1 study (CoE II); N = 27.⁸⁴
 - Inter-rater reliability for discriminating AD, FTD, and DLB: Kappa: 0.85 (3 raters).
 - Intra-rater reliability for discriminating AD, FTD, and DLB: not reported.
- **HMPAO-SPECT:**
 - Evidence base: 2 studies (CoE III); N = 16-57.^{41,100}
 - Inter-rater reliability for discriminating AD vs. FTD:
 - Kappa: 0.48 (1 study, 2 raters, N = 16).¹⁰⁰
 - Agreement between all raters: 35% cases. (1 study, 5 raters, N = 57)⁴¹
 - Intra-rater reliability for discriminating AD vs. FTD: not reported.
- **¹²³I-FT-CIT-SPECT:**
 - Evidence base: 2 studies (CoE I); N = 20-288.^{94,182}
 - Inter-rater reliability for differentiating between DLB and non-DLB dementias:
 - Kappa: 0.87 (95% CI, 0.79-0.94) (1 study, 3 raters, N = 288).⁹⁴
 - Agreement between all raters: 75% cases (1 study, 3 raters, N = 20).¹⁸²

- Intra-rater reliability for differentiating between DLB and non-DLB dementias: not reported.
- **fMRI, ASL:** No studies identified.

Context Question:

Provide a summary of the sensitivity and specificity of functional neuroimaging to diagnose AD, FTD, and Lewy body dementia in symptomatic dementia patients based on an appropriate gold standard (e.g., autopsy, genetic confirmation).

- **FDG-PET:**
 - Evidence base: 2 retrospective studies (one CoE II, one CoE IV); N = 55-138.^{68,163}
 - Gold standard: autopsy.
 - Visual assessments of FDG-PET to diagnose AD: 93-95% sensitivity; 63-73% specificity (2 studies, N = 55-138).^{68,163}
 - Combination of FDG-PET + clinical diagnosis: not reported.
 - Clinical diagnosis of probable or possible AD (according to NINCDS-ADRDA criteria): 79% sensitivity; 88% specificity (1 CoE IV study, N = 55).⁶⁸
- **HMPAO-SPECT:**
 - Evidence base: 1 retrospective study (CoE IV); N = 73.²³
 - Gold standard: autopsy.
 - Visual assessments of HMPAO-SPECT to diagnose AD: 93% (95% CI, 81-98%) sensitivity; 85% (95% CI, 64-95%) specificity.²³
 - Diagnostic accuracy of clinical diagnosis alone or the combination of FDG-PET and clinical diagnosis was not reported.
- **¹²³I-FT-CIT-SPECT:**
 - Evidence base: 1 prospective study (CoE I); N = 20.¹⁸²
 - Gold standard: autopsy.
 - Visual assessments of FP-CIT-SPECT to diagnose DLB: 88% sensitivity; 83% specificity.¹⁸²
 - Semi-quantitative interpretations of FP-CIT-SPECT to diagnose DLB: 88% sensitivity; 100% specificity.¹⁸²
 - Diagnostic accuracy of the combination of SPECT and clinical diagnosis was not reported.
 - Clinical diagnosis of DLB (Consensus DLB criteria): 75% sensitivity; 42% specificity.¹⁸²
- **¹¹C-DTBZ-PET, fMRI, ASL:** No studies identified.

Strength of evidence (SoE) for Key Question 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)?

Note that the focus is on the highest quality evidence for each test/primary outcome combination.

Imaging (classification)	Outcome	Studies (CoE)	Findings	Final SoE	Downgrade SoE					Starting SoE
					Risk of bias	Consistency	Directness	Precision	Publication bias	
<p>Baseline SoE: HIGH if the majority of articles were CoE I/II, or LOW if the majority of articles were CoE III/IV.</p> <p>Downgrade -1 or -2 levels for each of the following: risk of bias, inconsistency of results, indirectness of evidence (1 or 2), imprecision of effect estimates, or publication bias. See footnotes for reasons for downgrading in each case.</p> <p>Upgrade +1 or +2 for: large magnitude of effect</p>										
<p>FDG-PET: AD vs. FTD Gold standard: autopsy</p>										
FDG-PET (visual)	Sensitivity (AD diagnosis)	2 CoE II ^{54,57} N = 90	94 – 98%	Low	-1*	0	-1†	0	(undetected)	(high)
(SSP and/or SPM images only)	Specificity (AD diagnosis)	2 CoE II ^{54,57} N = 90	73 – 76%	Low	-1*	0	-1†	0	(undetected)	(high)
FDG-PET (automated)	Sensitivity (AD diagnosis)	1 CoE III ¹⁴⁶ N = 10	67%	Insufficient	-1‡	-1§	-1†	-1**	(undetected)	(low)
	Specificity (AD diagnosis)		100%	Insufficient	-1‡	-1§	-1†	-1**	(undetected)	(low)
<p>HMPAO-SPECT: AD vs. FTD Gold standard: autopsy</p>										
HMPAO-SPECT (visual)	Sensitivity (AD diagnosis)	1 CoE IV ¹⁰⁰ N = 56	65%	Insufficient	-1††	-1§	-1†	0	(undetected)	(low)
	Specificity (AD diagnosis)		72%	Insufficient	-1††	-1§	-1†	0	(undetected)	(low)
<p>FDG-PET: DLB vs. AD Gold standard: autopsy</p>										
FDG-PET (automated)	Sensitivity (DLB)	2 CoE III ^{104,174}	80 – 90%	Insufficient	-1‡	0	-1†	-1**	(undetected)	(low)

Imaging (classification)	Outcome	Studies (CoE)	Findings	Final SoE	Downgrade SoE				Starting SoE	
					Risk of bias	Consistency	Directness	Precision		Publication bias
	diagnosis)	N = 32								
	Specificity (DLB diagnosis)		80 – 100%	Insufficient	-1‡	0	-1†	-1**	(undetected)	(low)
No evidence (i.e., Insufficient SoE) found for of the following diagnostic tests: <ul style="list-style-type: none"> • ¹²³I-FP-CIT-SPECT • ¹¹C-DTBZ-PET • fMRI • ASL 										

*Risk of bias downgraded: retrospective study or studies

†Directness downgraded: intermediate outcome

‡Risk of bias downgraded: retrospective study, whether reference standard performed independently of diagnostic test not reported.

§Consistency unknown (single study)

**Precision downgraded: results likely imprecise, as they are based on interpretation of data for a relatively small number of patients (i.e., <50)

††Risk of bias downgraded: retrospective study, inadequate description of test and/or reference standard for replication, whether reference standard performed independently of diagnostic test not reported.

Strength of evidence (SoE) for Key Question 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?

Note that the focus is on the highest quality evidence for each test/outcome combination.

Imaging (classification)	Outcome	Studies (CoE)	Findings	Final SoE	Downgrade SoE					Starting SoE
					Risk of bias	Consistency	Directness	Precision	Publication bias	
<p>Baseline SoE: HIGH if the majority of articles were CoE I/II, or LOW if the majority of articles were CoE III/IV.</p> <p><u>Downgrade</u> -1 or -2 levels for each of the following: risk of bias, inconsistency of results, indirectness of evidence (1 or 2), imprecision of effect estimates, or publication bias. See footnotes for reasons for downgrading in each case.</p> <p><u>Upgrade</u> +1 or +2 for: large magnitude of effect</p>										
<p>FDG-PET: Patient progression (MCI to AD/dementia conversion) Reference standard: AD/dementia at follow-up</p>										
FDG-PET (visual)	Sensitivity	2 CoE II ^{43,48} N = 47 F/U: 1.3-1.6 yrs.	92-100%	Moderate	0	0	0	-1*	(undetected)	(high)
	Specificity		75-89%	Moderate	0	0	0	-1*	(undetected)	(high)
FDG-PET (automated)	Sensitivity	3 CoE III ^{80,85,144} N = 136 F/U: 1.3-3 yrs.	33-45%	Insufficient	-1†	0	0	0	(undetected)	(low)
	Specificity		33-45%	Insufficient	-1†	0	0	0	(undetected)	(low)
<p>FDG-PET: Patient progression (MCI to progressive cognitive decline) Reference standard: progressive cognitive decline at follow-up</p>										
FDG-PET (visual)	Sensitivity	1 CoE I ⁴⁸ N = 17 F/U: 1.6 yrs.	75%	Low	0	-1‡	0	-1*	(undetected)	(high)
	Specificity		88%	Low	0	-1‡	0	-1*	(undetected)	(high)
<p>FDG-PET: Cognitive decline</p>										
FDG-PET (visual)	Cognition (MMSE scores)	1 CoE III ¹⁶⁴ N = 95	Patients predicted to have	Insufficient	-1§	-1‡	0	0	(undetected)	(low)

Imaging (classification)	Outcome	Studies (CoE)	Findings	Final SoE	Downgrade SoE					Starting SoE
					Risk of bias	Consistency	Directness	Precision	Publication bias	
			progressive dementia with FDG-PET had significantly lower MMSE scores at follow-up than did those predicted to have non-progressive dementia (~18 vs. ~25.5, $P < 0.5$).							
FDG-PET: prediction of outcomes related to function, behavior, psychological status, depression, caregiver burden, and global health: No evidence (insufficient evidence).										
HMPAO- or IMP-SPECT: Patient progression (MCI to AD/dementia conversion) Reference standard: AD/dementia at follow-up										
<i>SPECT (automated)</i>	Sensitivity	1 CoE III ⁷⁴ N = 316 F/U: 3 yrs.	58%	Insufficient	-1**	-1‡	0	0	(undetected)	(low)
	Specificity		81%	Insufficient	-1**	-1‡	0	0	(undetected)	(low)
<i>SPECT (visual)</i>	Sensitivity	3 CoE III ^{36,39,74} N = 454 F/U: 1.3 – 4.1 yrs.	36-76%	Insufficient	-1††	0	0	-1‡‡	(undetected)	(low)
	Specificity		39-82%	Insufficient	-1††	0	0	-1‡‡	(undetected)	(low)

Imaging (classification)	Outcome	Studies (CoE)	Findings	Final SoE	Downgrade SoE					Starting SoE
					Risk of bias	Consistency	Directness	Precision	Publication bias	
SPECT: prediction of outcomes related to function, behavior, cognition, psychological status, depression, caregiver burden, and global health: No evidence (insufficient evidence).										
fMRI: Patient progression (MCI to dementia conversion) Reference standard: dementia at follow-up										
<i>fMRI (NR)</i>	Sensitivity	1 CoE III N = 33 F/U: 2.5 ± 0.8 yrs.	55%	Insufficient	-1††	-1‡	0	-1*	(undetected)	(low)
	Specificity		73%	Insufficient	-1††	-1‡	0	-1*	(undetected)	(low)
fMRI: prediction of outcomes related to function, behavior, cognition, psychological status, depression, caregiver burden, and global health: No evidence (insufficient evidence).										
No evidence (i.e., Insufficient SoE) found for of the following diagnostic tests: <ul style="list-style-type: none"> • ¹²³I-FP-CIT-SPECT • ¹¹C-DTBZ-PET • ASL • Comparison of one functional neuroimaging modality of interest versus another functional neuroimaging modality of interest in predicting progression and/or patient outcomes 										

*Risk of precision downgraded: results likely imprecise, as they are based on interpretation of data for a relatively small number of patients (i.e., <50)

† Risk of bias downgraded: retrospective studies, inadequate description of test and/or reference standard for replication, whether reference standard performed independently of diagnostic test not reported, and/or follow-up < 80%.

‡ Consistency unknown (single study)

§ Risk of bias downgraded: inadequate description of reference standard for replication, follow-up < 80% (results available for subset of 95/167 patients).

** Risk of bias downgraded: whether reference standard performed independently of diagnostic test not reported, follow-up < 80%.

†† Risk of bias downgraded: inadequate description of reference standard for replication, lack of blinded comparison of tests with baseline clinical data or clinical outcomes (or insufficient information to determine whether this was done), whether reference standard performed independently of diagnostic test not reported, and/or follow-up < 80%.

‡‡ Imprecise estimate (wide range of values).

Strength of evidence (SoE) for Key Question 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?

No evidence was identified.

Strength of evidence (SoE) for Key Question 4.

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

Note that the focus is on the highest quality evidence for each test/outcome combination.

Imaging	Outcome	Studies (CoE)	Findings	Final SoE	Downgrade SoE					Starting SoE
					Risk of bias	Consistency	Directness	Precision	Publication bias	
<p>Baseline SoE: HIGH if the majority of articles were CoE I/II, or LOW if the majority of articles were CoE III/IV.</p> <p>DOWNGRADE -1 or -2 levels for each of the following: risk of bias, inconsistency of results, indirectness of evidence (1 or 2), imprecision of effect estimates, or publication bias. See footnotes for reasons for downgrading in each case.</p> <p>UPGRADE +1 or +2 for: large magnitude of effect</p>										
FDG-PET	Injection-related short-term harms*	1 CoE III ⁸⁹ N = 36	0%	Insufficient	-1†	-1‡	0	-1§	(undetected)	(low)
¹²³I-FP-CIT-SPECT	Injection-related harms** (procedural and post-procedural only)	1 CoE III ⁹⁴ N = 326	2.8% patients (10 events)	Insufficient	0	-1‡	0	0	(undetected)	(low)
FDG-PET, ¹²³I-FP-CIT-SPECT	Other harms, including long-term harms and effect of missed diagnosis, false negative, or false positive	0 studies		Insufficient						
<p>No evidence (i.e., Insufficient SoE) found for of the following diagnostic tests:</p> <ul style="list-style-type: none"> • HMPAO-SPECT • ¹¹C-DTBZ-PET • fMRI • ASL 										

* Harms assessed: injection site pain, tenderness, redness, or swelling; or new fever, rash, breathing difficulties, diarrhea, headache, or muscle pain.

† Risk of bias: harms assessed by phone call to patients.

‡ Consistency unknown (single study)

§ Imprecise estimate: small sample size

** Harms reported, attribute to ligand injection: nausea (3 events), injection site hemorrhage (2 events), injection site erythema (2 events), dry mouth (1 event), vomiting (1 event), and headache (1 event).

Strength of evidence (SoE) for Key Question 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.

No evidence was identified.

Summary of evidence available for Key Question 6:

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

Because methods for determining the overall quality of evidence related to economic studies have not been reported, the overall strength of evidence for outcomes reported in Key Question 6 was not assessed.

Summary**• FDG-PET:**

- One cost-utility study⁹⁹ (QHEs 77) and two cost effectiveness studies (QHEs 64 & 71)^{109,162} explored the addition of FDG-PET to the conventional clinical work-up for the diagnosis of AD.
- Cost utility study:
 - Conducted in the US
 - Simulated cohort of hypothetical patients presenting with mild or moderate dementia.
 - A decision tree analysis and Markov modeling were used to estimate the long-term costs and QALYs gained (due to diagnosis and drug treatment).
 - Time horizon: 18 months.
 - The associated costs of care and drug treatment costs for the entire time horizon were included.
- Cost effectiveness studies:
 - One study conducted in the US¹⁶², the other in Belgium¹⁰⁹
 - Simulated cohort of hypothetical patients.
 - Decision tree analysis used to estimate the costs per accurate diagnosis.
 - One cost effectiveness study¹⁶² used a 6 month time horizon for patients with early cognitive symptoms.
 - The other cost effectiveness study¹⁰⁹ did not report a time horizon; the cohort represented patients with probable AD.
 - The costs of care were not included unless the patient was placed into the simulated group who received a false negative diagnosis (these costs were still less than those included in the cost utility study).
 - Similarly, the costs of medical treatment were not included unless the patient was placed into the group who received a false positive diagnosis.
- The costs of FDG-PET as well as other costs included in the conventional clinical work-up (lab tests, structural imaging, and physician consultations) were similar across all three studies.
- The cost utility study concluded that FDG-PET was more costly (imaging costs, additional travel days, caregiver time and consultation fees) and provided no benefit in QALYs, thus FDG-PET was not cost effective as an add-on in the diagnosis of AD.
- Conversely, the cost effectiveness studies^{109,162} found that the use of FDG-PET, when deemed appropriate, in addition to a conventional clinical evaluation, to be cost-effective for the diagnosis of AD, particularly because it was less costly and had increased accuracy over the conventional work-up.

- **SPECT (visual and computed)**
 - Two cost-utility studies (QHES 77)^{98,99} examined the use of SPECT as an add-on functional imaging modality to a conventional clinical work-up, compared with the conventional work-up alone.
 - Simulated; used hypothetical patients presenting with mild or moderate dementia, referred to a specialized AD clinic.
 - Conducted in the US
 - The same decision tree analysis with Markov modeling was used by both studies to estimate the costs and QALYs associated with diagnosis and drug treatment.
 - Time horizon: 18 months.
 - Drug treatment duration: 18 months for both diagnostic groups.
 - The costs associated with SPECT were slightly higher than those accrued for the conventional work-up alone due to the cost of the imaging (\$699-\$2,175, depending on the Medicare reimbursement schedule used and computed vs. visual SPECT).
 - The QALYs gained after diagnosis with SPECT were no higher than those associated with the conventional diagnostic approach.
 - Conclusion: SPECT was not cost-effective as an add-on to the conventional clinical evaluation in the diagnosis of AD.

- **fMRI:** No studies identified

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