Washington State Health Care Authority

Health Technology Assessment

Functional Neuroimaging for Primary Degenerative Dementia or Mild Cognitive Impairment

Final Evidence Report: Appendices

December 5, 2014

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Functional Neuroimaging for Primary Degenerative Dementia or Mild Cognitive Impairment

Provided by:

Spectrum Research, Inc.

Final Report
APPENDICES

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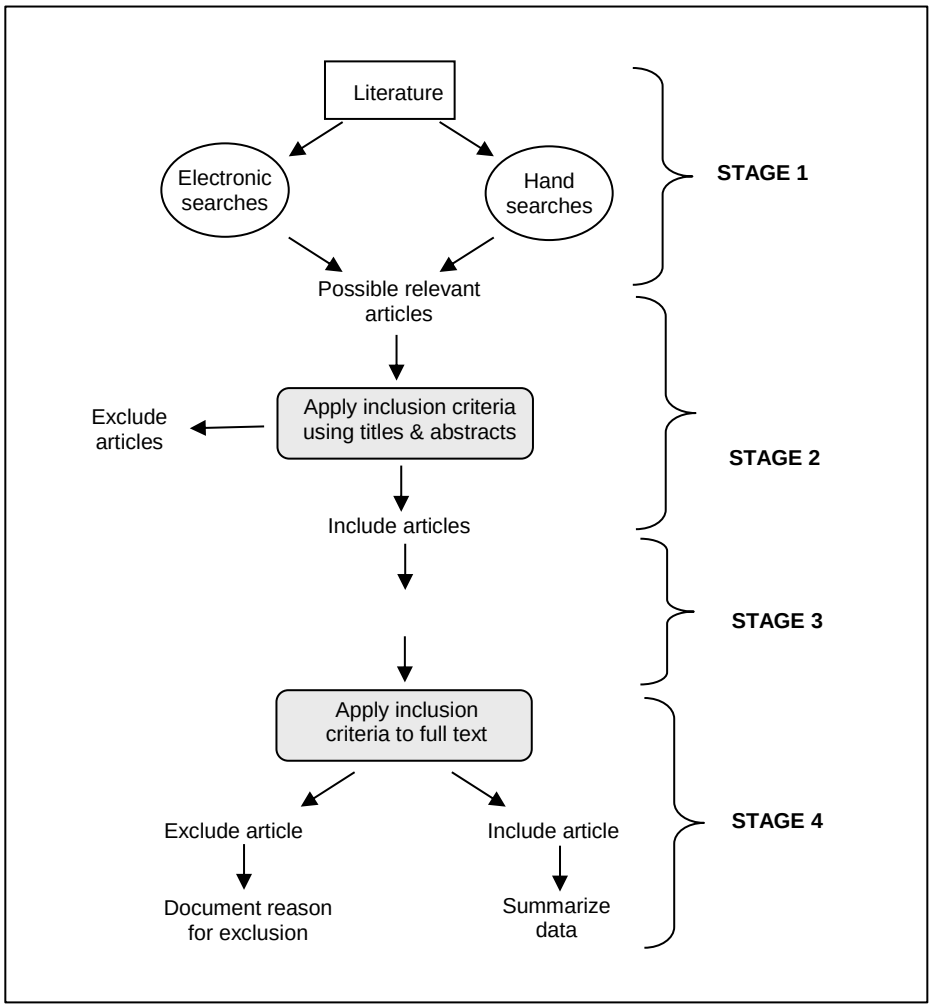
APPENDIX A. Algorithm for Article Selection



APPENDIX B. Search Strategies

Below is the search strategy for PubMed. Parallel strategies were used to search other electronic databases listed below. Keyword searches were conducted in the other listed resources.

Search strategy (PubMed)
Search date: 6/25/14

Filters: Abstract available, English

	Search Code	Number of Articles
1	"Dementia" OR Dementia[MeSH] OR Alzheimer* OR "Alzheimer Disease"[MeSH] OR "Lewy body dementia" OR (Lewy AND (disease OR dementia)) OR "Lewy Body Disease"[MeSH] OR "Frontotemporal dementia" OR "frontotemporal degeneration" OR (("FTD" OR "FTLD") AND "frontotemporal") OR "Frontotemporal Dementia"[MeSH] OR "Frontotemporal Lobar Degeneration"[MeSH] OR (frontotemporal AND (behavioral OR behavioural)) OR "bvFTD" OR "bvFTLD" OR "Pick's Disease" OR "Picks Disease" OR "Pick Disease" OR "Pick Disease of the Brain"[MeSH] OR "Primary Progressive Aphasia" OR "Aphasia, Primary Progressive"[MeSH] OR "Primary Progressive Nonfluent Aphasia"[MeSH] OR "Progressive supranuclear palsy" OR "Supranuclear Palsy, Progressive"[MeSH] OR Tauopathies[MeSH] OR "Neurofibrillary Tangles"[MeSH] OR "TDP-43 Proteinopathies"[MeSH] OR "mild cognitive impairment" OR "Mild Cognitive Impairment"[MeSH]	142,996
2	"functional neuroimaging" OR "functional imaging" OR "PET" OR "positron emission tomography" OR "Positron-Emission Tomography"[MeSH] OR "SPECT" OR (Single AND Photon AND Emission AND Computed AND Tomography) OR "Tomography, Emission-Computed, Single-Photon"[MeSH] OR "fMRI" OR "functional MRI" OR "functional magnetic resonance imaging" OR "EEG" OR "electroencephalogram" OR "electroencephalograms" OR "electroencephalography" OR electroencephalography[MeSH] OR "MEG" OR "magnetoencephalogram" OR "magnetoencephalograms" OR "magnetoencephalography" OR magnetoencephalography[MeSH] OR "arterial spin labeling" OR "arterial spin labelling" OR "magnetic resonance spectroscopy" OR "magnetic resonance spectroscopy"[MeSH] OR "near infrared spectroscopy" OR "near-infrared spectroscopy" OR "spectroscopy, near infrared"[MeSH] OR (contrast AND (enhanced OR enhanced) AND (magnetic OR MR OR MRI))	361,334
3	#1 AND #2	10,930

	Search Code	Number of Articles
4	"diagnosis" OR "diagnoses" OR "diagnostic" OR "Diagnosis"[MeSH] OR "Diagnosis, Differential"[MeSH] OR "Diagnostic Imaging"[MeSH] OR "Diagnostic Techniques, Neurological"[MeSH] OR "Decision Support Techniques"[MeSH] OR "Early Diagnosis"[MeSH] OR "Delayed Diagnosis"[MeSH] OR "Decision Trees"[MeSH]	4,882,832
5	#3 AND #4	8970
6	#5 NOT Case Reports[Publication Type]	7793
	Total references from Pubmed search	**7793**
	Additional references from other electronic and hand searches	**2616**
	Total number of references	**10,409**

Parallel strategies were used to search the Cochrane Library and others listed below. Keyword searches were conducted in the other listed resources.

Electronic Database Searches

The following databases have been searched for relevant information:

Agency for Healthcare Research and Quality (AHRQ)
Cumulative Index to Nursing and Allied Health (CINAHL)
Cochrane Database of Systematic Reviews
Cochrane Registry of Clinical Trials (CENTRAL)
Cochrane Review Methodology Database
Database of Reviews of Effectiveness (Cochrane Library)
EMBASE
PubMed
Informational Network of Agencies for Health Technology Assessment (INAHTA)
NHS Economic Evaluation Database
HSTAT (Health Services/Technology Assessment Text)
EconLIT

Additional Economics, Clinical Guideline and Gray Literature Databases

AHRQ - Healthcare Cost and Utilization Project
Canadian Agency for Drugs and Technologies in Health
Centers for Medicare and Medicaid Services (CMS)
Food and Drug Administration (FDA)
Google
Institute for Clinical Systems Improvement (ICSI)
National Guideline Clearinghouse

APPENDIX C. Excluded Articles

Note. As shown in Figure 1 of the Evidence Report, 77 studies were completely excluded from the report.

Articles excluded as primary studies after full text review, with reason for exclusion.

	Citation	Reason for Exclusion	Included In Different KQ Of Report?
	Studies considered and excluded for contextual question on diagnostic reliability* (n = 32)		
1.	Arlig A, Larsson A, Bergh AC, et al. A new method for the relative quantification of rCBF examined by 99Tcm-HMPAO SPECT. *Nucl Med Commun* 1994;15:814-23.	Diagnostic reliability not evaluated.	-
2.	Atri A, O'Brien JL, Sreenivasan A, et al. Test-retest reliability of memory task functional magnetic resonance imaging in Alzheimer disease clinical trials. *Arch Neurol* 2011;68:599-606.	Diagnostic reliability not evaluated.	-
3.	Blautzik J, Keeser D, Berman A, et al. Long-term test-retest reliability of resting-state networks in healthy elderly subjects and with amnestic mild cognitive impairment patients. *J Alzheimers Dis* 2013;34:741-54.	Diagnostic reliability not evaluated.	-
4.	Chow, T. W., et al. (2007). "Comparison of manual and semi-automated delineation of regions of interest for radioligand PET imaging analysis." BMC Nuclear Medicine **7**.	Less than ten patients evaluated.	
5.	Clement F, Belleville S. Test-retest reliability of fMRI verbal episodic memory paradigms in healthy older adults and in persons with mild cognitive impairment. *Hum Brain Mapp* 2009;30:4033-47.	Diagnostic reliability not evaluated.	-
6.	Colloby SJ, Firbank MJ, Pakrasi S, et al. A comparison of 99mTc-exametazime and 123I-FP-CIT SPECT imaging in the differential diagnosis of Alzheimer's disease and dementia with Lewy bodies. *Int Psychogeriatr* 2008;20:1124-40.	SPECT used to diagnose a mixed population (including >20% normal patients) rather than only patients presenting with dementia	-
7.	Hellman RS, Tikofsky RS, Van Heertum R, et al. A multi-institutional study of interobserver agreement in the evaluation of dementia with rCBF/SPET technetium-99m exametazime (HMPAO). *Eur J Nucl Med* 1994;21:306-13.	No direct diagnosing, only addressing degree of impairment of particular areas; only 44% of patients meet the inclusion criteria (the remaining patients have VaD, HIV, or normal controls)	

	Citation	Reason for Exclusion	Included In Different KQ Of Report?
8.	Herholz K, Westwood S, Haense C, et al. Evaluation of a calibrated (18)F-FDG PET score as a biomarker for progression in Alzheimer disease and mild cognitive impairment. *J Nucl Med* 2011;52:1218-26.	Diagnostic reliability not evaluated.	
9.	Heun, R., et al. (1997). "Proton magnetic resonance spectroscopy in dementia of Alzheimer type." Int J Geriatr Psychiatry **12**(3): 349-358.	Diagnostic reliability not evaluated.	
10.	Hierholzer J, Cordes M, Venz S, et al. Loss of dopamine-D2 receptor binding sites in Parkinsonian plus syndromes. *J Nucl Med* 1998;39:954-60.	Diagnostic reliability not evaluated.	
11.	Honda, N., et al. (2002). "Interobserver variation in diagnosis of dementia by brain perfusion SPECT." Radiat Med **20**(6): 281-289.	Diagnostic reliability not evaluated; population consisted of more than 20% normal patients.	
12.	Hooijer, C., et al. (1990). "Reliability, validity and follow-up of the EEG in senile dementia: sequelae of sequential measurement." Electroencephalogr Clin Neurophysiol **76**(5): 400-412.	Diagnostic reliability not evaluated.	
13.	Imabayashi E, Matsuda H, Asada T, et al. Superiority of 3-dimensional stereotactic surface projection analysis over visual inspection in discrimination of patients with very early Alzheimer's disease from controls using brain perfusion SPECT. *J Nucl Med* 2004;45:1450-7.	SPECT used to diagnose a mixed population (including >20% normal patients) rather than only patients presenting with dementia	
14.	Ito K, Shimano Y, Imabayashi E, et al. Concordance between Tc-ECD SPECT and F-FDG PET interpretations in patients with cognitive disorders diagnosed according to NIA-AA criteria. *Int J Geriatr Psychiatry* 2014.	Diagnostic reliability not evaluated.	
15.	Ito, K., et al. (2013). "Prediction of outcomes in MCI with (123)I-IMP-CBF SPECT: a multicenter prospective cohort study." Ann Nucl Med **27**(10): 898-906.	Reliability of prediction made, not current diagnosis.	KQ2
16.	Joshi A, Koeppe RA, Fessler JA. Reducing between scanner differences in multi-center PET studies. *Neuroimage* 2009;46:154-9.	Diagnostic reliability not evaluated.	
17.	Moretti, D. V., et al. (2011). "Volumetric differences in mapped hippocampal regions correlate with increase of high alpha rhythm in Alzheimer's disease." Int J Alzheimers Dis **2011**: 208218.	Diagnostic reliability not evaluated.	

	Citation	Reason for Exclusion	Included In Different KQ Of Report?
18.	Mosconi, L., et al. (2006). "Visual rating of medial temporal lobe metabolism in mild cognitive impairment and Alzheimer's disease using FDG-PET." Eur J Nucl Med Mol Imaging **33**(2): 210-221.	FDG-PET used to diagnose a mixed population (including >20% normal patients) rather than only patients presenting with dementia	
19.	Musiek ES, Chen Y, Korczykowski M, et al. Direct comparison of fluorodeoxyglucose positron emission tomography and arterial spin labeling magnetic resonance imaging in Alzheimer's disease. *Alzheimers Dement* 2012;8:51-9.	PET and SPECT used to diagnose a mixed population (including >20% normal patients) rather than only patients presenting with dementia	
20.	Ng S, Villemagne VL, Berlangieri S, et al. Visual assessment versus quantitative assessment of 11C-PIB PET and 18F-FDG PET for detection of Alzheimer's disease. *J Nucl Med* 2007;48:547-52.	PET used to diagnose a mixed population (including >20% normal patients) rather than only patients presenting with dementia	
21.	Okada, T., et al. (2007). "Reproducibility of magnetic resonance spectroscopy in correlation with signal-to-noise ratio." Psychiatry Res **156**(2): 169-174.	Diagnostic reliability not evaluated.	
22.	Pardo, J. V., et al. (2010). "Fluorodeoxyglucose positron emission tomography of mild cognitive impairment with clinical follow-up at 3 years." Alzheimers Dement **6**(4): 326-333.	Each rater used different methodology and scans for evaluating PET images for diagnosis: study not a true reflection of inter-rater reliability.	
23.	Pasquier, F., et al. (1997). "The use of SPECT in a multidisciplinary memory clinic." Dement Geriatr Cogn Disord **8**(2): 85-91.	Diagnostic reliability not evaluated.	
24.	Stockbridge, H. L., et al. (2002). "Brain SPECT: a controlled, blinded assessment of intra-reader and inter-reader agreement." Nucl Med Commun **23**(6): 537-544.	SPECT used to diagnose a mixed population (including >20% patients with excluded diagnoses, such as secondary dementia (VaD and dementia attributed to toxic chemicals) and normal controls) rather than only patients presenting with primary dementia.	
25.	Tang, B. N., et al. (2004). "Diagnosis of suspected Alzheimer's disease is improved by automated analysis of regional cerebral blood flow." Eur J Nucl Med Mol Imaging **31**(11): 1487-1494.	SPECT used to diagnose a mixed population (including >20% patients with excluded diagnoses, such as mental disorders, Parkinson's disease, cerebrovascular dementia,	

	Citation	Reason for Exclusion	Included In Different KQ Of Report?
		hydrocephalus, tumors, epilepsy, sleep apnea, etc.).	
26.	Tolboom N, van der Flier WM, N T, WM vdF, Boerhoff J, et al. Molecular imaging in the diagnosis of Alzheimer's disease: visual assessment of [11C]PIB and [18F]FDDNP PET images. *J Neurol Neurosurg Psychiatry.* 2010;81(8):882-884.	FDG-PET used to diagnose a mixed population (including >20% normal patients) rather than only patients presenting with dementia.	
27.	van Deursen, J. A., et al. (2008). "Increased EEG gamma band activity in Alzheimer's disease and mild cognitive impairment." J Neural Transm **115**(9): 1301-1311.	Diagnostic reliability not evaluated.	
28.	Waldemar, G., et al. (1994). "99mTc-bicisate (neurolite) SPECT brain imaging and cognitive impairment in dementia of the Alzheimer type: a blinded read of image sets from a multicenter SPECT trial." J Cereb Blood Flow Metab **14 Suppl 1**: S99-105.	Diagnostic reliability not evaluated.	
29.	Wang J, Zuo X, Dai Z, et al. Disrupted functional brain connectome in individuals at risk for Alzheimer's disease. *Biol Psychiatry* 2013;73:472-81.	Diagnostic reliability not evaluated.	
30.	Wenzel, F., et al. (2010). "B-spline-based stereotactical normalization of brain FDG PET scans in suspected neurodegenerative disease: impact on voxel-based statistical single-subject analysis." Neuroimage **50**(3): 994-1003.	FDG-PET used to diagnose a mixed population (including >20% normal patients) rather than only patients presenting with dementia	
31.	Wu X, Chen K, Yao L, et al. Assessing the reliability to detect cerebral hypometabolism in probable Alzheimer's disease and amnestic mild cognitive impairment. *J Neurosci Methods* 2010;192:277-85.	Diagnostic reliability not evaluated.	
32.	Zaknun JJ, Leblhuber F, Schucktanz H. Value of cerebral blood flow quantification in the diagnosis of dementia. *Nucl Med Commun* 2008;29:260-9.	Diagnostic reliability not evaluated.	
	Studies considered and excluded for contextual question on diagnostic accuracy and Key Question 1 (n = 15)		
1.	Bonte, F. J., et al. (2006). "Tc-99m HMPAO SPECT in the differential diagnosis of the dementias with histopathologic confirmation." Clin Nucl Med **31**(7): 376-378.	Smaller subset of population included in Bonte 2011.	
2.	Bonte, F. J., et al. (1997). "Brain blood flow in the dementias: SPECT with histopathologic correlation in	Smaller subset of population included in Bonte 2011.	

	Citation	Reason for Exclusion	Included In Different KQ Of Report?
	54 patients." Radiology **202**(3): 793-797.		
3.	Drzezga, A., et al. (2005). "Prediction of individual clinical outcome in MCI by means of genetic assessment and (18)F-FDG PET." J Nucl Med **46**(10): 1625-1632.	APOE not used as a reference standard. Reference standard was progression form MCI to AD.	KQ2
4.	Ettlin, T. M., et al. (1989). "Computed tomography, electroencephalography, and clinical features in the differential diagnosis of senile dementia. A prospective clinicopathologic study." Arch Neurol **46**(11): 1217-1220.	≥20% of patients had vascular dementia (not primary degenerative dementia).	
5.	Higuchi, M., et al. (2000). "Glucose hypometabolism and neuropathological correlates in brains of dementia with Lewy bodies." Exp Neurol **162**(2): 247-256.	Diagnostic accuracy of FDG-PET based on autopsy not reported.	
6.	Jagust, W., et al. (2001). "SPECT perfusion imaging in the diagnosis of Alzheimer's disease: a clinical-pathologic study." Neurology **56**(7): 950-956.	≥20% of patients were normal controls (no dementia) or had vascular dementia (not primary degenerative dementia).	
7.	Jagust, W., et al. (2007). "What does fluorodeoxyglucose PET imaging add to a clinical diagnosis of dementia?" Neurology **69**(9): 871-877.	≥20% of patients were normal controls (no dementia) or had vascular dementia (not primary degenerative dementia).	
8.	Jobst, K. A., et al. (1998). "Accurate prediction of histologically confirmed Alzheimer's disease and the differential diagnosis of dementia: the use of NINCDS-ADRDA and DSM-III-R criteria, SPECT, X-ray CT, and Apo E4 in medial temporal lobe dementias. Oxford Project to Investigate Memory and Aging." Int Psychogeriatr **10**(3): 271-302.	Diagnostic accuracy of SPECT for dementia patients not reported.	
9.	Kantarci, K., et al. (2008). "Alzheimer disease: postmortem neuropathologic correlates of antemortem 1H MR spectroscopy metabolite measurements." Radiology **248**(1): 210-220.	Diagnostic accuracy not reported for population of MCI and/or dementia patients only.	
10.	Read, S. L., et al. (1995). "SPECT in dementia: clinical and pathological correlation." J Am Geriatr Soc **43**(11): 1243-1247.	Unable to determine sensitivity or specificity.	
11.	Sanchez-Juan, P., et al. (2014). "Practical utility of amyloid and FDG-PET in an academic dementia center." Neurology **82**(3): 230-238.	Both FDG-PET and PiB-PET (excluded, evaluates presence of amyloid-beta) were performed; clinicians made	

	Citation	Reason for Exclusion	Included In Different KQ Of Report?
		diagnosis after PET was performed using data from both. Because of this, it was not possible to evaluate the effect that FDG-PET alone had on diagnostic changes because the physicians were also taking the results of the PiB-PET scans into account when making their final clinical diagnosis.	
12.	Seok, M. L., et al. (2009). "The 18F-FDG PET cingulate island sign and comparison to 123I-(beta)-CIT SPECT for diagnosis of dementia with lewy bodies." Journal of Nuclear Medicine **50**(10): 1638-1645.	<10 patients (n = 5) had gold standard of autopsy	
13.	Staffen, W., et al. (2006). "Brain perfusion SPECT in patients with mild cognitive impairment and Alzheimer's disease: comparison of a semiquantitative and a visual evaluation." J Neural Transm **113**(2): 195-203.	No acceptable gold standard used.	
14.	Womack, K. B., et al. (2011). "Temporoparietal hypometabolism in frontotemporal lobar degeneration and associated imaging diagnostic errors." Arch Neurol **68**(3): 329-337.	Overall diagnostic accuracy NR.	Context question (reliability)
15.	Yu, P., et al. (2012). "Enriching amnestic mild cognitive impairment populations for clinical trials: optimal combination of biomarkers to predict conversion to dementia." J Alzheimers Dis **32**(2): 373-385.	No acceptable gold standard used.	
	Studies considered and excluded for Key Question 2 (n = 27)		
1.	Albin, R. L., et al. (2013). "Assessing mild cognitive impairment with amyloid and dopamine terminal molecular imaging." J Nucl Med **54**(6): 887-893.	PET image classifications were made using both amyloid imaging (11C-PIB) and dopamine imaging (11C-dihydrotetrabenazine) PET; thus classifications for dopamine imaging (11C-dihydrotetrabenazine) PET could not be separated from those made from amyloid imaging.	
2.	Arbizu, J., et al. (2013). "Automated analysis of FDG PET as a tool for single-subject probabilistic	The prediction model (AD-Conv score) combined FDG-	

	Citation	Reason for Exclusion	Included In Different KQ Of Report?
	prediction and detection of Alzheimer's disease dementia." Eur J Nucl Med Mol Imaging **40**(9): 1394-1405.	PET, MMSE score, ApoE4 genotype, age, and gender. FDG-PET not considered as a predictive factor alone.	
3.	Banzo, I., et al. (2014). "Amyloid imaging with (11)C-PIB PET/CT and glucose metabolism with (18)F-FDG PET/CT in a study on cognitive impairment in the clinical setting." Nucl Med Commun **35**(3): 238-244.	Not a longitudinal study.	
4.	Borroni, B., et al. (2006). "Combined 99mTc-ECD SPECT and neuropsychological studies in MCI for the assessment of conversion to AD." Neurobiol Aging **27**(1): 24-31.	Exploratory proof of concept study.†	
5.	Bruck, A., et al. (2013). "[11C]PIB, [18F]FDG and MR imaging in patients with mild cognitive impairment." Eur J Nucl Med Mol Imaging **40**(10): 1567-1572.	Retrospective application of predictive criteria to the same population in which the predictive criteria were developed.	
6.	Cheng, B., et al. (2013). "Semi-supervised multimodal relevance vector regression improves cognitive performance estimation from imaging and biological biomarkers." Neuroinformatics **11**(3): 339-353.	Exploratory proof of concept study.†	
7.	Dukart, J., et al. (2013). "Generative FDG-PET and MRI model of aging and disease progression in Alzheimer's disease." PLoS Comput Biol 9(4): e1002987.	Exploratory proof of concept study.†	
8.	Fellgiebel, A., et al. (2004). "Association of elevated phospho-tau levels with Alzheimer-typical 18F-fluoro-2-deoxy-D-glucose positron emission tomography findings in patients with mild cognitive impairment." Biol Psychiatry **56**(4): 279-283.	Duplicate patient population and methods as reported in Fellgiebel 2007 (included).	
9.	Haense, C., et al. (2009). "Performance of FDG PET for detection of Alzheimer's disease in two independent multicentre samples (NEST-DD and ADNI)." Dement Geriatr Cogn Disord **28**(3): 259-266.	Does not address the KQ; tests the ability of a model to discriminate between healthy controls and AD patients not to predict progression.	-
10.	Herholz, K., et al. (2011). "Evaluation of a calibrated (18)F-FDG PET score as a biomarker for progression in Alzheimer disease and mild cognitive impairment." J Nucl Med 52(8): 1218-1226.	Retrospective application of predictive criteria to the same population in which the predictive criteria were developed.	

	Citation	Reason for Exclusion	Included In Different KQ Of Report?
11.	Kochan, N. A., et al. (2011). "Cortical responses to a graded working memory challenge predict functional decline in mild cognitive impairment." Biol Psychiatry **70**(2): 123-130.	Exploratory proof of concept study.†	
12.	Landau, S. M., et al. (2011). "Associations between cognitive, functional, and FDG-PET measures of decline in AD and MCI." Neurobiol Aging 32(7): 1207-1218.	Exploratory proof of concept study.†	
13.	Llano, D. A., et al. (2011). "Derivation of a new ADAS-cog composite using tree-based multivariate analysis: prediction of conversion from mild cognitive impairment to Alzheimer disease." Alzheimer Dis Assoc Disord 25(1): 73-84.	Retrospective application of predictive criteria to the same population in which the predictive criteria were developed.	-
14.	Lorenzi, M., et al. (2010). "Enrichment through biomarkers in clinical trials of Alzheimer's drugs in patients with mild cognitive impairment." Neurobiol Aging **31**(8): 1443-1451, 1451 e1441.	Study developed prediction model using FDG-PET data but the model was not validated in a separate population.	-
15.	Munoz-Ruiz, M. A., et al. (2014). "Comparing predictors of conversion to Alzheimer's disease using the disease state index." Neurodegener Dis 13(2-3): 200-202.	Study developed prediction model using FDG-PET data but the model was not validated in a separate population.	
16.	Panegyres, P. K., et al. (2009). "Fluorodeoxyglucose-positron emission tomography in the differential diagnosis of early-onset dementia: a prospective, community-based study." BMC Neurol **9**: 41.	Does not address the KQ (does not report progression or clinical outcomes).	
17.	Petrella, J. R., et al. (2011). "Default mode network connectivity in stable vs progressive mild cognitive impairment." Neurology **76**(6): 511-517.	Exploratory proof of concept study.†	
18.	Prestia, A., et al. (2013). "Prediction of dementia in MCI patients based on core diagnostic markers for Alzheimer disease." Neurology **80**(11): 1048-1056.	Study tests a combination of diagnostic modalities at once but does not provide results on the predictive ability of FDG-PET alone.	
19.	Siepel, F. J., et al. (2013). "(123I)FP-CIT SPECT in suspected dementia with Lewy bodies: a longitudinal case study." BMJ Open **3**(4).	Regarding the part of the study that is relevant to KQ2, the study evaluated the ability of SPECT to predict whether patients with dementia but without the clinical features of DLB would develop the features of DLB. To that end,	

	Citation	Reason for Exclusion	Included In Different KQ Of Report?
		only 7 patients were evaluated (n=10 required for inclusion).	
20.	Silverman, D. H., et al. (2001). "Positron emission tomography in evaluation of dementia: Regional brain metabolism and long-term outcome." JAMA **286**(17): 2120-2127.	For the part of the study that addresses this KQ, Silverman 2003 (included in KQ2) duplicates and extends the patient population.	Context question (accuracy)
21.	Silverman, D. H., et al. (2002). "Added clinical benefit of incorporating 2-deoxy-2-[18F]fluoro-D-glucose with positron emission tomography into the clinical evaluation of patients with cognitive impairment." Mol Imaging Biol **4**(4): 283-293.	Does not address KQ.	
22.	Trzepacz, P. T., et al. (2014). "Comparison of neuroimaging modalities for the prediction of conversion from mild cognitive impairment to Alzheimer's dementia." Neurobiol Aging 35(1): 143-151.	Study developed prediction model using FDG-PET data but the model was not validated in a separate population.	
23.	Walhovd, K. B., et al. (2010). "Combining MR imaging, positron-emission tomography, and CSF biomarkers in the diagnosis and prognosis of Alzheimer disease." AJNR Am J Neuroradiol 31(2): 347-354.	Exploratory proof of concept study.†	
24.	Wolfe, N., et al. (1995). "Temporal lobe perfusion on single photon emission computed tomography predicts the rate of cognitive decline in Alzheimer's disease." Arch Neurol **52**(3): 257-262.	Study correlated regional blood flow with conversion but did not make predictions regarding conversion.	
25.	Young, J., et al. (2013). "Accurate multimodal probabilistic prediction of conversion to Alzheimer's disease in patients with mild cognitive impairment." Neuroimage Clin **2**: 735-745.	Study developed prediction model using FDG-PET data in AD vs. normal as well as in MCI patients but the FDG-PET model was not validated in a separate population.	
26.	Zhang, D. and D. Shen (2012). "Multi-modal multi-task learning for joint prediction of multiple regression and classification variables in Alzheimer's disease." Neuroimage 59(2): 895-907.	Study developed prediction model using FDG-PET data but the model was not validated in a separate population.	
27.	Zhang, D., et al. (2011). "Multimodal classification of Alzheimer's disease and mild cognitive impairment." Neuroimage **55**(3): 856-867.	Study developed prediction model using FDG-PET data but the model was not validated in a separate population.	
	Studies considered and excluded for Key Question 3 (n = 8)		

	Citation	Reason for Exclusion	Included In Different KQ Of Report?
1.	Amen, D. G., et al. (2012). "Specific ways brain spect imaging enhances clinical psychiatric practice." Journal of Psychoactive Drugs **44**(2): 96-106.	Wrong population: only a small percentage of patients (10%) had dementia.	
2.	Bloom, M., et al. (1996). "Cerebral SPECT imaging: Effect on clinical management." Journal of Nuclear Medicine **37**(7): 1070-1074.	Wrong population: the majority of patients had excluded diagnosis (ischemic stroke, transient ischemia, intracranial hemorrhage, head trauma, cerebral arteriovenous malformations, encephalopathy).	
3.	Gabel, M. J., et al. (2010). "Validation of consensus panel diagnosis in dementia." Arch Neurol **67**(12): 1506-1512.	Does not address KQ.	KQ1 (accuracy)
4.	Laforce, R., Jr., et al. (2010). "The value of PET in mild cognitive impairment, typical and atypical/unclear dementias: A retrospective memory clinic study." Am J Alzheimers Dis Other Demen **25**(4): 324-332.	No comparison to patients who did not receive functional neuroimaging.	
5.	Kemp, P. M., et al. (2011). "Impact of 123I-FP-CIT (DaTSCAN) SPECT on the diagnosis and management of patients with dementia with Lewy bodies: a retrospective study." Nucl Med Commun **32**(4): 298-302.	Insufficient data reported: no details regarding how the results of functional neuroimaging altered clinical management (i.e., no info on how management changed after a positive versus a negative scan).	
6.	Sanchez-Juan, P., et al. (2014). "Practical utility of amyloid and FDG-PET in an academic dementia center." Neurology **82**(3): 230-238.	Both FDG-PET and PiB-PET (excluded, evaluates presence of amyloid-beta) were performed; clinicians made diagnosis after PET was performed using data from both. Because of this, it was not possible to evaluate the effect that FDG-PET alone had on diagnostic changes because the physicians were also taking the results of the PiB-PET scans into account when making their final clinical diagnosis.	
7.	Silverman, D. H., et al. (2002). "Added clinical benefit of incorporating 2-deoxy-2-[18F]fluoro-D-glucose with positron emission tomography into the clinical	Does not address KQ.	KQ6 (cost)

	Citation	Reason for Exclusion	Included In Different KQ Of Report?
	evaluation of patients with cognitive impairment." Mol Imaging Biol **4**(4): 283-293.		
8.	Smith, F. W., et al. (1988). "The use of technetium-99m-HM-PAO in the assessment of patients with dementia and other neuropsychiatric conditions." J Cereb Blood Flow Metab 8(6): S116-122.	14/19 patients who underwent HMPAO-SPECT as part of their diagnostic work-up were being evaluated for multi-infarct dementia, which is an excluded condition.	
	Studies considered and excluded for Key Question 4 (n = 1)		
1.	Grosset, D. G., et al. (2014). "Safety Analysis of 10 Clinical Trials and for 13 Years After First Approval of Ioflupane 123I Injection (DaTscan)." J Nucl Med.	Wrong population: only 20% had condition of interest (DLB).	
	Studies considered and excluded for Key Question 5 (n = 0)		
	(All studies included for KQ2 and KQ4 were considered for KQ5).		
	Studies considered and excluded for Key Question 6 (n = 3)		
1.	Handels, R. L., et al. (2012). "Diagnostic and economic evaluation of new biomarkers for Alzheimer's disease: the research protocol of a prospective cohort study." BMC Neurol **12**: 72.	No data reported.	
2.	Ollendorf, D. A., et al. (2012). "Toward evidence-based decisions in diagnostic radiology: a research and rating process for multiple decision-makers." Acad Radiol **19**(9): 1049-1054.	Narrative review	
3.	van Crevel, H., et al. (1999). "Early diagnosis of dementia: which tests are indicated? What are their costs?" J Neurol **246**(2): 73-78.	Narrative review	

*We had intended to review the full-text of Nihashi 2007 (reference below), but were unable to acquire the full-text article by a variety of means, including attempts to contact the publisher.
Nihashi, T., et al. (2007). "Direct comparison study between FDG-PET and IMP-SPECT for diagnosing Alzheimer's disease using 3D-SSP analysis in the same patients." Radiat Med 25(6): 255-262.)
†Exploratory proof of concept studies 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.

APPENDIX D. Class of Evidence and QHES Determination

Each study was critically appraised against the following pre-set criteria. The resulting Class of Evidence (CoE) rating was then used as a starting point to identify risk of bias. Correlations between CoE grades and risk of bias are provided in Table D1.

Table D1. Definition of the risk of bias

Class	Risk of Bias	Definition
I	**Low risk of bias**	Study adheres to commonly held tenets of high quality design, execution and avoidance of bias
II	**Moderately low risk of bias**	Study has potential for some bias; does not meet all criteria for class I but deficiencies not likely to invalidate results or introduce significant bias
III	**Moderately high risk of bias**	Study has flaws in design and/or execution that increase potential for bias that may invalidate study results
IV	**High risk of bias**	Study has significant potential for bias; does not include design features geared toward minimizing bias and/or does not have a comparison group

Table D2. Definition of the class of evidence for reliability studies

	Reliability Studies		
Class	**Risk of bias**	**Study design**	**Criteria**
I	Low risk of bias	Good quality study	• Broad spectrum of persons with the expected condition • Adequate description of methods for replication • Blinded comparison of tests, measurements or interpretation • Second test/interpretation performed independently of the first
II	Moderately low risk of bias	Moderate quality study	• Violation of any one of the criteria for a good quality study
III	Moderately high risk of bias	Poor quality study	• Violation of any two of the criteria
IV	High risk of bias	Very poor quality study	• Violation of three or four of the criteria

Table D3. Definition of the class of evidence for diagnostic test accuracy studies

	Diagnostic test accuracy studies		
Class	**Risk of bias**	**Study design**	**Criteria**
I	Low risk of bias	Good quality prospective study	• Broad spectrum of persons with the expected condition • Appropriate reference standard used • Adequate description of test and reference for replication • Blinded comparison of tests with appropriate reference standard • Reference standard performed independently of diagnostic test
II	Moderately low risk of bias	Moderate quality prospective study	• Violation of any one of the criteria for a good quality prospective study (LoE I)
		Good quality retrospective study	• Broad spectrum of persons with the expected condition • Appropriate reference standard used • Adequate description of test and reference for replication • Blinded comparison of tests with appropriate reference standard • Reference standard performed independently of diagnostic test
III	Moderately high risk of bias	Poor quality prospective study	• Violation of any two or more of the criteria for a good quality prospective study (LoE I)
		Moderate quality retrospective study	• Violation of any one of the criteria for a good quality retrospective study (LoE II)
IV	High risk of bias	Poor quality retrospective study	• Violation of any two or more of the criteria for a good quality retrospective study (LoE II)
		Case control study	

Table D4. Definition of the class of evidence and risk of bias for prognostic studies that evaluate the predictive ability of a diagnostic test

		Studies of Prognosis	
Class	**Risk of Bias**	**Study Design**	**Criteria**
I	Low risk of bias	Good quality cohort*	• Prospective design • Broad spectrum of persons with the expected condition • Patients at similar point in the course of their disease or treatment • Adequate description of test and reference for replication • Blinded comparison of tests with appropriate reference standard • Reference standard performed independently of diagnostic test • F/U rate of ≥ 80%† • Patients followed long enough for outcomes to occur

Class	Risk of Bias	Studies of Prognosis	
		Study Design	Criteria
II	Moderately low risk of bias	Moderate quality cohort	• Prospective design, with violation of one of the other criteria for good quality cohort study • Retrospective design, meeting all the rest of the criteria in class I
III	Moderately high risk of bias	Poor quality cohort Good quality case-control or cross-sectional study	• Prospective design with violation of 2 or more criteria for good quality cohort, or • Retrospective design with violation of 1 or more criteria for good quality cohort • A good case-control study‡ • A good cross-sectional study§
IV	High risk of bias	Poor quality case-control or cross-sectional Case series§	• Other than a good case-control study • Other than a good cross-sectional study • Any case series** design

*Cohort studies follow individuals with the exposure of interest over time and monitor for occurrence of the outcome of interest.

†Applies to cohort studies only.

‡A good case-control study must have the all of the following: all incident cases from the defined population over a specified time period, controls that represent the population from which the cases come, exposure that precedes an outcome of interest, and accounting for other prognostic factors.

§A good cross-sectional study must have all of the following: a representative sample of the population of interest, an exposure that precedes an outcome of interest (e.g., sex, genetic factor), an accounting for other prognostic factors, and for surveys, at least a 80% return rate.

**A case-series design for prognosis is one where all the patients in the study have the exposure of interest. Since all the patients have the exposure, risks of an outcome can be calculated only for those with the exposure, but cannot be compared with those who do not have the exposure. For example, a case-series evaluating the effect of smoking on spine fusion that only recruits patients who smoke can simply provide the risk of patients who smoke that result in pseudarthrosis but cannot compare this risk to those that do not smoke.

Table D5. Definition of the class of evidence and risk of bias for studies on harms of a diagnostic test

Class	Risk of Bias	Studies Of Harms Of Diagnostic Tests	
		Study Design	Criteria
I	Low risk of bias	Good quality cohort*	• Prospective design • Broad spectrum of persons with the expected condition • Adequate description of test for replication • Outcome evaluation blinded to diagnostic test performed • F/U rate of ≥ 80%† • Patients followed long enough for outcomes to occur
II	Moderately low risk of bias	Moderate quality cohort	• Prospective design, with violation of one of the other criteria for good quality cohort study • Retrospective design, meeting all the rest of the criteria in class I
III	Moderately high risk of bias	Poor quality cohort Good quality case-control or cross-	• Prospective design with violation of 2 or more criteria for good quality cohort, or • Retrospective design with violation of 1 or more criteria for

Class	Risk of Bias	Studies Of Harms Of Diagnostic Tests	
		Study Design	**Criteria**
		sectional study	good quality cohort • A good case-control study‡ • A good cross-sectional study§
IV	High risk of bias	Poor quality case-control or cross-sectional Case series§	• Other than a good case-control study • Other than a good cross-sectional study • Any case series** design

*Cohort studies follow individuals with the exposure of interest over time and monitor for occurrence of the outcome of interest.

†Applies to cohort studies only.

‡A good case-control study must have the all of the following: all incident cases from the defined population over a specified time period, controls that represent the population from which the cases come, exposure that precedes an outcome of interest, and accounting for other prognostic factors.

§A good cross-sectional study must have all of the following: a representative sample of the population of interest, an exposure that precedes an outcome of interest (e.g., sex, genetic factor), an accounting for other prognostic factors, and for surveys, at least a 80% return rate.

**A case-series design for prognosis is one where all the patients in the study have the exposure of interest. Since all the patients have the exposure, risks of an outcome can be calculated only for those with the exposure, but cannot be compared with those who do not have the exposure. For example, a case-series evaluating the effect of smoking on spine fusion that only recruits patients who smoke can simply provide the risk of patients who smoke that result in pseudarthrosis but cannot compare this risk to those that do not smoke.

Determination of Overall Strength of Evidence

Following the assessment of the quality of each individual study included in the report, an overall "strength of evidence" for the relevant question or topic is determined. Methods for determining the overall strength of evidence are variable across the literature and are most applicable to evaluation of therapeutic studies.

SRI's method incorporates the overall risk of bias (see primary domains of quality (CoE)), quantity of studies and consistency of results across studies as described by AHRQ.

The following four possible levels and their definition will be reported:

- **High** – High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate** - Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- **Low** - Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and likely to change the estimate.
- **Insufficient** – Evidence either is unavailable or does not permit a conclusion.

Table D5. Methodology outline for determining overall strength of evidence (SoE):

All AHRQ "required" and "additional" domains* are assessed. Only those that influence the baseline grade are listed in table.

Baseline strength: Risk of bias (including control of confounding) is accounted for in the individual article evaluations. HIGH = majority of articles Class I/II. LOW = majority of articles Class III/IV.

DOWNGRADE: Inconsistency** of results (1 or 2); Indirectness of evidence (1 or 2); Imprecision of effect estimates (1 or 2); Sub-group analyses not stated *a priori* and no test for interaction (2)

UPGRADE: Large magnitude of effect (1 or 2); Dose response gradient (1)

Outcome	Strength of Evidence	Conclusions & Comments	Baseline	DOWNGRADE	UPGRADE
Outcome	**HIGH**	Summary of findings	**HIGH** Class I/II studies	**NO** consistent, direct, and precise estimates	**NO**
Outcome	**LOW**	Summary of findings	**HIGH** Class I/II studies	**YES (2)** Inconsistent Indirect	**NO**

*Required domains: risk of bias, consistency, directness, precision, publication bias.

Additional domains: presence of plausible unmeasured confounding and bias that would decrease an observed effect or increase an effect if none was observed, large magnitude of effect (strength of association)

**Single study = "consistency unknown

Assessment of Economic Studies

Full formal economic analyses evaluate both costs and clinical outcomes of two or more alternative interventions. The four primary types are cost minimization analysis (CMA), cost-utility analysis (CUA), cost-effectiveness analysis (CEA), and cost-benefit analyses (CBA). Each employs different methodologies, potentially complicating critical appraisal, but some common criteria can be assessed across studies.

No standard, universally accepted method of critical appraisal of economic analyses is currently in use. A number of checklists [Canadian, BMJ, AMA] are available to facilitate critique of such studies. The Quality of Health Economic Studies (QHES) instrument developed by Ofman et al.[2] embodies the primary components relevant for critical appraisal of economic studies[1,2]. It also incorporates a weighted scoring process and which was used as one factor to assess included economic studies. This tool has not yet undergone extensive evaluation for broader use but provides a valuable starting point for critique.

In addition to assessment of criteria in the QHES, other factors are important in critical appraisal of studies from an epidemiologic perspective to assist in evaluation of generalizability and potential sources of study bias.

Such factors include:

- Are the interventions applied to similar populations (eg, with respect to age, gender, medical conditions, etc)? To what extent are the populations for each intervention comparable and are

differences considered or accounted for? To what extent are population characteristics consistent with "real world" applications of the comparators?

- Are the sample sizes adequate so as to provide a reasonable representation of individuals to whom the technology would be applied?
- What types of studies form the basis for the data used in the analyses? Data (e.g., complication rates) from randomized controlled trials or well-conducted, methodologically rigorous cohort studies for data collection are generally of highest quality compared with case series or studies with historical cohorts.
- Were the interventions applied in a comparable manner (e.g., similar protocols, follow-up procedures, evaluation of outcomes, etc.)?
- How were the data and/or patients selected or sampled (e.g., a random selection of claims for the intervention from a given year/source or all claims)? What specific inclusion/exclusion criteria or processes were used?
- Were the outcomes and consequences of the interventions being compared comparable for each? (e.g., were all of the relevant consequences/complications for each intervention considered or do they primarily reflect those for one intervention?)

Assessment of the overall strength of evidence for formal economic analyses does not appear to be documented in the literature. For the purposes of this HTA, overall strength was determined by:

- Quality of the individual studies: Where the majority of quality indicators described in the QHES met and were the methods related to patient/claim selection, patient population considerations and other factors listed above consistent with a high quality design?
- Number of formal analyses (3 or more)
- Consistency of findings and conclusions from analyses across studies.

APPENDIX E. Class of Evidence (CoE) and QHES Evaluation

Context Question: Reliability Studies

Methodological Principle	Foster 2007	Gabel 2010	Womack 2011	Hoffman 1996	Rabinovici 2011	Silverman 2001	Yamane 2014
Broad spectrum of persons with the expected condition	■	■	■	NR	■	■	■
Adequate description of methods for replication	■	■	■	■	■	■	■
Blinded comparison of tests, measurements or interpretation	■	■	■	■	■	■	■
Second test/interpretation performed independently of the first	■	■	■	NR	NR	■	■
CoE	**I**	**I**	**I**	**III**	**II**	**I**	**I**

Methodological Principle	Koeppe 2005	Doran 2005	McNeill 2007	McKeith 2007	Walker 2007
Broad spectrum of persons with the expected condition	■	NR	■	■	■
Adequate description of methods for replication	■	■		■	■
Blinded comparison of tests, measurements or interpretation	NR	■	■	■	■
Second test/interpretation performed independently of the first	NR	NR	NR	■	■
CoE	**III**	**III**	**III**	**I**	**I**

Blank cells indicate that the criterion was not met.

NR indicates that insufficient information was provided.

Context Question: Diagnostic accuracy studies

Methodological Principle	Hoffman 1996	Silverman 2001	Bonte 2011	Walker 2007
Prospective study				■
Retrospective study	■	■	■	
Case-control study				
Broad spectrum of persons with the expected condition	NR	■	NR	■
Appropriate reference standard used	■	■	■	■
Adequate description of test and reference for replication	■	■		■
Blinded comparison of tests with appropriate reference standard	■	■	■	■
Reference standard performed independently of diagnostic test	NR	■	NR	■
CoE	**IV**	**II**	**IV**	**I**

Blank cells indicate that the criterion was not met.

NR indicates that insufficient information was provided.

KQ1: Differential diagnostic accuracy studies

Methodological Principle	Foster 2007	Gabel 2010	Rabinovici 2011	McNeill 2007	Minoshima 2001	Toledo 2013
Prospective study						
Retrospective study	■	■	■	■	■	■
Case-control study						
Broad spectrum of persons with the expected condition	■	■	■	■	■	■
Appropriate reference standard used	■	■	■	■	■	■
Adequate description of test and reference for replication	■	■	■		■	■
Blinded comparison of tests with appropriate reference standard	■	■	■	■	■	■
Reference standard performed independently of diagnostic test	■	■	NR	NR	NR	NR
CoE	**II**	**II**	**III**	**IV**	**III**	**III**

Blank cells indicate that the criterion was not met.

KQ2: Longitudinal prognostic studies that evaluate the predictive ability of a diagnostic test

Methodological Principle	Dobert 2005	Drzezga 2005	Fellgiebel 2007	Hatashita 2013	Kakimoto 2011	Landau 2010	Pardo 2010
Prospective study		■	■				
Retrospective study	■			■	■	■	■
Case-control study							
Broad spectrum of persons with the expected condition	NR	■	■	■	■	■	NR
Patients at similar point in the course of their disease or treatment	■	■	■	■	■	■	■
Adequate description of test and standard (clinical outcome) for replication	■	■	■	■	■	■	Test: ■ Outcome: no credit
Blinded comparison of tests with baseline clinical data or appropriate reference standard (clinical outcome)	■	■	■	NR	■ (automated)	■ (automated)	■
Reference standard (clinical outcome) evaluated independently of diagnostic test	■	■	■	NR	NR	■	NR
F/U rate of ≥ 80%†	NR	■	■	NR	NR		NR
Patients followed long enough for outcomes to occur	■	■	■	■	■	■	■
CoE	**III**	**I**	**I**	**III**	**III**	**III**	**III**

Continued on next page…

Methodological Principle	Prestia 2013	Silverman 2003	Tripathi 2013	Devanand 2010	Ito 2013	Petrella 2007
Prospective study		■	■	■	■	■
Retrospective study	■					
Case-control study						
Broad spectrum of persons with the expected condition	■	■	NR	■	■	■
Patients at similar point in the course of their disease or treatment	■	■	■	■	■	■
Adequate description of test and reference for replication		Test: ■ Outcome: no credit	■	Test: no credit Outcome: ■	■	■
Blinded comparison of tests with baseline clinical data or appropriate reference standard (clinical outcome)	■ (automated)	■	NR		■	NR
Reference standard (clinical outcome) evaluated independently of diagnostic test	■	■	NR	■	NR	NR
F/U rate of ≥ 80%†	NR	NR	■	■		■
Patients followed long enough for outcomes to occur	■	■	■	■	■	■
CoE	**III**	**III**	**III**	**III**	**III**	**III**

Blank cells indicate that the criterion was not met.

*Cohort studies follow individuals with the exposure of interest over time and monitor for occurrence of the outcome of interest. Studies were considered to be retrospective unless clearly self-described as prospective.

†Applies to cohort studies only.

KQ4: Harms of diagnostic test

Methodological Principle	Lowe 2009	McKeith 2007
Prospective study		■
Retrospective study	■	
Case-control study		
Broad spectrum of persons with the expected condition	NR	■
Adequate description of test for replication	■	■
Outcome evaluation blinded to diagnostic test performed	NR	
F/U rate of ≥ 80%†	■	NR
Patients followed long enough for outcomes to occur	NR	NR
CoE	**III**	**III**

Quality of Health Economic Studies (QHES) score of included articles

QHES Question (pts possible)		McMahon (2000)	McMahon (2003)	Silverman (2002)	Moulin-Romsee (2005)
1.	Was the study objective presented in a clear, specific, and measurable manner? (7 pts)	7	7	7	7
2.	Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated? (4 pts)	4	4	4	0
3.	Were variable estimates used in the analysis from the best available source (i.e. randomized controlled trial = best, expert opinion = worst)? (8 pts)	0	0	0	0
4.	If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study? (1 pt)	1	1	1	1
5.	Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions? (9 pts)	9	9	9	9
6.	Was incremental analysis performed between alternatives for resources and costs? (6 pts)	6	6	6	6
7.	Was the methodology for data abstraction (including the value of health states and other benefits) stated? (5 pts)	5	5	5	5
8.	Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate? (7 pts)	7	7	0	0
9.	Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described? (8 pts)	8	8	8	8
10.	Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term, long-term and negative outcomes included? (6 pts)	0	0	0	0
11.	Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used? (7 pts)	7	7	7	7
12.	Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner? (8 pts)	8	8	0	0
13.	Were the choice of economic model, main assumptions, and limitations of the study stated and justified? (7 pts)	7	7	7	7

14.	Did the author(s) explicitly discuss direction and magnitude of potential biases? (6 pts)	0	0	6	6
15.	Were the conclusions/recommendations of the study justified and based on the study results? (8 pts)	8	8	8	8
16.	Was there a statement disclosing the source of funding for the study? (3 pts)	0	0	3	0
	Total score:	**77**	**77**	**71**	**64**
	Cost-Effectiveness Analysis Registry, Quality Score*:	**6 / 7**	**5 / 7**	**NR**	**NR**

*Scale of 1 (low) to 7 (high), organized by the Tufts Medical Center, Institute for Clinical Research and Health Policy Studies, The Center for Evaluation of Value and Risk in Health (https://research.tufts-nemc.org/cear4/Default.aspx). The Registry reviews published, English-language cost-utility analyses with original cost-utility estimates. An auditing form contains methodology, cost-effectiveness ratios and utility weight sections, which is independently reviewed by two trained readers. The final quality score is a consensus score from these two reviewers.

APPENDIX F. Inclusion/Exclusion Criteria of Included Studies

Context Question: Reliability. Inclusion/Exclusion criteria of included studies

Study	Imaging Modality	Inclusion	Exclusion
Foster 2007	FDG-PET	• Individuals with retrievable parametric PET images that included most of the brain in the field of view • AD patients met NIA-Reagan neuropathological criteria for either high or intermediate likelihood of AD	• NR
Gabel 2010	FDG-PET	• Individuals with retrievable parametric PET images that included most of the brain in the field of view • AD patients met NIA-Reagan neuropathological criteria for either high or intermediate likelihood of AD	• NR
Hoffman 2000	FDG-PET	• Subjective complaints • Performance of 1.5 or more SDs below the age norm on the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) delayed verbal recall test • A Clinical Dementia Rating (CDR) score of 0.5, and preserved basic activities of daily living (ADL) • Patients were included in the study after informed consent had been obtained	• If they met diagnostic criteria for manifest dementia or for any other functional psychiatric disorder, including major depression • If they showed any characteristic symptoms of diseases or abnormalities sufficient to cause memory impairment, such as normal pressure hydrocephalus, Parkinson's disease, or progressive supranuclear palsy • Patients were also excluded if they showed any major structural abnormalities or signs of major vascular pathology in MRI, such as status after infarction, extensive leucoencephalopathy or atrophy, intracerebral aneurysm or arteriovenous malformation • The National Institute of Neurological Disorders and Stroke–International Association for Research and Teaching in Neurosciences (NINDS–AIREN) criteria were used to exclude relevant ischemic processes causing cognitive impairment in the patients • Other extracerebral causes possibly influencing neuropsychologic function, such as psychotropic medication (e.g., antidepressants, neuroleptics) or substance abuse, were excluded

Study	Imaging Modality	Inclusion	Exclusion
Rabinovici 2011	FDG-PET	• Patients were required to meet research criteria for AD or the FTLD syndromes behavioral variant frontotemporal dementia, semantic dementia, or progression nonfluent aphasia • Patients with posterior cortical atrophy and logopenic aphasia, visuospatial and language-predominant syndromes associated with AD pathology were included in the AD group to represent the full clinical spectrum of early-onset AD	• Clinical features consistent with an alternative primary neurologic disorder (e.g., significant cerebrovascular disease, epilepsy, tumors, dementia with Lewy bodies, prion disease), major medical illness, and pre-morbid psychiatric disease
Silverman 2001	FDG-PET	• Patients presenting with symptoms of dementia • Two groups of patients were included 1) those studied with PET followed longitudinally for at least 2 years and 2) those studied with PET whose disease • All patients prospectively enrolled at UCLA provided written informed consent and were studied in accordance with a protocol approved by the UCLA institutional review board	• NR
Yamane 2014	FDG-PET	• Patients were registered as 1 of 3 clinical groups (mild AD, MCI, or NC) • Project was approved by the ethics committee of each site in which J-ADNI data were acquired, and written informed consent was obtained from each subject before participating in J-ADNI	• Depression, cerebrovascular disorders, and other neurologic or psychiatric disorders • Use of medication known or suspected to interact with the striatal binding of 123I-FP_CIT to the DAT, which included psychopharmaca such as cocaine, amphetamine, mazindol, methyphenidate, benzatropine, bupropion, and sertaline
Koeppe 2005	C-DTBZ PET	• The study was approved by the University of Michigan Medical School IRB • Informed consent was obtained from all participants or their caregivers	• NR
Doran 2005	^{99m}Tc-HMPAO-SPECT	• Patient were referred from CFC:WCNN to two nuclear medicine centers, the Department of Nuclear Medicine, Royal Liverpool University Hospital, Liverpool, or Wrexham Maelor Hospital	• NR

Study	Imaging Modality	Inclusion	Exclusion
McNeill 2007	^{99m}Tc-HMPAO-SPECT	• SPECT images available for analysis • Consent for postmortem examination had been obtained during life and confirmed at death • Study is a part of a larger research programme and ethical approval has been obtained	• NR
McKeith 2007	^{123}I-FP-CIT SPECT	• Patients met the criteria for demential detailed in the diagnostic and statistical manual of mental disorders—fourth edition (DSM-IV) and fulfilled at least one of the following: consensus criteria for probable or possible DLB, National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable or possible Alzheimer's disease, or National Institute of Neurological Disorders and Stroke-Association Internationale Pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria for probable or possible vascular dementia. • Mini-mental state examination (MMSE) score of 10 or more was required to ensure patients could complete sufficient assessments to provide useful diagnostic information • The study was done in accordance with the current revision of the Declaration of Helsinki and the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonisation and applicable to national ad local laws and regulations • At every participating site, the study protocol and all amendments were approved by an IRB or independent ethics committee • All patients and their caregivers gave written informed consent	• Patients in any diagnostic group with structural imaging findings indicative of infarction in the region of the basal ganglia, including the internal capsule
Walker 2007	^{123}I-FP-CIT SPECT	• Patients were clinically diagnosed based on Consensus DLB criteria or NINCDS-ADRDA criteria	• NR

Context Question: Accuracy. Inclusion/Exclusion criteria of included studies

Study	Imaging Modality	Inclusion	Exclusion
Hoffman 2000	FDG-PET	• Subjective complaints • Performance of 1.5 or more SDs below the age norm on the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) delayed verbal recall test • A Clinical Dementia Rating (CDR) score of 0.5, and preserved basic activities of daily living (ADL) • Patients were included in the study after informed consent had been obtained	• If they met diagnostic criteria for manifest dementia or for any other functional psychiatric disorder, including major depression • If they showed any characteristic symptoms of diseases or abnormalities sufficient to cause memory impairment, such as normal pressure hydrocephalus, Parkinson's disease, or progressive supranuclear palsy • Patients were also excluded if they showed any major structural abnormalities or signs of major vascular pathology in MRI, such as status after infarction, extensive leucoencephalopathy or atrophy, intracerebral aneurysm or arteriovenous malformation • The National Institute of Neurological Disorders and Stroke–International Association for Research and Teaching in Neurosciences (NINDS–AIREN) criteria were used to exclude relevant ischemic processes causing cognitive impairment in the patients • Other extracerebral causes possibly influencing neuropsychologic function, such as psychotropic medication (e.g., antidepressants, neuroleptics) or substance abuse, were excluded
Silverman 2001	FDG-PET	• Patients presenting with symptoms of dementia • Two groups of patients were included 1) those studied with PET followed longitudinally for at least 2 years and 2) those studied with PET whose disease • All patients prospectively enrolled at UCLA provided written informed consent and were studied in accordance with a protocol approved by the UCLA institutional review board	• NR
Bonte 2011	Tc-99m HMPAO SPECT	• NR	• NR

Study	Imaging Modality	Inclusion	Exclusion
Walker 2007	^{123}I-FP-CIT SPECT	• Patients were clinically diagnosed based on Consensus DLB criteria or NINCDS-ADRDA criteria	• NR

Key Question 1. Inclusion/Exclusion criteria of included studies, AD versus FTD

Study	Imaging Modality	Inclusion	Exclusion
McNeill 2007	HMPAO-SPECT	• SPECT images available for analysis • Consent for postmortem examination had been obtained during life and confirmed at death • Study is a part of a larger research program and ethical approval has been obtained	• NR
Foster 2007	FDG PET	• Individuals with retrievable parametric PET images that included most of the brain in the field of view • AD patients met NIA-Reagan neuropathological criteria for either high or intermediate likelihood of AD	• NR
Gabel 2010	FDG PET (see Foster 2007)	• Individuals with retrievable parametric PET images that included most of the brain in the field of view • AD patients met NIA-Reagan neuropathological criteria for either high or intermediate likelihood of AD	• NR
Rabinovici 2011	FDG-PET	• Patients were required to meet research criteria for AD or the FTLD syndromes behavioral variant frontotemporal dementia, semantic dementia, or progression nonfluent aphasia • Patients with posterior cortical atrophy and logopenic aphasia, visuospatial and language-predominant syndromes associated with AD pathology were included in the AD group to represent the full clinical spectrum of early-onset ADincluded most of the brain in the field of view • Patient were required to meet research criteria for AD or the FTLD syndromes behavior variant frontotemporal dementia, semantic dementia, or progressive nonfluent aphasia	• Clinical features consistent with an alternative primary neurologic disorder (e.g., significant cerebrovascular disease, epilepsy, tumors, dementia with Lewy bodies, prion disease), major medical illness, and pre-morbid psychiatric disease

Key Question 1. Inclusion/Exclusions criteria of included studies, AD versus DLB

Study	Imaging Modality	Inclusion	Exclusion
Minoshima 2001	FDG-PET	• Patients with pure AD or DLB • AD diagnosis made according to age-specific quantitative criteria established by Khachaturian • DLB diagnosis was made when at least three Lewy bodies per x20 field were present in four fields on ubiquitin-stained sections in three of the four most commonly affected areas, namely transentorhinal cortex, anterior cingulate cortex, amygdala, and insular cortex • For Lewy body variant of Alzheimer's disease (LBVAD), both sets of the above criteria had to be met	• NR
Toledo 2013	FDG-PET	• Diagnosis of MCI was established and DAT was based on the NINDCDS-ADRDA criteria for probable AD	• NR

Key Question 2. Inclusion/Exclusion criteria of included studies

Study	Imaging Modality	Inclusion	Exclusion
Drzezga 2005	FDG-PET	• Subjective complaints • Performance of 1.5 or more SDs below the age norm on the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) delayed verbal recall test • A Clinical Dementia Rating (CDR) score of 0.5, and preserved basic activities of daily living (ADL) • Patients were included in the study after informed consent had been obtained	• If they met diagnostic criteria for manifest dementia or for any other functional psychiatric disorder, including major depression • If they showed any characteristic symptoms of diseases or abnormalities sufficient to cause memory impairment, such as normal pressure hydrocephalus, Parkinson's disease, or progressive supranuclear palsy • Patients were also excluded if they showed any major structural abnormalities or signs of major vascular pathology in MRI, such as status after infarction, extensive leucoencephalopathy or atrophy, intracerebral aneurysm or arteriovenous malformation • The National Institute of Neurological Disorders and Stroke–International Association for Research and Teaching in Neurosciences (NINDS–AIREN) criteria were used to exclude relevant ischemic processes causing cognitive impairment in the patients • Other extracerebral causes possibly influencing neuropsychologic function, such as psychotropic medication (e.g., antidepressants, neuroleptics) or substance abuse, were excluded
Fellgiebel 2007	FDG-PET	• Patients who consulted the University Memory Clinic for diagnostic evaluation • The study was approved by the local Ethics Committee, and all subjects gave written informed consent	• Patients with metabolic diseases that could interfere with cognitive functioning • Patients with other brain diseases • Patients with a diagnosis of present depression according to DSM-IV criteria
Hatashita 2013 FDG-PET	FDG-PET	• Patients who met the Core Clinical Criteria for MIC proposed by the NIA-Alzheimer's Association workgroup (including concern about a change in cognition, impairment in one or more cognitive domains, preservation of independence in functional abilities, and no dementia)	• Patients with systemic or brain diseases that could account for the decline in cognition, including degenerative, vascular, depressive, traumatic, medical comorbidities, or mixed disease

Study	Imaging Modality	Inclusion	Exclusion
		• Each subject or their caregiver provided written informed consent for participation	
Kakimoto 2012	FDG-PET	• written informed consent was obtained from each participant after detail explanation of this study	• NR
Landau 2010	FDG-PET	• Between age 55 and 90 years • Completed at least 6 years of education • Fluent in English or Spanish • Free of any other significant neurologic diseases • The procedures for this study were approved by institutional review boards of all participating institutions • All subjects gave written, informed consent to blood sampling, lumbar puncture, cognitive testing, and neuroimaging prior to participation	• NR
Pardo 2010	FDG-PET	• MCI patients referred for imaging from the memory loss in the Geriatric, Research, Education, and Clinical Center (GRECC) at the Minneapolis Veterans Affairs Medical Center (MVAMC) • All subjects gave informed consent approved by the Institutional Review Board (IRB) of both the VAMC and the University of Minnesota	• NR
Prestia 2013	FDG-PET	• MCI patients with prodromal AD (pAD) taken from ADNI and TOMC databases, with available baseline structural MRI, FDG-PET, and CSF sampling • Patients come from two independent data sets: the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Translational Outpatient Memory Clinic (TOMC) • Control patients were stable MCI patients from the same databases	• MCI patients who converted to non-AD dementia
Silverman 2001	FDG-PET	• Patients presenting with symptoms of dementia • Two groups of patients were included 1) those studied with PET followed longitudinally for at least 2	• NR

Study	Imaging Modality	Inclusion	Exclusion
		years and 2) those studied with PET whose disease • All patients prospectively enrolled at UCLA provided written informed consent and were studied in accordance with a protocol approved by the UCLA institutional review board	
Silverman 2003	FDG-PET	• Patients referred for cognitive and/or behavioral complaints between 1991 and 1999 to a university Nuclear Medicine clinic for brain PET	• NR
Tripathi 2013	FDG-PET	• All patients had a detailed neurological, neuropsychological, and magnetic resonance imaging (MRI) evaluation prior to referral • Control group: age, gender, and education matched subjects with no history of any neurological or psychiatric illness were included • Informed consent was taken from each subject included and the need for a follow-up visit to the clinic at the end of 24 months was explained to each patient included in the study • Ethical permission was obtained from the Institutional Review Board	• NR
Devanand 2010	SPECT	• age 41-85 years, cognitive impairment lasting ≥ 6 months and ≤ 10 years, and Folstein MMSE score ≥ 22/30 • Neuropsychological screening inclusion guidelines were Folstein MMSE recall ≤ 2/3 objects at 5 minutes, or Selective Reminding Test (SRT) delayed recall score > 1 SD below norms, or Wechsler Adult Intelligence Scale-Revised (WAIS-R) performance IQ score ≥ 10 points below WAIS-R verbal IQ score • Patients without these deficits were eligible if they met three criteria: subjective complaint of memory decline, informant's confirmation of memory decline, and modified Blessed Functional Activity Scale score ≥ 1 on the first 8 memoryrelated cognitive and functional items	• a diagnosis of dementia, schizophrenia, current major affective disorder, alcohol/substance dependence, history of stroke, cortical stroke or infarct ≥ 2 cm in diameter based on MRI, cognitive impairment entirely caused by medications • other major neurological illness, e.g., Parkinson's disease • Low dose hypnotics, antidepressants, cholinesterase inhibitors and memantine (latter two prescribed in < 10% of patients) were permitted, with stable dosage required for 30 days pre-SPECT scan

Study	Imaging Modality	Inclusion	Exclusion
		• For all subjects who met the above criteria, final determination for inclusion was based on a consensus diagnosis between two expert raters who reviewed clinical, functional and neuropsychological information, laboratory test results, and MRI radiological reads • Control subjects: normative MMSE and SRT test scores, met all other inclusion/exclusion criteria, signed informed consent, and were group-matched to patients on age and sex • All subjects signed informed consent in this IRB-approved protocol	
Ito 2013	SPECT	• subjects with amnestic MCI were recruited between January 2004 and June 2005 • all subjects were living independently in the community at the time of their baseline evaluation • Patients were diagnosed as having amnestic MCI according to the following criteria: • (1) a subjective and/or objective memory complaint screened through the Everyday Memory Check List (EMCL) questionnaire on forgetfulness in daily activities or in recent events • (2) an objective memory impairment documented by B13 (approximately 1.5 standard deviations (SD) below normal in Japanese subjects) on the Wechsler Memory Scale–Revised Logical Memory immediate–recall (WMSR-LM) score • (3) preservation of general cognitive functioning documented by a mini-mental state examination (MMSE) score between 24 and 30 • (4) preservation of instrumental activities of daily living • (5) National Institute of Neurological and Communication Disorders and Stroke/ Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for probable AD not met • (6) a global score on the Clinical	• patients with history of major psychiatric or neurological disease • those with neurological signs including hemiparesis, extrapyramidal signs, bulbar palsy, ataxia, oculomotor palsy, aphasia, apraxia, agnosia, unilateral spatial neglect, and seizures • those with psychiatric symptoms including depression, hallucinations, and delusions • Patients with small subcortical ischemic lesions that were clinically and historically silent and patients with insignificant white matter changes on MRI or CT were *not excluded*

Study	Imaging Modality	Inclusion	Exclusion
		Dementia Rating (CDR) of 0.5, memory box score of 0.5, and either 0 or 0.5 on all other box scores • Each subject signed an informed consent form after the nature of the procedures had been fully explained	
Petrella 2007	fMRI	MCI (amnestic type) subjects met the following criteria: • Recent history of symptomatic worsening in memory • A Rosen-modified Hachinski score of ≤ 4 • Impaired delayed recall memory performance • MMSE score of 22-30 • CDR global score of 0.5, with a memory score of ≥ 0.5 • Did not meet NINDS or DSM-IV criteria for dementia • Normal or near normal independent function • Absence of other factors that might have better explained memory loss, for example, current major depression	• Uncontrolled depression or other significant psychiatric or neurological illness such as recent stroke • Taking psychoactive medications known to substantially affect memory • Standard contraindications to MRI • Technical difficulties that prevented the completion of successful anatomical imaging or at least 2 or 3 functional fMRI runs, or both • Excessive motion during the functional MRI exam in excess of 5mm in any of three orthogonal directions, determined by center of mass plots • Inability to adequately monitor subject behavioral responses while in the scanner, evidenced by greater than 50% non-responses

NR: not reported

APPENDIX G. Evidence Tables for Included Studies

Context Question: Reliability

Study	Study Type	Imaging Modality/Tracer	Clinical Diagnosis* (n)	Severity of disease	Method for Interpreting Test
Foster 2007	Inter-rater (n = 6) (6 neurologists, a mix of expert and novice at rating FDG-PET scans)	FDG-PET	• AD (n = 31) • FTD (n = 14)	<u>AD patients:</u> Symptom duration: 4.0 ± 2.6 (range, 1-15) yrs MMSE: 14.0 ± 8.7 (range, 0-27) <u>FTD patients:</u> Symptom duration: 3.9 ± 3.3 (range, 1-10) yrs MMSE: 15.5 ± 9.5 (range, 0-24)	Transaxial images of glucose metabolism relative to pons were assessed, as were SSP metabolic and statistical maps. (1) Overall scan was graded as normal, uncertain abnormal, somewhat abnormal, or very abnormal. (2) Decide whether metabolism was normal or abnormal in specific regions. (3) Decide whether the hypometabolism was symmetrical or asymmetrical for the left vs. right cerebral hemispheres. (4) Make a diagnosis of AD or FTD: • 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	Inter-rater (n = 6) (6 expert raters)	FDG-PET	• See Foster 2007	See Foster 2007	See Foster 2007
Hoffman 1996	Inter-rater (n = 3) Intra-rater	FDG-PET	• Probable AD (n = 18) • Possible AD (n = 33) • Dementia (n = 26) • MMI (n =17) Other (n = 16) • Pick's disease (n = 2) • Huntington's disease (n = 1) JCD (n = 1) • Subcortical	Duration of symptoms: NR MMSE: Probable AD: 20.4 ± 5.9 Possible AD: 12.3 ± 4.9 Dementia: 19.6 ± 6.3 MMI: 25.5 ± 3.2	Scans obtained with images oriented parallel to the orbitomeatal line; images reconstructed using calculated or geometric attenuationation. Raters blinded to clinical information evaluated the degree of bilateral temporoparietal hypometabolism on a scale of 0-4 (0: normal, 1: equivocal, 2: present, 3: profound, or 4: abnormal but not AD). • The study considered bilateral temporoparietal hypometabolism to be the typical AD pattern and thus reported the intra- and inter-observer agreement for the AD pattern.

Study	Study Type	Imaging Modality/Tracer	Clinical Diagnosis* (n)	Severity of disease	Method for Interpreting Test
			dementia (n = 2) • Vascular dementia (n = 3) • Tumor (n = 1) • Encephalitis (n = 1) • Toxic encelphalopathy (n = 2) • Anxiety disorder (n = 1) • Healthy controls (n = 2)		
Rabinovici 2011	Inter-rater (n = 2)	FDG-PET	• AD (n =62) • FTLD (n = 45) • Normal controls (n = 25) ‡	AD • MMSE = 22.3 ± 5.7 • CDR = 0.9 ± 0.5 • CDR SB = 4.9 ± 3.1 FTLD • MMSE = 22.0 ± 8.1 • CDR = 1.1 ± 0.8 CDR SB = 6.0 ± 4.3	Frames for each subject were summed and normalized to mean activity in the pons. Blinded raters assessed each PET scan as: • AD if hypometabolism was greatest in temporoparietal cortex • FTLD if hypometabolism was most severe in in frontal or anterior temporal cortex

Study	Study Type	Imaging Modality/Tracer	Clinical Diagnosis* (n)	Severity of disease	Method for Interpreting Test
Silverman 2001	Inter-rater (n = 2)	FDG-PET	• Dementia (n = 100)	Initial MMSE scores**: 29 – 30: 45% 20 – 25: 22% 10 – 19: 14% 0 – 9: 4.0%	Reconstructed images were displayed in axial and coronal orientations. Blinded physician rated scans as progressive (abnormal) according to the following criteria: 1) focal cortical hypometabolism in parietal, temporal, and/or frontal lobes, or 2) diffuse hypometabolism in associate cortex with relative sparing of sensorimotor cortex, or 3) pattern of cerebral metabolism pathognomonic for a known neurodegenerative disease associated with progressive cognitive decline, with neither 1 nor 2 accounted for by matched findings on CT or MRI indicative of cerebrovascular disease, in those instance (n = 125) in which structural imaging data had been obtained. Scans with no abnormal findings were rated as nonprogressive. • Scans were evaluated for presence or absence of AD by evaluation of progressive PET patterns consistent with presence of AD: focal cortical hypometabolism in parietal, temporal, and/or frontal lobes.
Yamane 2014	Inter-rater (n = 3)	FDG-PET	• Mild AD (n = 67) • MCI (n = 100)	AD • MMSE-Japanese = 20–26 • Clinical Dementia Rating-Japanese = 0.5–1.0 MCI • MMSE-Japanese = 24–30 • Clinical Dementia Rating- • Japanese = 0.5	Images processed with 3D-SSP to generate z score maps. Blinded raters were trained in FDG-PET evaluation according to methods in Silverman et al§ prior to experiment. FDG-PET uptake patterns were classified into 7 categories (FDG-7): progressive patterns P1, P1+, P2, and P3, and non-progressive patterns N1, N2, and N3. P1 represents characteristic AD pattern, and P1+ represents non-characteristic AD pattern. Additionally, the 7 FDG-7 categories were further categorized into binary FDG-2 categories, which indicated if the FDG-7 category was posterior-predominant hypometabolism (AD and AD-variant) patterns (P1, P1+) or not (N1, N2, N3, P2, and P3). Summary: **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) or **AD:** For FDG with 2 categories for diagnosis, AD in scans with posterior-predominat hypometabolism patterns

Study	Study Type	Imaging Modality/Tracer	Clinical Diagnosis* (n)	Severity of disease	Method for Interpreting Test
Koeppe 2005	Inter-rater (n = 3)	C-DTBZ PET	• FTD (n = 6) • AD (n = 8) • DLB (n = 8) • NC (n = 5)‡	AD • MMSE = 15 ± 7 (range, 2–27) • Disease duration = 5 ± 3 y (range, 8-29) DLB • MMSE= 17 ± 6 (range, 8–29) • Disease duration = 5 ± 3 y (range, 2–13) FTD • MMSE = 23 ± 5 (range, 15–29) • Disease duration = 4 ± 2 y (range, 2–8)	Transaxial images processed with a single transformation based on the patient's summed images was calculated and applied. "^{11}C-DTBZ scans were classified using a composite of transaxial K_1 and DV images at 10 brain levels. The primary criteria for classifying patients as FTD was the presence of primary K_1 deficits in frontal or temporal cortex, with frontal deficits being greater than posterior deficits. Each of three raters was asked to choose the single best diagnosis (AD, FTD, DLB, or normal) based on visual inspection. • **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
Doran 2005	Inter-rater (n = 5)	^{99m}Tc-HMPAO-SPECT	• Cognitively impaired, diagnosis uncertain (n = 57) • Note: young patient population (59 ± 11 years)	NR	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.

Study	Study Type	Imaging Modality/Tracer	Clinical Diagnosis* (n)	Severity of disease	Method for Interpreting Test
McNeill 2007	Inter-rater (n = 2)	^{99m}Tc-HMPAO-SPECT	• FTD (n = 25) • AD (n = 31) Note. Reliability outcomes evaluated for 16 scans selected randomly from the population	FTD MMSE: 20 ± 7 Duration: 4 ± 4 yrs AD MMSE: 16 ± 6 Duration: 4 ± 2 yrs	Images reconstructed and transaxial images produced. Blinded readers rated the scans 0 or 1 for normal or abnormal CBF, respectively. This rating was performed regionally for frontal, parietal, temporal and occipital regions on the left and right. Asymmetry was rated as either absent or present. Blood flow was assessed using a colored magenta heat scale. Areas were considered abnormal if they were below the halfway point of this scale on more than two sections. Finally, a diagnosis was made using a choice of FTD, AD or ''non-specific''. Although the study evaluated how hypoperfusion in each individual region (frontal, parietal, temporal and occipital) correlated with pathology of FTD vs. AD, no clear description of how a final diagnosis of FTD vs. AD via SPECT images was provided.
McKeith 2007	Inter-rater (n = 3)	^{123}I-FP-CIT SPECT	• 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)	Probable DLB MMSE (SD): 20.0 (4.5) CDR (SD): 1.4 (0.69) CAMCOG (SD): 60.6 (17.6) Possible DLB MMSE (SD): 20.9 (4.2) CDR (SD): 1.2 (0.62) CAMCOG-R (SD): 63.1 (15.9) Non-DLB Dementia MMSE (SD): 21.5 (4.4) CDR (SD): 1.2 (0.69) CAMCOG-R (SD): 65.4 (16.1) No diagnosis MMSE (SD): 23.0	Three blinded nuclear physicians with expertise in DAT imaging verified the projection data and assessed reconstructed images, then visually interpreted the SPECT scans in a random order, classifying the images and normal or abnormal. • Abnormal scans were looking for changes associated with DLB, and were classified based on 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.

Study	Study Type	Imaging Modality/Tracer	Clinical Diagnosis* (n)	Severity of disease	Method for Interpreting Test
				(2.6) CDR (SD): 1.3 (0.70) CAMCOG-R (SD): 68.2 (14.4)	
Walker 2007	Inter-rater (n = 3)	^{123}I-FP-CIT SPECT	DLB (n=13) AD (n=6) Corticobasal degeneration (n=1)	Pathological diagnosis of DLB (n=8): MMSE: 17 ± 5.6 CAMCOG: 60 ± 21 CDR: 1.4 ± 0.9 Pathological diagnosis of "non-DLB" (n=12): MMSE: 16.6 ± 8.8 CAMCOG: 41 ± 27 CDR: 1.7 ± 0.9	Blinded raters visually assessed scans randomly, and scored as follows: normal uptake in all regions (left and right caudate and left and right putamen) = 0; slight reduction in uptake in any of the four regions = 1; and significant reduction in uptake in any of the four regions = 2. Scans with scores of 0 or 1 were combined into a "normal" group and scans with a score of 2 were declared "abnormal". • Abnormal scans were looking for changes associated with DLB, and were classified based on significantly reduced uptake in any of the following regions: right caudate, left caudate, right putamen, left putamen

3D-SSP: fully automated stereotactic surface projection; 99mTc-HMPAO-SPECT; AD: Alzheimer's disease; CAMCOG-R: Cambridge Cognitive Examination – Revised Version; CDR: Clinical Dementia Rating; C-DTBZ DV: C-dihydrotetrabenazine distribution volume; C-DTBZ K1: C-dihydrotetrabenazine ligand influx rate; CDR: Clinical Dementia Rating; CDR SB: Clinical Dementia Rating Sum of Boxes; CI: Confidence Interval; CJD: Creutzfeldt-Jakob Disease; CO: Carbon monoxide; CVD: Cerebrovascular disease; FDG-PET: Fluorodeoxyglucose positron emission tomography; FTD: Frontotemporal dementia; FTDP-17T: Frontotemporal dementia with Parkinsonism-17FTLD: Frontotemporal lobular dementia; LBD: Lewy body disease; MCI: Mild cognitive impairment; MMI: Mild memory impairment; MMS: Mini mental score; MMSE: Mini mental score evaluation; NIA-Reagan: National Institute on Aging-Reagan: NR: Not reported; SPECT: Single photon emission computed tomography; SSP: stereotactic surface projection; Tc-ECD-SPECT: Technium ethylcysteine dimer single photon emission computed tomography; VaD: Vascular dementia

* Entry diagnosis based on standard clinical, neuropsychological, and structural imaging assessments

† Scans were interpreted either without any clinical information (blind viewing) or with pertinent clinical information (informed viewing)

‡ Normal controls consisted of less than 20% of the total patient population evaluated, so the study was included.

§ Silverman DH, Small GW, Chang CY, et al. Positron emission tomography in evaluation of dementia: regional brain metabolism and long-term outcome. *JAMA* 2001;286:2120 –27

** Reliability for only 100/284 patients

†† Severity of disease for only 146/284 patients.

Context Question: Diagnostic Accuracy

Study	Imaging Modality/ Tracer	Gold Standard	Interval Between Imaging & Gold Standard	Entry Diagnosis	Diagnosis	Severity Of Disease	Method For Interpreting Test
Hoffman 2000	FDG-PET	Autopsy (n = 19) Biopsy (n = 2) Autopsy and biopsy (n = 1)	24.9 ± 28.1 months	Dementia (N = 22) (diagnostically challenging using standard clinical criteria)	**Gold standard diagnosis:** • AD: 15 (68%) • AD + LBD: 1 (5%) • AD + PSP: 1 (5%) • LBD: 1 (5%) • Neuronal degeneration: 1 (5%) • Pre-amyloid: 1 (5%) • MLCD: 1 (5%) • PSP: 1 (5%) • CJD: 1 (5%) **Clinical diagnosis:** • Probable AD: 10 (45%) • Possible AD: 2 (9%) • Dementia: 5 (23%) • PD/LBD: 1 (5%) • Pick's (FTD): 1 (5%) • PSP: 1 (5%) • Toxic encelph.: 1 (5%) CFD: 1 (5%)	NR	Transaxial FDG-PET images assessed by nuclear medicine physician after filtering and reconstruction using standard techniques. • Metabolically distinctive AD pattern defined as: Classic bilateral temporo-parietal hypometabolism or abnormal with varying degree of bilateral temporo-parietal hypometabolism.

Study	Imaging Modality/ Tracer	Gold Standard	Interval Between Imaging & Gold Standard	Entry Diagnosis	Diagnosis	Severity Of Disease	Method For Interpreting Test
Silverman 2001	FDG-PET Scans performed 1984-1998	Autopsy	2.9 years (range, 0.1-9.5 years)	Dementia	Diagnosis of AD, "neurodegenerative disease other than AD", or "no neurodegenerative disease present". **Gold standard diagnosis:** • AD: 97 (70.3%) • Neurodegenerative disease (not AD): 23 (16.7%) • No neurodegenerative dementia: 18 (13.0%)	Dementia severity ratings available for 79/138 patients: • Questionable: 17/79 • Mild: 38/79 • Moderate: 13 • Severe: 11	Reconstructed images were displayed in axial and coronal orientations. Scan results classified by nuclear medicine physician blinded to all clinical and pathological information except age/sex. Scans reconstructed using an attenuation correction algorithm. Classified scans as being positive for AD, any other neurodegenerative dementia, or no neurodegenerative dementia (no abnormal findings or abnormal findings that did not meet definition of progressive)). • **Findings on "progressive AD" scans:** Focal cortical hypometabolism in parietal, temporal, and/or frontal lobes
Bonte (2011)	Tc-99m HMPAO SPECT	Autopsy	Mean 71 (1-181) months	Entry diagnosis: possible dementia Clinical diagnosis: NR	**Gold standard diagnosis** • AD (with or without Lewy bodies): 47 (64%) • Not AD: 26 (36%)	NR	SPECT data processed by SPM and displayed to show brain volumes within which regional cerebral blood flow was below the value derived from a group of normal patients of similar age. • Scans classified as AD based on 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).

Study	Imaging Modality/ Tracer	Gold Standard	Interval Between Imaging & Gold Standard	Entry Diagnosis	Diagnosis	Severity Of Disease	Method For Interpreting Test
Walker 2007	FP-CIT-SPECT	Autopsy	34 months (mean)	Entry diagnosis NR **Clinical diagnosis:** DLB: 13 (65%) AD: 6 (30%) CBD: 1 (5%)	**Gold standard diagnosis:** DLB: 4 (20%) DLB + AD: 3 (15%) DLB + VaD: 1 (5%) AD: 3 (15%) AD + VaD: 6 (30%) FTLD: 1 (5%) CBD: 1 (5%) Unspecified: 1 (5%)	Pathological diagnosis of DLB (n=8): MMSE: 17 ± 5.6 CAMCOG: 60 ± 21 CDR: 1.4 ± 0.9 Pathological diagnosis of “non-DLB” (n=12): MMSE: 16.6 ± 8.8 CAMCOG: 41 ± 27 CDR: 1.7 ± 0.9	Blinded raters visually assessed scans randomly, and scored as follows: normal uptake in all regions (left and right caudate and left and right putamen) = 0; slight reduction in uptake in any of the four regions = 1; and significant reduction in uptake in any of the four regions = 2. Scans with scores of 0 or 1 were combined into a “normal” group (i.e., no DLB)and scans with a score of 2 were declared “abnormal” (i.e., DLB). Semi-quantitative assessment of scans performed as well. Processed scans with a quantified decrease in ligand binding (more than 2 standard deviations less than mean of control patients) in the right and left posterior putamen were considered “abnormal” (i.e., DLB).

KQ1: Differential Diagnostic Accuracy: AD versus FTD

Study	Imaging	Gold Standard	Interval Between Imaging And Gold Standard	Clinical Diagnosis	Demographics	Method For Interpreting Image
McNeill 2007	HMPAO-SPECT	Autopsy	NR	• Initial diagnosis: NR • Clinical diagnosis: AD or FTD (n = NR) • Clinical diagnosis based on cognitive and behavioral history, clinical neurological exam, neuropsychological exam (including behavioral and cognitive testing).	**Gold standard diagnosis: AD** • N = 31 • Age: 61 ± 7 years • % male: 65% • MMSE: 16 ± 6* **Gold standard diagnosis: FTD** • N = 25 • Age: 58 ± 10 years • % male: 72% • MMSE: 20 ± 7*	SPECT • Baseline images evaluated nuclear medicine specialist; blinded to clinical scenarios autopsy results • Image processing: Manual processing • Reference standard: NR • Positive FDG-PET, AD: greater hypometabolism in the posterior cingulate cortex and posterior cingulate gyrus than in the anterior regions. • Blood flow was assessed using a colored magenta heat scale; areas were considered abnormal if they were below the halfway point of this scale on more than two sections. • 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. A diagnosis of AD, FTD, or "non-specific" was made.
Foster 2007	FDG-PET (Scan dates: 1984-	Autopsy	4.7 ± 2.3 years	• Initial diagnosis: dementia	**Gold standard diagnosis: AD**	FDG-PET • Baseline images

Study	Imaging	Gold Standard	Interval Between Imaging And Gold Standard	Clinical Diagnosis	Demographics	Method For Interpreting Image
	1998)			• Clinical diagnosis: AD (n = 44), Creutzfeldt-Jakob disease (n = 1) • Clinical diagnosis based on interpreting the clinical scenario with the Symptom Checklist Score • Note: FTD diagnostic criteria not published until 1995 (i.e., end of study).	• N = 31 • Age: 66 ± 11 years • % male: 65% • MMSE: 14.1 ± 8.7 • Symptom onset to clinical visit: 4.0 ± 2.6 years • Clinic visit to PET: 0.9 ± 1.1 years **Gold standard diagnosis: FTD** • N = 14 • Age: 66 ± 6 years • % male: 50% • MMSE: 15.5 ± 9.5 • Symptom onset to clinical visit: 3.9 ± 3.3 years • Clinic visit to PET: 1.0 ± 1.0 years	evaluated by 6 neurologists; blinded to clinical scenarios autopsy results • Image processing done manually for transaxial images (varied with scan date; all scans obtained from archived files); SSP • Reference standard: NR for transaxial images; Pons for metabolic map image; normal control for statistical map image • SSP: raters received 2 SSP images; (1) a metabolic map that showed values of glucose metabolism relative to the pons; (2) a statistical map showing pixel-by-pixel z-scores derived from comparing the scan to that of normal controls (only pixels with significant glucose hypometabolism compared to the control population are shown) • Patients classified as AD or FTD based on the region of interest with greater degree of hypometabolism: • Positive FDG-PET, AD: greater hypometabolism in the posterior cingulate

Study	Imaging	Gold Standard	Interval Between Imaging And Gold Standard	Clinical Diagnosis	Demographics	Method For Interpreting Image
						cortex and posterior cingulate gyrus than in the anterior regions. • Positive FDG-PET, FTD: greater hypometabolism in the frontal association cortex, anterior temporal cortex, and anterior cingulate gyrus than in the posterior regions
Gabel 2010	See Foster 2007	See Foster 2007	See Foster 2007	See Foster 2007	See Foster 2007	See Foster 2007
Rabinovici 2011	FDG-PET	Autopsy (n = 10) FTD mutation carrier (n = 1)	2.5 years (for gold standard of autopsy (n = 10))	• Initial diagnosis: NR • Clinical diagnosis: AD (n = 3) or FTD (n = 7) • Clinical diagnosis based on NINCDS-ADRDA (1984) (for AD) and FTD consensus diagnostic criteria (1998) and MRI scans	**Gold standard diagnosis: AD** • N = 3 • Age: 73.1 years • % male: 100% • MMSE: NR • Symptom onset to clinical visit: NR • Clinic visit to PET: NR **Gold standard diagnosis: FTD** • N = 7 • Age: 65.7 years • % male: 86% • MMSE: NR • Symptom onset to clinical visit: NR • Clinic visit to PET: NR	<u>FDG-PET</u> • Baseline images evaluated by 2 neurologists; blinded to clinical diagnosis, autopsy results • Image processing: SPM • Reference standard: pons • Patients classified as AD or FTD based on the region of interest with greater degree of hypometabolism (visual ratings) or the lower z-score (automated method): • Positive FDG-PET, AD: lateral and medial temporoparietal cortex. • Positive FDG-PET, FTD: 2 ROIs- the frontal cortex anterior to precentral gyrus; & the temporal

Study	Imaging	Gold Standard	Interval Between Imaging And Gold Standard	Clinical Diagnosis	Demographics	Method For Interpreting Image
						pole and amygdala

SSP: sterotactic surface projection
* $P < 0.05$

KQ1: Differential Diagnostic Accuracy: AD versus DLB

Study	Imaging	Gold Standard	Interval Between Imaging And Gold Standard	Clinical Diagnosis	Demographics	Method For Interpreting Image
Minoshima 2001	FDG-PET	Autopsy	Range of means for each diagnosis: 3.1-3.4 years	• Clinical diagnosis: • AD (n = 18) • PD with dementia (n = 3)	**Gold standard diagnosis: AD (pure)** • N = 10 • Age: 69 ± 6 years • % male: 90% • MMSE: 14 ± 6 • CDR: 1.7 ± 1.0 • Symptom onset to clinical visit: NR • Clinic visit to PET: NR **Gold standard diagnosis: AD with Lewy bodies** • N = 7 • Age: 72 ± 6 years • % male: 43% • MMSE: 11 ± 7 • CDR: 2.0 ± 1.0 • Symptom onset to clinical visit: NR • Clinic visit to PET: NR **Gold standard diagnosis: DLB (pure)** • N = 4 • Age: 71 ± 8 years • % male: 75% • MMSE: 18 ± 13 • CDR: 1.7 ± 1.2 • Symptom onset to clinical visit: NR • Clinic visit to PET: NR	FDG-PET • Images evaluated using automated methods • Image processing: 3D-SSP • Reference standard: pons • Z-scores calculated for calculated between AD and DLB at each pixel, and the z-score threshold was -2.4. • Patients classified as DLB based on hypometabolism in the occipital lobe

Study	Imaging	Gold Standard	Interval Between Imaging And Gold Standard	Clinical Diagnosis	Demographics	Method For Interpreting Image
Toledo 2013	FDG-PET	Autopsy	3.8 years (mean)‡	Entry diagnosis NR • Clinical diagnosis: AD or MCI	**Gold standard diagnosis:** • AD with DLB: 5 (45%) • AD without DLB: 6 (55%)	FDG-PET • Images evaluated using automated methods • Image processing: reconstructed using a standardized attenuation correction algorithm, and SPM processing was used for computations • Reference standard: whole brain • Voxel-wise 2-sample independent t-test in SPM-5 accounting for whole brain counts; threshold was t = 1.48. • Patients classified as DLB based on hypometabolism in the occipital lobe.

CDR: clinical dementia rating

Key Question 2: Ability of functional neuroimaging to predict progression and clinical outcomes: MCI to AD (or dementia) conversion

Study Design Funding/CoI	Baseline Characteristics (mean ± SD)	Decline Assessed (F/U)	Method For Interpreting Image	Clinical Outcomes/ Definition Of Clinical Decline	Outcomes (95% CI)
Dobert 2005 Longitudinal retrospective cohort Funding/ CoI: NR	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	MCI to: AD, VaD, or (1.3 ± 1 year, % f/u NR)	FDG-PET • Baseline images evaluated by 2 nuclear medicine physicians; blinded to other clinical baseline information • Image processing: iterative reconstruction algorithm • Images available: transaxial, sagittal, and coronal • Reference standard: NR • Positive FDG-PET, AD: bilaterally reduced tracer uptake in AD affected areas (parietal, parietotemporal, temporal cortex).	AD: • Diagnostic criteria used NINCDS-ADRDA • Diagnosis made by multiprofessional team resulting in consensus diagnosis • Diagnosis made blinded to PET/SPECT imaging results	Converted to AD: 5/12 (42%) Converted to VaD: 1/12 (8%) NOTE: The remaining data exclude the one patient who converted to VaD. FDG-PET: • FDG-PET positive: 5/11 • TP: 5 • FP: 1 • FN: 0 • TN: 5 • Accuracy (calculated): 91% • Sensitivity (calculated): 100% • Specificity (calculated): 83% • PPV (calculated): 83% • NPV (calculated): 100% • LR+ (calculated): 6.0 • LR- (calculated): 0.0 Subgroup analysis: NR

Study Design Funding/CoI	Baseline Characteristics (mean ± SD)	Decline Assessed (F/U)	Method For Interpreting Image	Clinical Outcomes/ Definition Of Clinical Decline	Outcomes (95% CI)
Drzezga 2005 Longitudinal prospective cohort Funding/ CoI: NR	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 (Ɛ4 positive): 57%	MCI to AD (16 mos.; 100% f/u)	FDG-PET • Baseline images evaluated; blinded to other clinical baseline information • Image processing: NEUROSTAT (automated) • Scans of MCI patients compared to a reference normal database of 22 age-matched healthy controls • Significant hypometabolism defined as z-score > 1.64 based on previous studies • 3D SSP (stereotactic surface projections) of the z-scores were generated to allow visualization of abnormalities. • Predefined set of 20 regions of interest (ROIs) was placed automatically onto the 3D SSP images, allowing visualization of hypometabolism in various regions of the brain. • Positive FDG-PET: suggestive of early AD • Positive FDG-PET: significant hypometabolism (z-score > 1.64) in surface ROIs covering the posterior cingulate cortex accompanied by cortical hypometabolism in at least unilateral temporoparietal	AD: • Diagnostic criteria used NINCDS-ADRDA • Diagnosis made by physician at research memory clinic • Diagnosis made after comprehensive work-up (interview with patient and informant; medical, psychiatric, and neurologic exams; neuropsychologic exams (details NR); physicians blinded to PET results and APOE genotype.	Converted to AD: 12/30 (40%) FDG-PET: • FDG-PET positive: 43% (13/30) • TP: 11 • FP: 2 • FN: 1 • TN: 16 • Accuracy: 90% • Sensitivity: 92% (95% CI, 62%, 99%) • Specificity: 89% (95% CI, 65%, 98%) • PPV: 85% • NPV: 94% • LR+ (calculated): 8.25 • LR- (calculated): 0.09 • ROC area under the curve: 0.90 Subgroup analysis: NR

Study Design Funding/CoI	Baseline Characteristics (mean ± SD)	Decline Assessed (F/U)	Method For Interpreting Image	Clinical Outcomes/ Definition Of Clinical Decline	Outcomes (95% CI)
			areas.		
Fellgiebel 2007 Longitudinal prospective cohort <u>Funding/ CoI:</u> NR	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	aMCI to dementia aMCI to progressive cognitive decline (mean 19 mos.; 94% (16/17) f/u)	<u>FDG-PET</u> • Baseline images evaluated by 2 raters blinded to all other test results • Image processing: software that generates 3D-SSP images • Scans of MCI patients compared to a reference normal database of 25 healthy controls of similar age • Positive FDG-PET: suggestive of early AD • Positive FDG-PET: significant decrease (z-score > 2 in more than 50 adjacent pixels) of cerebral glucose metabolism in at least one of the brain regions that have been	• Dementia: CDR ≥ 1 • Progressive cognitive decline: an MMSE score reduction of ≥ 2 points and a clinical judgment of cognitive deterioration • Diagnosis made by clinician at memory clinic • Physicians blinded to FDG-PET and CSF findings	• Progressive cognitive impairment: 50% (8/16) • Dementia: 25% (4/16) <u>FDG-PET:</u> • FDG-PET positive: 44% (7/16) • TP: 6 • FP: 1 • FN: 2 • TN: 7 • Accuracy: 81% • Sensitivity: 75% • Specificity: 88% • PPV (calculated): 86% • NPV (calculated): 78% • LR+ (calculated): 6.0 • LR- (calculated): 0.29 FDG-PET predictive of dementia: • TP: 4

Study Design Funding/CoI	Baseline Characteristics (mean ± SD)	Decline Assessed (F/U)	Method For Interpreting Image	Clinical Outcomes/ Definition Of Clinical Decline	Outcomes (95% CI)
			shown to be typically involved in early AD (parietal mesial or posterior cingulate and temporal region) • Cut-off value used in a referenced article		• FP: 3 • FN: 0 • TN: 9 • Accuracy: 81% • Sensitivity: 100% • Specificity: 75% • PPV (calculated): 57% • NPV (calculated): 100% • LR+ (calculated): 4.0 • LR- (calculated): 0.0 Kaplan-Meier survival analysis found that for PET+ vs. PET- scans in the probability of conversion from MCI to: • Was not significantly predictive regarding conversion to progressive cognitive impairment (p=0.20) • Significantly predictive regarding conversion to dementia (p=0.033) <u>Subgroup analysis</u>: NR
Hatashita 2013 Longitudinal retrospective cohort <u>Funding/ CoI:</u> authors state no support or funding of report	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	MCI to AD (mean 19.2 ± 7.1 mos.; % f/u NR)	<u>FDG-PET</u> • Baseline images evaluated; blinding of image interpretation NR • Image processing: NR • Scans normalized to cerebellar cortex as reference standard • Scans co-registered with	• Diagnostic criteria used: NINCDS-ADRDA for AD diagnosis • Diagnosis made by physician at memory clinic • No information provided regarding clinical diagnosis and blinding to	Conversion to AD: 44.1% (30/68) converted to AD • Rate of MCI progression to AD: 23.4% per year <u>FDG-PET:</u> • FDG positive: 84% (57/68) • TP: 28 • FP: 29

Study Design Funding/CoI	Baseline Characteristics (mean ± SD)	Decline Assessed (F/U)	Method For Interpreting Image	Clinical Outcomes/ Definition Of Clinical Decline	Outcomes (95% CI)
	ApoE genotype (Ɛ4/4, Ɛ3/4 positive): 41%		MRI images • ROIs manually drawn on the co-registered image for the following cortical regions: lateral temporal cortex, medial temporal cortex, frontal cortex, occipital cortex, parietal cortex, sensory motor cortex, anterior cingulate gyrus, posterior cingulate gyrus, precuneus cortex and cerebellar cortex • Positive PET: prodromal AD • Positive PET: Reduced glucose metabolism (defined as standardized uptake value ratio ≤ 0.99 normalized to the cerebellar cortex as reference) in whole cortical regions • The reason for selecting this SUVR cut-off value was not described; no references provided.	PET results.	• FN: 2 • TN: 9 • Accuracy (calculated): 54% • Sensitivity: 93% • Specificity: 24% • PPV: 49% • NPV: 82% • LR+ (calculated): 1.2 • LR- (calculated): 0.28 <u>Subgroup analysis</u>: NR
Kakimoto 2012 Longitudinal retrospective cohort <u>Funding/ CoI:</u> supported by the grants from several	N = 24 Diagnosis: aMCI Age: 69.2 ± 9.9 years Male: 37.5% Duration of symptoms: NR MMSE: 25.4 ADAS-Cog: NR	aMCI to AD (3 years, % f/u NR)	<u>FDG-PET</u> • Baseline images evaluated; automated interpretation done (blinding not applicable) • Normalized images to Talairach's standard brain images using 3D-SSP; the standard uptake value	• AD according to NINCDS-ADRDA & DSM-IV criteria • Blinding to PET results NR	• 42% (10/24) patients converted <u>FDG-PET:</u> • FDG-PET positive: 38% (9/24) • TP: 8 • FP: 1 • FN: 2 • TN:13

Study Design Funding/CoI	Baseline Characteristics (mean ± SD)	Decline Assessed (F/U)	Method For Interpreting Image	Clinical Outcomes/ Definition Of Clinical Decline	Outcomes (95% CI)
national and nongovernmental research foundations	Global CDR: NR ApoE genotype (Ɛ4 positive): NR		(SUV) of the whole brain of set of normal patients was used as a reference for normalization • Brodmann area demarcated on the brain surface projection atlas (MRI template, from 3D-SSP tools): 34 areas total; lateral views only • The mean SUV ratio (SUVR) of each pixel in the Brodmann areas was calculated (ratio of SUV of MCI patient to reference set of normal patients) • Hypometabolism cutoff was a mean z-score of each Brodmann area of -1.0 (which was determined in preliminary experiments) • Total z-score provides an overall score for hypometabolism in the cerebral cortex (vs. normal controls) was assessed • Classification of PET findings: A total Z-score ≤-1.9 was used to distinguish AD from non-AD patients; this cut-off value was derived based on the ROC and AUC for total z-scores for AD vs. normal patients.		• Accuracy: 88% • Sensitivity: 80% • Specificity: 93% • PPV (calculated): 89% • NPV (calculated): 87% • LR+ (calculated): 11.2 • LR- (calculated): 0.22 Subgroup analysis: NR

Study Design Funding/CoI	Baseline Characteristics (mean ± SD)	Decline Assessed (F/U)	Method For Interpreting Image	Clinical Outcomes/ Definition Of Clinical Decline	Outcomes (95% CI)
Landau 2010 Longitudinal retrospective cohort <u>Funding/ CoI:</u> Alzheimer's Disease Neuroimaging Initiative (ADNI) (NIH Grant); authors disclose various grant support as well as industry involvement	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 (Ɛ4 positive): 30% <u>NOTE.</u> All patient data obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI)	MCI to AD Also: cognitive decline (1.9 ± 0.4 years; % f/u NR)	<u>FDG-PET</u> • Baseline images evaluated; automated interpretation • ADNI PET data acquisition described on the ADNI site (link provided in study • Image processing: methods described, no software listed Normalized images of each PET scan to the standard PET template done using SPM5 with a voxel size of $2mm^3$ • PET volumes were intensity normalized to a single region made up of the cerebellar vermis and the pons • Total z-score provides an overall score for hypometabolism in the cerebral cortex (vs. normal controls) was assessed • Positive FDG-PET: The study determined the cutoff for classification of FDG-PET positive or negative (i.e., AD+ or AD-) using ROC analyses with AD and normal controls from the ADNI database. The cutoff value was selected by choosing the threshold that optimized both sensitivity and sensitivity,	• AD according to NINCDS-ADRDA criteria • Cognitive decline: ADAS-Cog, no threshold defined • Conversion established at individual recruitment sites, with central review • Clinical diagnosis was made in a manner blinded to PET	• 32.9% (28/85) converted to AD • 17.2% annual rate of conversion to AD <u>FDG-PET:</u> • FDG-PET positive: NR *Conversion to AD:* • TP: NR • FP: NR • FN: NR • TN:NR • Accuracy: NR • Sensitivity: NR • Specificity: NR • PPV: 41% • NPV: 79% • LR+ : NR • LR- : NR • Univariate analysis (Cox proportional hazard models): HR 2.94 (95% CI, 1.23,7.04) (p=0.02) *Cognitive decline:* Univariate analysis (mixed model): HR NR (p=0.003) <u>MRI:</u> • MRI positive: NR *Conversion to AD:* • TP: NR • FP: NR • FN: NR • TN:NR • Accuracy: NR • Sensitivity: NR

Study Design Funding/CoI	Baseline Characteristics (mean ± SD)	Decline Assessed (F/U)	Method For Interpreting Image	Clinical Outcomes/ Definition Of Clinical Decline	Outcomes (95% CI)
			and was set at 1.21. <u>MRI (hippocampal volume)</u> • Baseline images evaluated • Image analysis: Freesurfer software • Positive FDG-PET: AD pathology • Positive FDG-PET: The study determined the cutoff for classification of MRI positive or negative (i.e., AD+ or AD-) using ROC analyses with AD and normal controls from the ADNI database. The cutoff value was selected by choosing the threshold that optimized both sensitivity and specificity.		• Specificity: NR • PPV: 41% • NPV: 78% • LR+ : NR • LR- : NR • Univariate analysis (Cox proportional hazard models): HR 2.49 (95% CI, 1.02, 5.96) (p=0.04) *Cognitive decline:* Univariate analysis (mixed model): HR NR (p=0.03) <u>Subgroup analysis</u>: NR
Pardo 2010 Longitudinal retrospective cohort <u>Funding:</u> NR <u>CoI:</u> authors declare no CoI	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	MCI to: AD, FTD, or DLB (3 years, % f/u NR)	<u>FDG-PET</u> • Baseline images analyzed; both readers were blinded • Image processing: NEUROSTAT used to adjust scans to a whole-brain mean activity and to perform sterotactic normalization Positive FDG-PET: AD, DLB, or FTD pathology • PET scans were each compared voxel-wise to the normative dataset after age regression to generate	• AD: NR • FTD: NR • DLB: NR • Blinding to PET data NR • No information regarding who made the diagnosis	• 47% (9/19) converted to probable or possible AD • 10% (2/19) converted to LDB • 10% (2/19) converted to FTD <u>FDG-PET, visual reading of transverse sections (rater 1):</u> • FDG-PET positive for AD: 6 • FDG-PET positive for FTD: 1 • FDG-PET positive for DLB: 0 • TP: 3 • FP: 4 • FN: 9 • TN: 3

Study Design Funding/CoI	Baseline Characteristics (mean ± SD)	Decline Assessed (F/U)	Method For Interpreting Image	Clinical Outcomes/ Definition Of Clinical Decline	Outcomes (95% CI)
			difference images; images colored according to degree of hypometabolism (see below) • Hypometabolism ranged from t ≤ -2 (minimum hypometabolism, colored purple on image) to t ≤ -6 (maximum hypometabolism, displayed as white) • Two blinded readers interpreted scans; one had access to only the transverse images, the other used software (iiv) that allowed visualization of all perspectives (coronal, sagittal, and transverse) • Classification of PET findings: AD: hypometabolism in the medial parietal cortex and lateral parietal regions; FTD: hypometabolism in anterior/superior temporal cortex and mesial/lateral prefrontal cortex, especially with greater involvement in the left than in the right sides; DLB: occipital hypometabolism <u>NOTE:</u> The study also reported the ability of		• Accuracy (calculated): 32% • Sensitivity (calculated): 25% • Specificity (calculated): 43% • PPV (calculated): 43% • NPV (calculated): 25% • LR+ (calculated): 0.44 • LR- (calculated): 1.75 <u>FDG-PET, visual reading of all sections with iiv software (rater 2):</u> • FDG-PET positive for AD: 10 • FDG-PET positive for FTD: 4 • FDG-PET positive for DLB: 0 • TP: 4 • FP: 10 • FN: 5 • TN: 0 • Accuracy (calculated): 21% • Sensitivity (calculated): 44% • Specificity (calculated): 0% • PPV (calculated): 29% • NPV (calculated): 0% • LR+ (calculated): 0.44 • LR- (calculated): not calculable <u>Subgroup analysis</u>: NR

Study Design Funding/CoI	Baseline Characteristics (mean ± SD)	Decline Assessed (F/U)	Method For Interpreting Image	Clinical Outcomes/ Definition Of Clinical Decline	Outcomes (95% CI)
			automated analysis to predict conversion to AD, FTD, or DLB; however because this portion of the study determined a cut-off value using the same population, this portion of the study is not included in our report. For inclusion, a prediction model cannot be generated in the same population it is then tested in.		
Prestia 2013 Longitudinal retrospective cohort <u>Funding/ CoI:</u> Alzheimer's Disease Neuroimaging Initiative; ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering and receives funding through many other grants and companies of industry.	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	MCI to AD (mean 32 mos., range, 12-48 mos.; % f/u NR)	<u>FDG-PET</u> • Baseline images evaluated; blinding NR but because images interpreted solely on the basis of the cutoff scores, credit was given for blinding • Image analysis: 3 different automated or semi-automated methods used to assess cortical hypometabolism: ○ **PALZ score:** combines voxel-based parametric mapping with the diagnostic information on brain regions typically affected in AD; each FDG-PET scan is compared with a database of scans from normal elderly persons. For this, a voxel-wise t-	AD: • Diagnosis made after assessment of clinical criteria every 12 mos. • Diagnostic criteria used: NINCDS-ADRDA for AD • Statement made that clinical diagnoses were made without taking potential positive PET scans into account, and that although baseline PET info were available to the clinician, progression to AD was determined on the basis of clinical information	Converted to AD: 42/93 (45%) <u>FDG-PET, PALZ score:</u> • FDG-PET PALZ positive: NR • TP: NR • FP: NR • FN: NR • TN: NR • Accuracy: 61% • Sensitivity: 50% • Specificity: 69% • PPV (%): NR • NPV (%): NR • LR+: NR • LR-: NR <u>FDG-PET, HCI score:</u> • FDG-PET HCI positive: NR • TP: NR • FP: NR • FN: NR • TN: NR

Study Design Funding/CoI	Baseline Characteristics (mean ± SD)	Decline Assessed (F/U)	Method For Interpreting Image	Clinical Outcomes/ Definition Of Clinical Decline	Outcomes (95% CI)
COI NR.			test is use (which includes age as a confounding variable), and the PALZ score is computed as the voxel-by-voxel sum of t scores in a predefined AD pattern mask (not defined). ○ **HCI**: fully automated algorithms based on SPM; PET scan compared to a healthy control from a predefined normative database through a voxelwise *t* test, HCI is calculated as the inner product of the resulting *t* score map (converted to a z score map) and a predefined AD z score map (not defined) ○ **RoI average**: computed on spatially and intensity-normalized PET scans as average of the mean counts in 5 meta-ROI volumes, originally computed based on a meta-analysis of studies carrying out direct whole-brain contrasts of FDG-PET data and reporting z score or *t*-values in voxels to show		• Accuracy: 62% • Sensitivity: 67% • Specificity: 59% • PPV (%): NR • NPV (%): NR • LR+: NR • LR-: NR <u>FDG-PET, RoI score:</u> • FDG-PET meta-RoI positive: NR • TP: NR • FP: NR • FN: NR • TN: NR • Accuracy: 57% • Sensitivity: 50% • Specificity: 67% • PPV (%): NR • NPV (%): NR • LR+: NR • LR-: NR <u>MRI, hippocampal volume, automated:</u> • MRI positive: NR • TP: NR • FP: NR • FN: NR • TN: NR • Accuracy: 56% • Sensitivity: 47% • Specificity: 65% • PPV (%): NR • NPV (%): NR

Study Design Funding/CoI	Baseline Characteristics (mean ± SD)	Decline Assessed (F/U)	Method For Interpreting Image	Clinical Outcomes/ Definition Of Clinical Decline	Outcomes (95% CI)
			significantly different FDG uptake between healthy and AD or MCI patients (regions not defined). (Note that pertinent age corrected scores (W scores) were computed based on previous literature to account for age) • Positive FDG-PET: AD pathology • Positive FDG-PET: 3 different definitions used: ○ PALZ score: t ≥ 13,481 ○ HcL ≥ 1055 ○ RoI average: w ≥ -2.60 • Thresholds were determined based on their performance in correctly identifying 148 normal elderly controls with 95% specificity. <u>MRI, hippocampal volume</u> • Baseline images evaluated • Image analysis: Freesurfer software (automated) • Positive MRI: AD pathology • Positive MRI: ○ Hippocampal volume: w ≥ -2.14 or -2.76 (-2.14 used in subset of patients from ADNI		• LR+: NR • LR-: NR <u>Subgroup analysis</u>: NR

Study Design Funding/CoI	Baseline Characteristics (mean ± SD)	Decline Assessed (F/U)	Method For Interpreting Image	Clinical Outcomes/ Definition Of Clinical Decline	Outcomes (95% CI)
			database; -2.76 used in subset of patients from TOMC memory clinic); • Thresholds were determined based on their performance in correctly identifying 66 normal elderly controls with 95% specificity.		
Silverman 2003 Longitudinal prospective cohort <u>Funding:</u> Los Angeles Alzheimer's Association/ Turken Family Fund; National Institutes of Health/National Institute on Aging Alzheimer's Disease Center Grants; Alzheimer's Disease Research Center of California Grant; and the Sidell-Kagan Foundation. <u>COI:</u> NR	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	MCI to progressive dementia (primarily AD) (3 (range, 2-10 years); % f/u NR)	FDG-PET • Baseline images evaluated; blinded to all clinical data except age, sex, and CT/MRI reports • Image processing: images reconstructed; no software mentioned • Axial and coronal views were available • PET scans were interpreted visually: results classified by nuclear medicine physician as indicative of a progressive or non-progressive clinical course based on the images • Positive scans had focal cortical hypometabolism in parietal, temporal, and/or frontal lobes, or diffuse cortical hypometabolism with sparing of sensorimotor ± visual cortex, with cortical deficits	Progressive cognitive impairment: • Memory, language or functional abilities progressively diminished at a pace faster than would be expected as a consequence of normal aging processes (unless there were changes clearly associated with CT/MRI-documented cerebrovascular disease). • 2 physicians independently assessed progression (blinded to PET scans), disagreements were evaluated with discussion and consensus	**<u>NOTE:</u>** Results presented for the subset of 128 patients with a working clinical diagnosis (i.e., non-progressive or progressive) before PET **<u>Outcome: clinical progression</u>** Patients with clinical progressive decline: 64.1% (82/128) <u>FDG-PET</u> • FDG-PET positive: 68.0% (87/128) • TP: 75 • FP: 12 • FN: 7 • TN: 34 • Accuracy (calculated): 85.2% • Sensitivity (calculated): 91.5% • Specificity (calculated): 73.9% • PPV (calculated): 86.2% • NPV (calculated): 82.9%

Study Design Funding/CoI	Baseline Characteristics (mean ± SD)	Decline Assessed (F/U)	Method For Interpreting Image	Clinical Outcomes/ Definition Of Clinical Decline	Outcomes (95% CI)
	diagnosis before PET: Diagnosis: • Non-progressive: 34% (44/128) • Indeterminate: 20% (26/128) • Progressive: 45% (58/128) Definitions: • Non-progressive: cognitive impairment thought to be secondary to potentially reversible or stable processes or when complaints were thought to represent normal changes. • Indeterminate: not defined • Progressive: cognitive impairment thought to be due to a neurodegenerative process such as AD, FTD, DLB, or a Parkinsonian syndrome.		unaccounted for by matched findings on CT or MRI indicating of cerebrovascular disease in those instances in which structural imaging had previously been obtained (n=85)		• LR+ (calculated): 3.51 • LR- (calculated): 0.12 <u>Clinical diagnosis (non-progressive versus progressive; subset of 102 patients)</u> Patients with clinical progression: 64.1% (64/102) • Clinical diagnosis of progressive dementia: 43.1% (44/102) • TP: 49 • FP: 9 • FN: 15 • TN: 29 • Accuracy (calculated): 76.5% • Sensitivity: 77% (95% CI, 66-87%) • Specificity: 76% (95% CI, 63-90%) • PPV (calculated): 84.5% • NPV (calculated): 65.9% • LR+ (calculated): 3.23 • LR- (calculated): 0.31 <u>FDG-PET for subset of 102 patients with working clinical diagnosis</u> Patients with clinical progression: 64.1% (64/102) • FDG-PET positive: 67.6% (69/102) • TP: 61 • FP: 8 • FN: 3 • TN: 30

Study Design Funding/CoI	Baseline Characteristics (mean ± SD)	Decline Assessed (F/U)	Method For Interpreting Image	Clinical Outcomes/ Definition Of Clinical Decline	Outcomes (95% CI)

					• Accuracy (calculated): 89.2%
					• Sensitivity: 95% (95% CI, 90-100%)
					• Specificity: 79% (95% CI, 66-92%)
					• PPV (calculated): 88.4%
					• NPV (calculated): 90.9%
					• LR+ (calculated): 4.53
					• LR- (calculated): 0.06
					
					Outcome: MMSE scores
					Results presented for 95 patients
					
					FDG-PET, mean MMSE score (estimated from graph)
					• 0 ± 0.5 years post-PET
					  ○ FDG-PET positive: ~22
					  ○ FDG-PET negative: ~26
					  ○ p ≥ 0.05
					• 1.5 ± 1.0 years post-PET
					  ○ FDG-PET positive: ~19.5
					  ○ FDG-PET negative: ~25
					  ○ p < 0.05
					• 3.5 ± 1.0 years post-PET
					  ○ FDG-PET positive: ~18
					  ○ FDG-PET negative: ~25.5
					  ○ p < 0.05
					
					Subgroup analysis: NR

Study Design Funding/CoI	Baseline Characteristics (mean ± SD)	Decline Assessed (F/U)	Method For Interpreting Image	Clinical Outcomes/ Definition Of Clinical Decline	Outcomes (95% CI)
Tripathi 2013 Longitudinal prospective cohort <u>Funding/ CoI:</u> funded by an intramural grand from INMAS; no CoI declared	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	aMCI to AD (24 mos., 100% f/u)	FDG-PET • Baseline images evaluated; blinded to clinical information • Image processing: images reconstructed using 3D VUE algorithm • Images interpreted visually (without additional analysis) and visually but after SPM-5 analysis • Visual interpretation: images were displayed scaled to a common maximum in standard color scale, with all images from each patient scaled to his/her own global maximal voxel value. Readers were to focus on the relative intensity between various cortical and subcortical regions rather than absolute values of any particular region • SPM-5 used for voxel-based analysis of images. Each patient was compared statistically to the reference group of 20 healthy control subjects with a 2-sample t-test. Proportional scaling to the global mean was used, which scales each image	• Probable or possible AD diagnosed using NINCDS/ADRDA criteria • Blinding to PET data NR	• Converted to AD: 11% (4/35) <u>FDG-PET:</u> • FDG-PET positive (high or intermediate likelihood of AD): 37% (13/35) • TP: 4 • FP: 7 • FN: 0 • TN: 24 • Accuracy (calculated): 80% • Sensitivity (calculated): 100% • Specificity (calculated): 77% • PPV (calculated): 36% • NPV (calculated): 100% • LR+ (calculated): 4.43 • LR- (calculated): 0.0 <u>Subgroup analysis</u>: NR

Study Design Funding/CoI	Baseline Characteristics (mean ± SD)	Decline Assessed (F/U)	Method For Interpreting Image	Clinical Outcomes/ Definition Of Clinical Decline	Outcomes (95% CI)
			according to a reference count, which is the global brain activity to a physiologically realistic value of 50ml/dl/min. The resulting matrix was used to define contrasts in order to provide a map of voxels showing increased or decreased glucose metabolism in each patient compared to the control group above the statistical threshold of P<0.05. These t-maps were overlaid onto the MRI template image in SPM-5; increased glucose metabolism displayed in "hot" colors and decreased glucose metabolism displayed in "winter" colors. • Final image interpretation: on visual AND SPM analysis, 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)		

Study Design Funding/CoI	Baseline Characteristics (mean ± SD)	Decline Assessed (F/U)	Method For Interpreting Image	Clinical Outcomes/ Definition Of Clinical Decline	Outcomes (95% CI)
Devanand 2010 Prospective cohort <u>Funding/CoI:</u> Funded by NIH grants. Authors report support from Novartis, GSK, and Sepracor, Amgen and Pfizer and consultantcy to GSK, Bristol Myers Squibb, and Sanofi-Aventis.	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 (Ɛ4 positive): 27.6%	MCI to AD (4.1 (range, 1-9) years). Note that converters had significantly shorter f/u than non-converters (1.9 vs. 4.8 years, respective-ly) (100% f/u)	SPECT: • SPECT scans were collected within 3 months of baseline; raters had information on patient age and sex as well as brief clinical history but were blinded to neuropsychological, MRI, and follow-up clinical data. • Image processing: images reconstructed using NeuroFocus software • Image analysis: visual ratings (see note at bottom of column) • Positive SPECT, visual analysis (2 raters): Consensus global ratings for AD were made (absent, questionable, possible, or probable) 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. <u>NOTE:</u> SPECT data was also analyzed using quantitative regions of interest analysis (ROI) but the only cutoff used	• AD: diagnosis of possible or probable AD based on NINCDS-ADRDA criteria on two consecutive annual visits by 2 raters who were blind to data from prior visits • Dementia diagnosis based on DSM-IV criteria	• Converted to AD: 24.4% (31/127) <u>SPECT, visual interpretation (consensus of 2 raters)</u>: • SPECT positive: 23.6% (30/127) • TP: 13 • FP: 17 • FN (calculated): 18 • TN (calculated): 79 • Accuracy (calculated): 72% • Sensitivity: 42% • Specificity: 82% • PPV: 43% • NPV: 81% • LR+ (calculated): 2.37 • LR- (calculated): 0.71 • Survival analysis: SPECT positive scans predicted time to conversion to AD; p=0.005) <u>Subgroup analysis</u>: NR

Study Design Funding/CoI	Baseline Characteristics (mean ± SD)	Decline Assessed (F/U)	Method For Interpreting Image	Clinical Outcomes/ Definition Of Clinical Decline	Outcomes (95% CI)
			was the median value in MCI patients; no basis or explanation for using this cutoff was provided, thus these results were not abstracted.		
Dobert 2005 Longitudinal retrospective cohort <u>Funding/ CoI:</u> NR	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	MCI to: AD, VaD, or FTD (1.3 ± 1 year, % f/u NR)	<u>HMPAO-SPECT</u> • Baseline images evaluated by 2 nuclear medicine physicians; blinded to other clinical baseline information • Image processing: filtered backprojection method using Butterworth filter as a preprocessing filter • Images available: transaxial, sagittal, and coronal • Reference standard: NR • Positive SPECT, AD: bilaterally reduced tracer uptake in AD affected areas (parietal, parietotemporal, temporal cortex). • Positive SPECT, FTD: frontal and/or Frontotemporal reduced tracer accumulation • Positive SPECT, VaD: focal regional tracer uptake reductions compared to the contralateral side	AD: • Diagnostic criteria used NINCDS-ADRDA • Diagnosis made by multiprofessional team resulting in consensus diagnosis • Diagnosis made blinded to PET/SPECT imaging results •	Converted to AD: 5/12 (42%) Remained stable (“no dementia”): 6/12 Converted to VaD: 1/12 (8%) <u>NOTE:</u> The remaining data exclude the one patient who converted to VaD. <u>HMPAO-SPECT:</u> • SPECT positive: 7/11 • TP: 2 (correct positive diagnosis, could include AD, VaD, or FTD, but both patients had AD or AD/VaD)2 • FP: 5 (includes diagnosis of AD, VaD, or FTD) • FN: 2 • TN: 2 • Accuracy (calculated): 36% • Sensitivity (calculated): 50% • Specificity (calculated): 29% • PPV (calculated): 29% • NPV (calculated): 50% • LR+ (calculated): 0.70 • LR- (calculated): 1.75

Study Design Funding/CoI	Baseline Characteristics (mean ± SD)	Decline Assessed (F/U)	Method For Interpreting Image	Clinical Outcomes/ Definition Of Clinical Decline	Outcomes (95% CI)
Ito 2013 Prospective cohort Funding: Japanese Foundation for Aging and Health CoI: NR	Patients included N = 316 Age: 73.6 ± 6.6 Male: 32.6% Duration of symptoms: NR MMSE: 26.4 (all ≥24) Diagnosis: amnestic MCI (aMCI) (100%) ApoE genotype (Ɛ4 positive): NR Patients with complete f/u who were included in the analysis N = 216 Age: 73.7 ± 6.3 Male: 31.9% Duration of symptoms: NR MMSE: 26.4 ± 1.8 (all ≥24) Diagnosis: amnestic MCI (100%) ApoE genotype (Ɛ4 positive): NR	aMCI to AD (36 mos., 68% f/u)	^{123}I-IMP-CBF SPECT • Baseline images evaluated; 4 raters blinded to clinical information • Image processing: images reconstructed using standard software supplied by scanner manufacturers • Image analysis: SSP used to generate z-score maps; Normalized images of each PET scan to a database of healthy subjects (no info on age of these patients); both visual analysis and automated ROI analysis were used • Positive SPECT: suggestive of early AD or DLB • Central image interpretation performed by four experts blinded to clinical information; used the 3D-SSP z-score map to classify the images into AD/DLB pattern or non-AD/DLB pattern; a final diagnosis was chosen. Disagreements among raters were discussed to form agreement. • Automated ROI analysis: 3D-SSP was used; for each image, a z-score was calculated for each pixel	AD: • Patient fulfilled NINCDS-ADRDA criteria for probable AD and • Clinical Dementia Rating global score became ≥ 1 • Blinding to PET data NR Note. For DLB diagnosis, the diagnostic criteria published by the Consortium on DLB criteria used (McKeith 1996)	NOTE. Results based on the patients with complete follow-up (denominators varied slightly, we reported here the data reported in the article). Converted to AD or DLB: 99/212 (46.7%) SPECT (visual interpretation, agreement among 4 raters): • SPECT positive (calculated): 67.9% (144/212) • TP: 75 • FP: 69 • FN: 24 • TN: 44 • Accuracy: 56% • Sensitivity: 76% • Specificity: 39% • PPV: 52% • NPV: 64% • LR+ (calculated): 1.24 • LR- (calculated): 0.62 SPECT (automated ROI analysis): • SPECT positive (calculated): 71.2% (151/212) • TP: 80 • FP: 71 • FN: 19 • TN: 42 • Accuracy: 58%

Study Design Funding/CoI	Baseline Characteristics (mean ± SD)	Decline Assessed (F/U)	Method For Interpreting Image	Clinical Outcomes/ Definition Of Clinical Decline	Outcomes (95% CI)
			and shown as a z-score map. The summed z-scores in each area of the predefined AD ROI map was calculated. Threshold values were set at a mean of +2 SD. A diagnosis of AD was made in any subject with at least 2 areas in the bilateral parietal association areas and posterior cingulate cortices, where the summed z-scores exceeded the thresholds as AD.		• Sensitivity: 81% • Specificity: 37% • PPV: 53% • NPV: 69% • LR+ (calculated): 1.29 • LR- (calculated): 0.52 <u>Subgroup analysis</u>: NR
Petrella 2007 Prospective cohort study <u>Funding/CoI:</u>	N = 33 Age at scan: 73.6 ± 8.5. Male: 45% MMSE at scan: 26.8 ± 1.7 Symptom duration (at scan): ≥ 1 yr.	MCI to dementia (2.5 yrs., 94% f/u)	During fMRI, patients exposed to 60 novel and 2 familiar face-name pairs presented in 3 runs, for 6 minutes (50 seconds per run). Scans recorded in coronal plan; images processed using SPM-2 software. The magnitude of blood-oxygen-level-dependent signal changes were assessed on a voxelwise basis. A contrast map created for each subject, depicting mean signal magnitude change between the novel and	Dementia: CDR ≥ 1.0; diagnosis confirmed by physician evaluations and neuropsychological tests	Converted to dementia: 11/33 (33.3%) <u>fMRI:</u> • fMRI positive ("activators": 11/33 (33%) • TP: 6 • FP: 6 • FN: 5 • TN: 16 • Accuracy (calculated): 67% • Sensitivity (calculated): 55% • Specificity (calculated): 73% • PPV (calculated): 50% • NPV (calculated): 76% • LR+ (calculated): 2.00 • LR- (calculated): 0.62

Study Design Funding/CoI	Baseline Characteristics (mean ± SD)	Decline Assessed (F/U)	Method For Interpreting Image	Clinical Outcomes/ Definition Of Clinical Decline	Outcomes (95% CI)
			familiar encoding conditions across the entire brain. "Activation" in the posteromedial cortex (PMC) (precuneus, posterior cingulate, and retrosplenial cortices): activation magnitude ≥ 0. This		

aMCI: amnestic mild cognitive impairment; AD: Alzheimer's disease; ADL: activities of daily living; CDR: clinical dementia rating; CI: confidence interval; CoI: conflict of interest; DVRT: Delayed Verbal Recall Test; FDG-PET: fluorodeoxyglucose positron emission tomography; FTD: frontotemporal dementia; F/U: follow up; HCI: hypometabolic convergence index; INMAS: Institute of Nuclear Medicine and Allied Sciences; LDB: Lewy body dementia; MCI: mild cognitive impairment; NPV: negative predictive value; NR: not reported; PALZ: PMOD Alzheimer's discrimination analysis tool; PPA: primary progressive apahasia; PPV: Positive Predictive Value; ROI: region of interest; SP: specificity; SS: sensitivity; SPM: Statistical Parametric Mapping; SUV/SUVR: standardized uptake value/ standardized uptake value ratio

Key Question 2: Ability of different types functional neuroimaging to predict progression and clinical outcomes

- **No studies met the inclusion criteria**

Key Question 3: Impact of functional neuroimaging on therapeutic decisions or clinical management compared to patients who did not receive functional neuroimaging

- **No studies met the inclusion criteria**

Key Question 4: Harms associated with functional neuroimaging

Study	Imaging Modality/ Tracer	Demographics	Clinical Diagnosis (N)	Safety Outcomes
Lowe 2009	FDG-PET	N = 56 Mean age: 76.9 years % male: NR	• Mild probable AD (n = 13) • Nonamnestic MCI (n = 6) • aMCI (n = 17) • Healthy control (n = 20)	0% (0/56) No patient-reported adverse events occurred that could be directly attributed to the PET scan, such as: • Pain, swelling, tenderness, or redness at injection site • New fever, rash, breathing difficulties, headache, diarrhea, or muscle pain
McKeith 2007	^{123}I-FT-CIT SPECT (DaTscan)	N = 326 Mean age: 74.3 years % male: 68.1	• 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)	2.8% (9/326) patients experienced adverse events attributed to the injection of the tracer (rather than a sensitivity to the tracer itself) (10 adverse events in 9 patients, patients could have more than one event), reported below as # of events/326 total patients • Nausea: 3 events /326 patients • Injection site hemorrhage: 2 events /326 patients • Injection site erythema: 2 events /326 patients • Dry mouth: 1 event /326 patients • Vomiting: 1 event /326 patients • Headache: 1 event /326 patients

AD: Alzheimer's disease; aMCI: amnestic mild cognitive impairment; DLB: dementia with lewy bodies; FTD: frontotemporal disease; NR: not reported; PET: positron emission tomography; SPECT: single photon emission computed tomography; SUV: standardized uptake values;

Key Question 5: Differential ability of functional neuroimaging to predict progression, clinical outcomes, or harms in subpopulations

- **No studies met the inclusion criteria**

Key Question 6: Cost-effectiveness of incorporating diagnostic functional neuroimaging into the comprehensive initial diagnostic work-up

Author (Year) Country	Population Diagnostic Tests	Study Characteristics	Outcomes

McMahon (2000) USA	**Population:** patients with mild or moderate dementia referred to AD clinic (N = NA; simulation study)
	Population source: literature review and Massachusetts General Hospital
	
	Diagnostic test comparisons:
	• Conventional clinical work-up with structural brain imaging
	• Conventional work-up plus visual SPECT (performed at a second visit)
	• Conventional work-up plus computed SPECT (performed at a second visit)
		CoI: Author reports relations to industry (deputy director of PEEMT at HSPH)
		Funding: NR
		Design: CUA
		Perspective: Societal
		Assumptions:
		▪ Patients who receive a diagnosis of probable AD receive treatment with donepezil or with a hypothetical higher-efficacy drug
		▪ Patient progresses to severe AD: no further drug treatment is given
		▪ Treatment with donepezil will not be discontinued unless the patient dies or progresses to severe AD (time NR)
		▪ Duration of drug treatment and effectiveness was 18 mos.
		▪ Ratio of mild to moderate AD, 1.5:1
		▪ 44% of patients would have no AD, remaining others would have mild or moderate AD
		▪ QoL weights for patients w/o AD (or with other dementia): 0.826 (scale 0 – 1), AD patients based on HUI 2 (depending on care setting): mild AD: 0.68-0.71; moderate AD: 0.48-0.54; severe AD: 0.31-0.37
		▪ Sensitivity/specificity
		  ▪ Conventional work-up: 0.75/0.9
		  ▪ Visual SPECT: 0.50-0.74/1.0
		  ▪ Computed SPECT: 0.90/0.87
		Model: Decision tree, Markov modeling
		▪ Three cohorts (n=32,000) were simulated for each diagnostic trial, results were averaged
		▪ Each 6-week cycle, patients were classified into disease states (no AD or other, mild AD, moderate AD, severe AD, or dead) and by health care settings (community or nursing home)
		▪ Transition probabilities derived from literature
		▪ Probability of death (NCHS) - Annual probability of death at 76 years (mean age of patients with AD at presentation to our institution)
		▪ Beneficial effects of donepezil treatment as a 50% reduction in the probability of transition from mild to moderate AD and a 2.36-fold increase in the probably of progression from moderate to mild AD
		Currency: 1998 US dollars
			BASE CASE:
			Mean costs ($ per patient)/QALY:
			Costs reflect the mean cumulative cost of diagnosis, treatment, and care.
			▪ Conventional: 54,762/0.9889
			▪ Visual SPECT: 55,362/0.9851
			▪ Computed SPECT: 55,549/0.9888
			
			ICER (compared with conventional clinical work-up):
			▪ Visual SPECT: Dominated (i.e., less cost-effective) (higher cost, lower QALYs)
			▪ Computed SPECT: Dominated (i.e., less cost-effective) (higher cost, lower QALYs)
			
			1-WAY SENSITIVITY ANALYSIS
			Variables
			▪ Computed SPECT Sensitivity: Lower for mild AD (0.88), higher for moderate AD (0.92)
			▪ Conventional: Lower sensitivity (0.50) and specificity (0.80)
			▪ Hypothetical perfect test with sensitivity and specificity of 1.0
			▪ Hypothetical drugs (same costs, treatment duration, and duration of effectiveness as donepezil)
			  ▪ Drug X (0.1 RR of mild to moderate AD transition, 10.0 RR of moderate to mild AD)
			  ▪ Drug Y (0.25 RR of mild to moderate AD transition, 5.0 RR of moderate to mild AD)
			▪ Duration of drug effectiveness: 6-48 mos.
			▪ Disease progression probabilities: lower probability of death in patients with no-AD (other dementia), ± 10% in annual transition (mild to moderate, etc.)

		Time horizon: 18 mos. **Cost source:** ▪ Massachusetts General Hospital (data for frequency of follow-up visits and accounting system) ▪ Literature sources ▪ Medicare reimbursement rates for imaging costs ▪ Costs of living from Consumer Expenditure Survey **Costs used for analysis ($USA):** ▪ Two physician consultations (internal medicine and neurology): 184 ▪ Lab tests: 70 ▪ Structural imaging exam: 212 ▪ Donepezil: 4.13 per day ▪ 2 follow-up visits per year: 96 per visit ▪ Visual/computed SPECT: 699/787 ▪ Travel expenses: 40 per day ▪ Cost of caretaker and time cost for patient: 102 per day, 50 per day, respectively ▪ Cost for caring for AD patient: cost of care plus annual cost of living for an average age-matched individual (value NR) **Discounting:** Costs and QALYs discounted 3% annually	▪ Prevalence at diagnosis: lower rate of no-AD (other dementia), different ratios of mild to moderate AD (2:1, 1:1, 1:1.5) ▪ Costs: No patient time costs, no caretaker costs, no travel costs, lower and higher estimated imaging costs (SPECT) ▪ QoL weights: ± 0.1 for each scenario, lower QoL weight for no-AD (other dementia) **ICER range from sensitivity analysis (compared with conventional clinical work-up):** Visual SPECT: dominated (i.e., less cost-effective) Computed SPECT: $180,200 - $1.9 million *ICER most sensitive to prevalence of disease (ratio of mild to moderate AD) and QoL weights*

McMahon (2003) USA	**Population:** patients with mild or moderate dementia referred to AD clinic (N = NA; simulation study)
	Population source: literature review and Massachusetts General Hospital
	
	Diagnostic test comparisons:
	• Conventional clinical work-
		CoI: NR
		Funding: May have been supported at least in part by grants from the National Cancer Institute, National Library of Medicine, U.S. Dept. of the Army.
		Design: CUA
		Perspective: Societal
		Assumptions:
		▪ Patients who receive a diagnosis of probable AD receive treatment with donepezil or with a hypothetical higher-efficacy drug
		▪ QoL weights for patients w/o AD (but other dementia): 0.80 (scale 0 - 1), AD patients based on HUI3 (depending on care setting): mild AD: 0.37-0.52; moderate AD: 0.18-0.21; severe AD: 0.00-0.02
		▪ Sensitivity/specificity:
		  ▪ Conventional work-up: 0.70-0.80/0.73
		  ▪ Computed SPECT: 0.90/0.87
		  ▪ FDG-PET: 0.94/0.72
		▪ Other details same as in McMahon et al. 2000
		Model: Decision tree, Markov modeling
		▪ Each scenario was simulated for each diagnostic trial (n=100,000), results were averaged
			<u>BASE CASE:</u>
			<u>Mean costs ± SD ($ per patient)/QALY ± SD:</u>
			▪ Conventional: 56,859 ± 18,569 / 0.7092 ± 0.4120
			▪ Computed SPECT: 58,872 ± 18,736 / 0.7093 ± 0.4137
			▪ FDG-PET: 58,590 ± 18,799 / 0.7063 ± 0.4127
			
			ICER (compared with conventional clinical work-up):
			▪ Computed SPECT: Dominated (i.e., less cost-effective) (higher cost, lower QALYs)
			▪ FDG-PET: Dominated (i.e., less cost-effective) (higher cost, lower QALYs)
			
			<u>1-WAY SENSITIVITY ANALYSIS</u>
			<u>Variables</u>
			▪ Lenient treatment rule: treat possible and probable AD (higher conventional work-up sensitivity (0.93) but lower specificity (0.48))
			▪ FDG PET: higher/lower specificity (0.45, 1.0)

	up with structural brain imaging • Conventional work-up plus computed SPECT (performed at a second visit) • Conventional work-up plus FDG-PET (performed at a second visit)	▪ Other details same as in McMahon et al. 2000 **Currency:** 1999 US dollars **Time horizon:** 18 mos. **Cost source:** ▪ Massachusetts General Hospital (data for frequency of follow-up visits and accounting system) ▪ Literature sources ▪ Medicare reimbursement rates for imaging costs ▪ Costs of living from Consumer Expenditure Survey **Costs used for analysis ($USA):** ▪ Two physician consultations (internal medicine and neurology): 181 ▪ Lab tests: 88 ▪ Structural imaging exam: 264 ▪ Donepezil: 4 per day ▪ 2 follow-up visits per year: 96 per visit ▪ Computed SPECT: 2,175 ▪ Transaxial PET: 1,671 ▪ Travel expenses: 40 per day ▪ Cost of caretaker and time cost for patient: 169 per day, 102 per day, respectively ▪ Cost of care plus annual cost of living for an average age-matched individual **Discounting:** Costs and QALYs discounted 3% annually	▪ FDG PET offered to all patients who received a diagnosis "AD unlikely or excluded" ▪ Hypothetical drugs (same costs and duration of effectiveness as donepezil) ▪ Drug X (0.1 RR of mild to moderate AD transition, 10.0 RR of moderate to mild AD) ▪ Drug Y (0.25 RR of mild to moderate AD transition, 5.0 RR of moderate to mild AD) ▪ Duration of drug effectiveness: 6 or 48 mos. ▪ QoL weights: matching HUI2 (McMahon 2000 base case), 0.05 QALY decrease in false-positive cases (no-AD or other dementia treated with drugs modeling negative side effects) ▪ "Treat all" strategy, confirming diagnosis and providing donepezil treatment (no imaging or lab tests) **ICER range from sensitivity analysis:** Computed SPECT: Dominated (i.e., less cost-effective) FDG-PET: $334,200 – dominated (i.e., less cost-effective) *ICER most sensitive to duration of drug effectiveness (6 mos. vs. 48 mos.)*
Moulin-Romsee (2005) Belgium	**Population:** probable AD (N = NA; simulation study) **Population source:** literature review **Diagnostic test comparisons:** • Conventional clinical work-up • Conventional work-up plus	**CoI:** NR **Funding:** NR **Design:** CEA **Perspective:** Societal (not explicitly stated) **F/U:** NR **Assumptions:** ▪ Prevalence of probable AD patients in population undergoing tests was estimated at 52%, based on literature values ▪ MRI assigned to all patients (routinely used to rule out structural abnormalities in clinical practice) ▪ Assumed that patients receive care only once the cognitive decline progresses. Three care settings evaluated: ▪ Home care with minimal costs (only professional care and material costs accounted for) ▪ Home care with all costs (includes professional costs and time	**<u>BASE CASE:</u>** **<u>Costs for evaluation & management (Euros per patient):</u>** **Retirement home:** ▪ Conventional: 1,942 ▪ FDG PET: 1,426 ▪ Δ Cost: 516 **Home care (minimal costs):** ▪ Conventional: 1,444 ▪ FDG PET: 1,239 ▪ Δ Cost: 205 **Home care (all costs):** ▪ Conventional: 6,893 ▪ FDG PET: 3,283 ▪ Δ Cost: 3,610

	FDG-PET	invested by family members to care for patient) ▪ Retirement home ▪ For patients who received a false-negative diagnosis, assumed a 9 month conservative delay in treatment ▪ Expected number of accurate diagnoses based on probabilities of AD outcomes, sensitivity and specificity from literature ▪ Sensitivities and specificities were determined from literature and take into consideration the accuracy of each compared with histopathology ▪ Sensitivity/specificity: ▪ Conventional clinical work-up: 0.84/0.525 ▪ FDG PET: 0.94/0.73 ▪ Accuracy of conventional work-up 68.7%; conventional plus FDG-PET 83.8% ▪ Study was adapted from Silverman et al. 2002 **Model:** Decision tree ▪ Direct treatment and diagnosis costs and indirect costs to society were summed ▪ Decision tree transition probabilities for conventional and FDG PET algorithms taken from literature ▪ Looked at 3 follow-up situations: placement in a retirement home, care-taking at home with minimal costs, and care-taking at home with all costs included ▪ Model was adapted from Silverman et al. 2002 **Currency:** Euros **Time horizon:** NR **Cost source:** ▪ Belgium Health Insurance Institution ▪ Hospital data (location NR) ▪ Local government reimbursement of FDG-PET imaging ▪ Higher Institute of Employment (Pacolet et al. 2001) **Costs used for analysis (Euros):** ▪ Initial/follow-up exams: 31.9 ▪ MRI: 155 (without contrast) or 255 (with contrast) ▪ Neuropsychological tests: 97 ▪ Lab tests: 81.2 ▪ FDG-PET: 507 ▪ Cholinesterase inhibitors (1 year) (unnecessarily prescribed to non-AD patients due to false-positive results): 1000 ▪ Cost of care for 1 year (implemented after cognitive decline): ▪ Home care with minimal cost: only professional care and material	**Costs per accurate diagnosis (Euros per patient)** **Retirement home:** ▪ Conventional: 2,825 ▪ FDG PET: 1,701 ▪ Δ Cost: 1,124 **Home care (minimal costs):** ▪ Conventional: 2,101 ▪ FDG PET: 1,478 ▪ Δ Cost: 623 **Home care (all costs):** ▪ Conventional: 10,026 ▪ FDG PET: 3,916 ▪ Δ Cost: 6,110 **1-WAY SENSITIVITY ANALYSIS** **Variables** ▪ Cost of FDG PET (0 – 6,000 Euros) ▪ Sensitivity of FDG PET (0.75-1.0) ▪ Specificity of FDG PET (0.2-0.9) ▪ Additional cost of care due to false-negative diagnosis (mos. delay in medical treatment: 1 week-12 mos.) ▪ Country of care (though not all data was available for each country) **Cost savings range from sensitivity analysis:** FDG PET remains cost-effective if: ▪ cost of the imaging < 1,000 Euros for the home care setting with minimal costs ▪ cost of the imaging < 1500 Euros for the retirement home setting ▪ cost of the imaging < ~5500 Euros for the home care setting with all costs included ▪ sensitivity of the test > 0.85 (all care settings) ▪ specificity of the test > 0.30 (for both home care); retirement home setting remains cost-effective < 0.20 In the case of a delay in treatment because of a

		costs accounted for: 14,550 ▪ Home care with all costs included: includes professional costs and time invested by family members to care for patient: 102,544 ▪ Retirement home: 22,585 ▪ Extra care needed for AD patient progressing past early stages but not being treated because of false-negative results (cost of care for 9 month delay in treatment) = 0.75 X cost for 1 year (see above) **Discounting:** NR	false-negative diagnosis, FDG PET remains cost effective if the delay in treatment is ≥ 1 month for the retirement home setting and home care setting with minimal costs included For the home care setting with all costs included, FDG PET remained cost-effective with any treatment delay (assessed effect of delay ranging from 0-12 mos.) *Cost savings (interpreted from graphical representation of the results) most sensitive to increase FDG PET sensitivity and price of FDG PET)*
Silverman (2002) USA	**Population:** early cognitive symptoms (non-AAN studies had to have patients ≥ 60 years, with MMSE ≥ 20 [mild dementia]) (N = NA; simulation study) **Population source:** literature review **Diagnostic test comparisons:** • Conventional clinical work-up based on 1994 guidelines by the AAN • Conventional work-up plus FDG PET	**CoI:** NR **Funding:** Department of Energy, Los Angeles Alzheimer's Association, Turken Family Foundation Award and the National Institutes of Health/National Institute on Aging **Design:** CEA **Perspective:** Payer (Medicare) **Assumptions:** ▪ Outcome probability variables were taken from the 1994 AAN guidelines or a study using AAN parameters for the decision model, if not available other literature values were used ▪ Structural imaging (MRI) ordered for 62.5% of patients in each arm ▪ Syphilis serology testing recommended as part of the routine blood laboratory panel ▪ Average sensitivity and specificity were taken from the AAN and literature values ▪ Prevalence of 51.6% in the studied symptomatic population ▪ Specialized tests were included in the cost diagrams for completeness but not in the calculation because they were rare in the literature and were likely of equal occurrence in the two groups ▪ Sensitivity and specificity of conventional work-up were assumed over a period of 6 mos. for total diagnostic evaluation time ▪ Sensitivity/specificity: ▪ Conventional work-up: 0.84/0.525 ▪ FDG PET: 0.94/0.73 ▪ Accuracy of conventional work-up 68.7%; FDG-PET 84.8% ▪ False positive rate for conventional work-up: 23.01%; false-negative rate: 8.25%; false positive rate for FDG PET: 12.04%; false-negative rate: 3.14%	**BASE CASE:** **Mean costs for evaluation & management (dollars per patient):** ▪ Conventional: 3,564 ▪ FDG PET: 3,433 ▪ Δ Cost: 131 less with FDG PET **Costs per accurate diagnosis (dollars per patient)** ▪ Conventional: 5,185 ▪ FDG PET: 4,047 ▪ Δ Cost: 1,138 less with FDG PET **SENSITIVITY ANALYSIS** **Variables** ▪ Cost of FDG PET ($1,500-1,800) ▪ Using a recent update (2001) of AAN guidelines (MRI without contrast obtained for 100% of all patients evaluated; syphilis serology testing ($11.40) not included in lab costs) ▪ Sensitivity of FDG PET (0.88-0.96) ▪ Specificity of FDG PET (0.67-0.97) ▪ Varying the estimated time delay to treatment for false-negatives, added costs of care (6 to 12 mos. delay) **Cost savings range from sensitivity analysis:** FDG PET remains cost-effective if the cost of imaging < $2,728.

		▪ For patients who received a false-negative diagnosis, assumed a 9 month conservative delay in treatment **Model:** Decision tree ▪ Probabilities were calculated using standard Bayesian analytic methods ▪ Frequency of structural neuroimaging was set at levels determined by the AAN guidelines, conventional and proposed (functional neuroimaging) were always equal for this branch ▪ Cost of each strategy was summed based on the probability of the branch and the cost values ▪ Cost savings determined by subtracting the cost per accurate diagnosis of the FDG PET algorithm from the conventional approach **Currency:** US dollars **Time horizon:** 6 mos. **Cost source:** ▪ 2001 Medicare reimbursement rates **Costs used for analysis ($USA):** ▪ History and physical exam: $149.47, plus follow-up $38.36 – $62.33 ▪ MRI: $608.12 - $1,294.17, neuropsychological test: $84.33 ▪ Lab tests: $3.73 - $44.25 ▪ 1 year supply of cholinesterase inhibitor unnecessarily prescribed (false-positive): $1,500 ▪ Extra care needed for AD patient who is untreated in the early stage (false-negative): $30,000 ▪ FDG PET: $1,661 (determined Medicare reimbursement rate with whole-body to brain rate for private insurance (factor of 0.70) **Discounting:** No	FDG remains cost-effective when using the 2001 AAN guidelines, cost savings per accurate diagnosis $1,256 (no syphilis serology tests), $1,325 (100% MRI) FDG PET remains cost-effective if the sensitivity > 0.80 FDG PET remains cost-effective if the specificity > 0.35 FDG PET provides a cost savings per accurate diagnosis of >$400 if delay is 6 mos., >$2000 if delay is 12 mos. *Cost savings most sensitive to extra care needed for patients who is not diagnosed (and treated) in a timely manner, due to delay in treatment for false-negatives*

AAN: American Academy of Neurology; AD: Alzheimer's disease; FDG-PET: ^{18}fluorodeoxyglucose positron emission tomography; HSPH: Harvard School of Public Health; HUI: Health Utilities Index; NCHS: National Center for Health Statistics; NR: not reported; PEEMT: Program on the Economic Evaluation of Medical Technology; QoL: quality of life; SPECT: single-photon emission computed tomography

APPENDIX H. Commonly used diagnostic criteria for dementias

Condition	Diagnostic Criteria
Dementia	National Institute of Aging-Alzheimer's Association workgroups diagnostic guidelines (2011){McKhann, 2011 #19649} ***Criteria for all-cause dementia (core clinical criteria)*** The diagnosis of dementia is intended to encompass the spectrum of severity, ranging from the mildest to the most severe stages of dementia. The methodology for staging of dementia severity was beyond the charge of the workgroup. Dementia is diagnosed when there are cognitive or behavioral (neuropsychiatric) symptoms that: 1. Interfere with the ability to function at work or at usual activities; and 2. Represent a decline from previous levels of functioning and performing; and 3. Are not explained by delirium or major psychiatric disorder; 4. Cognitive impairment is detected and diagnosed through a combination of (1) history-taking from the patient and a knowledgeable informant and (2) an objective cognitive assessment, either a "bedside" mental status examination or neuropsychological testing. Neuropsychological testing should be performed when the routine history and bedside mental status examination cannot provide a confident diagnosis. 5. The cognitive or behavioral impairment involves a minimum of two of the following domains: a. Impaired ability to acquire and remember new information—symptoms include: repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar route. b. Impaired reasoning and handling of complex tasks, poor judgment—symptoms include: poor understanding of safety risks, inability to manage finances, poor decision-making ability, inability to plan complex or sequential activities. c. Impaired visuospatial abilities—symptoms include: inability to recognize faces or common objects or to find objects in direct view despite good acuity, inability to operate simple implements, or orient clothing to the body. d. Impaired language functions (speaking, reading, writing)—symptoms include: difficulty thinking of common words while speaking, hesitations; speech, spelling, and writing errors. e. Changes in personality, behavior, or comportment—symptoms include: uncharacteristic mood fluctuations such as agitation, impaired motivation, initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive or obsessive behaviors, socially unacceptable behaviors.

Condition	Diagnostic Criteria
	The differentiation of dementia from MCI rests on the determination of whether or not there is significant interference in the ability to function at work or in usual daily activities. This is inherently a clinical judgment made by a skilled clinician on the basis of the individual circumstances of the patient and the description of daily affairs of the patient obtained from the patient and from a knowledgeable informant.
Alzheimer's disease	National Institute of Aging-Alzheimer's Association workgroups diagnostic guidelines (2011){McKhann, 2011 #19649} ***Core clinical criteria for probable and possible AD dementia*** We propose the following terminology for classifying individuals with dementia caused by AD: (1) Probable AD dementia, (2) Possible AD dementia, and (3) Probable or possible AD dementia with evidence of the AD pathophysiological proccess. The first two are intended for use in all clinical settings. The third is currently intended for research purposes. ***Probable AD dementia: Core clinical criteria*** Probable AD dementia is diagnosed when the patient: 1. Meets criteria for dementia described earlier in the text (See "Dementia" section), and in addition, has the following characteristics: A. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days; B. Clear-cut history of worsening of cognition by report or observation; and C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories. a. Amnestic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text. b. Nonamnestic presentations: • Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present. • Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present. • Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present. D. The diagnosis of probable AD dementia should not be applied when there is evidence of (a) substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or

Condition	Diagnostic Criteria
	(b) core features of Dementia with Lewy bodies other than dementia itself; or (c) prominent features of behavioral variant frontotemporal dementia; or (d) prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia; or (e) evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition. Note: All patients who met criteria for "probable AD" by the 1984 NINCDS–ADRDA criteria [1] would meet the current criteria for probable AD dementia mentioned in the present article. ***Probable AD dementia with increased level of certainty*** Probable AD dementia with documented decline: In persons who meet the core clinical criteria for probable AD dementia, documented cognitive decline increases the certainty that the condition represents an active, evolving pathologic process, but it does not specifically increase the certainty that the process is that of AD pathophysiology. Probable AD dementia with documented decline is defined as follows: evidence of progressive cognitive decline on subsequent evaluations based on information from informants and cognitive testing in the context of either formal neuropsychological evaluation or standardized mental status examinations. ***Probable AD dementia in a carrier of a causative AD genetic mutation*** In persons who meet the core clinical criteria for probable AD dementia, evidence of a causative genetic mutation (in APP, PSEN1, or PSEN2), increases the certainty that the condition is caused by AD pathology. The workgroup noted that carriage of the 34 allele of the apolipoprotein E gene was not sufficiently specific [20] to be considered in this category. ***Possible AD dementia: Core clinical criteria:*** A diagnosis of possible AD dementia should be made in either of the circumstances mentioned in the following paragraphs. <u>1. Atypical course</u> Atypical course meets the core clinical criteria in terms of the nature of the cognitive deficits for AD dementia, but either has a sudden onset of cognitive impairment or demonstrates insufficient historical detail or objective cognitive documentation of progressive decline, Or <u>2. Etiologically mixed presentation</u> Etiologically mixed presentation meets all core clinical criteria for AD dementia but has evidence of (a) concomitant cerebrovascular disease, defined by a history of stroke

Condition	Diagnostic Criteria
	temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) features of Dementia with Lewy bodies other than the dementia itself; or (c) evidence for another neurological disease or a non-neurological medical comorbidity or medication use that could have a substantial effect on cognition Note: A diagnosis of "possible AD" by the 1984 NINCDS-ADRDA criteria [1] would not necessarily meet the current criteria for possible AD dementia. Such a patient would need to be re-evaluated. _____ NINCDS-ADRDA criteria for the diagnosis of AD{Dubois, 2007 #11377} ***Diagnostic criteria for AD*** <u>Probable AD: A plus one or more supportive features B, C, D, or E</u> <u>Core diagnostic criteria:</u> A. Presence of an early and significant episodic memory impairment that includes the following features: 1. Gradual and progressive change in memory function reported by patients or informants over more than 6 months 2. Objective evidence of significantly impaired episodic memory on testing: this generally consists of recall deficit that does not improve significantly or does not normalise with cueing or recognition testing and after effective encoding of information has been previously controlled 3. The episodic memory impairment can be isolated or associated with other cognitive changes at the onset of AD or as AD advances <u>Supportive features:</u> B. Presence of medial temporal lobe atrophy • Volume loss of hippocampi, entorhinal cortex, amygdala evidenced on MRI with qualitative ratings using visual scoring (referenced to well characterised population with age norms) or quantitative volumetry of regions of interest (referenced to well characterised population with age norms) C. Abnormal cerebrospinal fluid biomarker • Low amyloid β1–42 concentrations, increased total tau concentrations, or increased phospho-tau concentrations, or combinations of the three • Other well validated markers to be discovered in the future D. Specific pattern on functional neuroimaging with PET • Reduced glucose metabolism in bilateral temporal parietal regions • Other well validated ligands, including those that foreseeably will emerge such as Pittsburg compound B or FDDNP E. Proven AD autosomal dominant mutation within the immediate family <u>Exclusion criteria:</u> History

Condition	Diagnostic Criteria
	• Sudden onset • Early occurrence of the following symptoms: gait disturbances, seizures, behavioural changes Clinical features • Focal neurological features including hemiparesis, sensory loss, visual field deficits • Early extrapyramidal signs Other medical disorders severe enough to account for memory and related symptoms • Non-AD dementia • Major depression • Cerebrovascular disease • Toxic and metabolic abnormalities, all of which may require specific investigations • MRI FLAIR or T2 signal abnormalities in the medial temporal lobe that are consistent with infectious or vascular insults <u>Criteria for definite AD</u> AD is considered definite if the following are present: • Both clinical and histopathological (brain biopsy or autopsy) evidence of the disease, as required by the NIA-Reagan criteria for the post-mortem diagnosis of AD; criteria must both be present • Both clinical and genetic evidence (mutation on chromosome 1, 14, or 21) of AD; criteria must both be present _____ DSM-V{American Psychiatric Association, 2013 #19650} ***Major or Mild Neurocognitive Disorder Due to Alzheimer's Disease*** *Diagnostic Criteria* A. The criteria are met for major or mild neurocognitive disorder. B. There is insidious onset and gradual progression of impairment in one or more cognitive domains (for major neurocognitive disorder, at least two domains must be impaired). C. Criteria are met for either probable or possible Alzheimer's disease as follows: *For major neurocognitive disorder:* Probable Alzheimer's disease is diagnosed if either of the following is present; otherwise, possible Alzheimer'sdisease should be diagnosed. 1. Evidence of a causative Alzheimer's disease genetic mutation from family history or genetic testing. 2. All three of the following are present: a. Clear evidence of decline in memory and learning and at least one other cognitive domain (based on detailed history or serial neuropsychological testing). b. Steadily progressive, gradual decline in cognition, without extended plateaus. c. No evidence of mixed etiology (i.e., absence of other neurodegenerative or

Condition	Diagnostic Criteria
	cerebrovascular disease, or another neurological, mental, or systemic disease or condition likely contributing to cognitive decline). ***For mild neurocognitive disorder:*** Probable Alzheimer's disease is diagnosed if there is evidence of a causative Alzheimer's disease genetic mutation from either genetic testing or family history. *Possible Alzheimer's disease* is diagnosed if there is no evidence of a causative Alzheimer's disease genetic mutation from either genetic testing or family history, and all three of the following are present: 1. Clear evidence of decline in memory and learning. 2. Steadily progressive, gradual decline in cognition, without extended plateaus. 3. No evidence of mixed etiology (i.e., absence of other neurodegenerative or cerebrovascular disease, or another neurological or systemic disease or condition likely contributing to cognitive decline). D. The disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance, or another mental, neurological, or systemic disorder. Diagnostic Features Beyond the neurocognitive disorder (NCD) syndrome (Criterion A), the core features of major or mild NCD due to Alzheimer's disease include an insidious onset and gradual progression of cognitive and behavioral symptoms (Criterion B) (Albert et al. 2011; McKhann et al. 2011). The typical presentation is amnestic (i.e., with impairment in memory and learning). Unusual nonamnestic presentations, particularly visuospatial and logopenic aphasic variants, also exist. At the mild NCD phase, Alzheimer's disease manifests typically with impairment in memory and learning, sometimes accompanied by deficits in executive function. At the major NCD phase, visuoconstructional/perceptual-motor ability and language will also be impaired, particularly when the NCD is moderate to severe. Social cognition tends to be preserved until late in the course of the disease. A level of diagnostic certainty must be specified denoting Alzheimer's disease as the "probable" or "possible" etiology (Criterion C). Probable Alzheimer's disease is diagnosed in both major and mild NCD if there is evidence of a causative Alzheimer's disease gene, either from genetic testing or from an autosomal dominant family history coupled with autopsy confirmation or a genetic test in an affected family member. For major NCD, a typical clinical picture, without extended plateaus or evidence of mixed etiology, can also be diagnosed as due to probable Alzheimer's disease. For mild NCD, given the lesser degree of certainty that the deficits will progress, these features are only sufficient for a possible Alzheimer's etiology. If the etiology appears mixed, mild NCD due to multiple etiologies should be diagnosed. In any case, for both mild and major NCD due to Alzheimer's disease, the clinical features must not suggest another primary etiology for the NCD (Criterion D). Associated Features Supporting Diagnosis

Condition	Diagnostic Criteria
	In specialty clinical settings, approximately 80% of individuals with major NCD due to Alzheimer's disease have behavioral and psychological manifestations; these features are also frequent at the mild NCD stage of impairment (Apostolova and Cummings 2008). These symptoms are as or more distressing than cognitive manifestations and are frequently the reason that health care is sought. At the mild NCD stage or the mildest level of major NCD, depression and/or apathy are often seen. With moderately severe major NCD, psychotic features, irritability, agitation, combativeness, and wandering are common. Late in the illness, gait disturbance, dysphagia, incontinence, myoclonus, and seizures are observed. <u>Diagnostic Markers</u> Cortical atrophy, amyloid-predominant neuritic plaques, and tau-predominant neurofibrillary tangles are hallmarks of the pathological diagnosis of Alzheimer's disease and may be confirmed via postmortem histopathological examination. For early onset cases with autosomal dominant inheritance, a mutation in one of the known causative Alzheimer's disease genes—amyloid precursor protein (APP), presenilin 1 (PSEN1), or presenilin 2 (PSEN2)—may be involved, and genetic testing for such mutations is commercially available, at least for PSEN1. Apolipoprotein E4 cannot serve as a diagnostic marker because it is only a risk factor and neither necessary nor sufficient for disease occurrence. Since amyloid beta-42 deposition in the brain occurs early in the pathophysiological cascade, amyloid-based diagnostic testssuch as amyloid imaging on brain positron emission tomography (PET) scans and reduced levels of amyloid beta-42 in the cerebrospinal fluid (CSF) may have diagnostic value. Signs of neuronal injury, such as hippocampal and temporoparietal cortical atrophy on a magnetic resonance image scan, temporoparietal hypometabolism on a fluorodeoxyglucose PET scan, and evidence for elevated total tau and phospho-tau levels in CSF (Jack et al. 2011), provide evidence of neuronal damage but are less specific for Alzheimer's disease. At present, these biomarkers are not fully validated, and many are available only in tertiary care settings. However, some of them, along with novel biomarkers, will likely move into wider clinical practice in the coming years.
Frontotemporal dementia	-Lund-Manchester Criteria{Brun, 1994 #19651} **Clinical diagnostic features of frontotemporal dementia** CORE DIAGNOSTIC FEATURES <u>Behavioural disorder</u> • Insidious onset and slow progression • Early loss of personal awareness (neglect of personal hygiene and grooming) • Early loss of social awareness (lack of social tact, misdemeanours such as shoplifting) • Early signs of disinhibition (such as unrestrained sexuality, violent behaviour, inappropriate jocularity, restless pacing) • Mental rigidity and inflexibility • Hyperorality (oral/dietary changes, overeating, food fads, excessive smoking and

Condition	Diagnostic Criteria
	alcohol consumption, oral exploration of objects) • Stereotyped and perservative behavior (wandering, mannerisms such as clapping, singing, dancing, ritualistic preoccupation such as hoarding, toileting, and dressing) • Utilisation behaviour (unrestrained exploration of objects in the environment) • Distractibility, impulsivity, and impersistence • Early loss of insight into the fact that the altered condition is due to a pathological change of own mental state. Affective symptoms • Depression, anxiety, excessive sentimentality, suicidal and fixed ideation, delusion (early and evanescent) • Hypochondriasis, bizarre somatic preoccupation (early and evanescent) • Emotional unconcern (emotional indifference and remoteness, lack of empathy and sympathy, apathy) • Amimia (inertia, aspontaneity). Speech disorder • Progressive reduction of speech (aspontaneity and economy of utterance) • Stereotypy of speech (repetition of limited repertoire of words, pharases, or themes) • Echolalia and perseveration • Late mutism. Spatial orientation and praxis preserved (intact abilities to negotiate the environment). Physical signs • Early primitive reflexes • Early incontinence • Late akinesia, rigidity, tremor • Low and labile blood pressure. Investigations • Normal EEG despite clinically evident dementia • Brain imaging (structural or functional, or both): predominant frontal or anterior temporal abnormality, or both • Neuropsychology (profound failure on "frontal lobe" tests in the absence of severe amnesia, aphasia, or perceptual spatial disorder). SUPPORTIVE DIAGNOSTIC FEATURES • Onset before 65 • Positive family history of similar disorder in a first degree relative • Bulbar palsy, muscular weakness and wasting, fasciculations (motor neuron disease). DIAGNOSTIC EXCLUSION FEATURES • Abrupt onset with ictal events • Head trauma related to onset • Early severe amnesia • Early spatial disorientation, lost in surroundings, defective localisation of object • Early severe apraxia • Logoclonic speech with rapid loss of train of thought

Condition	Diagnostic Criteria
	• Myoclonus • Cortical bulbar and spinal deficit • Cerebellar ataxia • Choreo-athetosis • Early, severe, pathological EEG • Brain imaging (predominant post-central structural or functional deficit. Multifocal cerebral lesions on CT or MRI) • Laboratory tests indicating brain involvement or inflammatory disorder (such as multiple sclerosis, syphilis, AIDS and herpes simplex encephalitis). RELATIVE DIAGNOSTIC EXCLUSION FEATURES • Typical history of chronic alcoholism • Sustained hypertension • History of vascular disease (such as angina,claudication). **Neuropathological diagnostic features ofronto-temporal dementia** FRONTAL LOBE DEGENERATION TYPE <u>Gross changes</u> These include slight symmetrical convolutional atrophy in frontal and anterior temporal lobes, neither circumscribed nor of a knife blade type; atrophy can be severe in a few cases. The ventricular system is widened frontally. Usually there is no gross atrophy of the striatum, amygdala or hippocampus although, in some instances, severe involvement of these regions can occur. <u>Distribution of microscopic changes</u> Changes are seen in the frontal convexity cortex, sometimes in the orbitofrontal cortex, often in the anterior third of the temporal cortex, and the anterior, but rarely the posterior, cingulate gyrus. The superior temporal gyrus is conspicuously spared. The parietal cortex is mildly involved in a few patients, more so in rare, advanced cases. In some patients with pronounced stereotypic behaviours, there is less neocortical involvement, with mostly striatal, amygdala, and hippocampal changes. These may represent a possible subtype. <u>Microscopic characteristics, grey matter</u> Microvacuolation and mild-to-moderate astrocytic gliosis affecting chiefly laminae I-III are seen, sometimes one or the other change prevailing. There is atrophy/loss of neurons in laminae II and III, whereas those of lamina V are mildly affected, being atrophic rather than lost. Occasionally there are a few dystrophic neurites. There are no Pick bodies, inflated neurons or Lewy bodies. Immunohistochemistry for tau or ubiquitin reveals no distinctive features. In the substantia nigra of some patients, there is mild-to-moderate loss of pigmented neurons. <u>Microscopic characteristics, white matter</u> White matter astrocytic gliosis, moderate to mild, is seen in subcortical u-fibres. There is very mild astrocytic gliosis in deeper white matter, sometimes with slight

Condition	Diagnostic Criteria
	attenuation and loss of myelin. The distribution is related to grey matter changes. Sometimes there is also ischaemic white matter attenuation. PICK-TYPE Gross changes These have the same topographic localization as frontal lobe degeneration, but generally more intense and usually more circumscribed. Asymmetry and striatal atrophy is common. Distribution of microscopic changes These are the same as frontal lobe degeneration, in agreement with the gross distribution. Microscopic characteristics, grey and white matter The main characteristics are the same as frontal lobe degeneration, but with intense involvement of all cortical layers. Inflated neurons and Pick bodies, which are silver positive, tau and ubiquitin immunoreactive, are present. There is more intense white matter involvement. Patients with intense astrocytosis but without inflated neurons or inclusions, or both, may for the present be included. MOTOR NEURON DISEASE TYPE Gross changes These are the same as frontal lobe degeneration, although usually less severe. Distribution of microscopic changes and microscopic characteristics in grey and white matter These are the same as for frontal lobe degeneration. There is spinal motor neuron degeneration, affecting cervical and thoracic levels more than lumbar or sacral. There is greater cell loss in medial than lateral cell columns. Motor neurons, layer II neurons in frontal and temporal cortex, and hippocampal dentate gyrus neurons show inclusions that are ubiquitin positive but not silver or tau reactive. Nigral cell loss is severe in many patients. There is also hypoglossal degeneration in some. DIAGNOSTIC EXCLUSION FEATURES There are senile plaques, diffuse amyloid deposits, and amyloid angiopathy with anti-ßprotein antibodies, tangles, and neuropil threads, with anti-tau and ubiquitin antibodies, more than normal for age. Prion protein are present with anti-prion antibodies. _____ DSM-V{American Psychiatric Association, 2013 #19650} **Major or Mild Frontotemporal Neurocognitive Disorder** Diagnostic Criteria

Condition	Diagnostic Criteria
	A. The criteria are met for major or mild neurocognitive disorder. B. The disturbance has insidious onset and gradual progression. C. Either (1) or (2): 1. Behavioral variant: a. Three or more of the following behavioral symptoms: i. Behavioral disinhibition. ii. Apathy or inertia. iii. Loss of sympathy or empathy. iv. Perseverative, stereotyped or compulsive/ritualistic behavior. v. Hyperorality and dietary changes. b. Prominent decline in social cognition and/or executive abilities. 2. Language variant: a. Prominent decline in language ability, in the form of speech production, word finding, object naming, grammar, or word comprehension. D. Relative sparing of learning and memory and perceptual-motor function. E. The disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance, or another mental, neurological, or systemic disorder. •Probable frontotemporal neurocognitive disorder is diagnosed if either of the following is present; otherwise, possible frontotemporal neurocognitive disorder should be diagnosed: 1. Evidence of a causative frontotemporal neurocognitive disorder genetic mutation, from either family history or genetic testing. 2. Evidence of disproportionate frontal and/or temporal lobe involvement from neuroimaging. Possible frontotemporal neurocognitive disorder is diagnosed if there is no evidence of a genetic mutation, and neuroimaging has not been performed. <u>Diagnostic Features</u> Major or mild frontotemporal neurocognitive disorder (NCD) comprises a number of syndromic variants characterized by the progressive development of behavioral and personality change and/or language impairment. The behavioral variant and three language variants (semantic, agrammatic/nonfluent, and logopenic) exhibit distinct patterns of brain atrophy and some distinctive neuropathology. The criteria must be met for either the behavioral or the language variant to make the diagnosis, but many individuals present with features of both. Individuals with behavioral-variant major or mild frontotemporal NCD present with varying degrees of apathy or disinhibition (Rascovsky et al. 2011). They may lose interest in socialization, self-care, and personal responsibilities, or display socially inappropriate behaviors. Insight is usually impaired, and this often delays medical consultation. The first referral is often to a psychiatrist. Individuals may develop changes in social style, and in religious and political beliefs, with

Condition	Diagnostic Criteria
	repetitive movements, hoarding, changes in eating behavior, and hyperorality (Rabinovici and Miller 2010). In later stages, loss of sphincter control may occur. Cognitive decline is less prominent, and formal testing may show relatively few deficits in the early stages. Common neurocognitive symptoms are lack of planning and organization, distractibility, and poor judgment. Deficits in executive function, such as poor performance on tests of mental flexibility, abstract reasoning, and response inhibition, are present, but learning and memory are relatively spared, and perceptual-motor abilities are almost always preserved in the early stages. Individuals with language-variant major or mild frontotemporal NCD present with primary progressive aphasia with gradual onset (Mesulam 1987), with three subtypes commonly described: semantic variant, agrammatic/nonfluent variant, and logopenic variant (Gorno-Tempini et al. 2011; Josephs 2008), and each variant has distinctive features and corresponding neuropathology. “Probable” is distinguished from “possible” frontotemporal NCD by the presence of causative genetic factors (e.g., mutations in the gene coding for microtubule-associated protein tau) or by the presence of distinctive atrophy or reduced activity in frontotemporal regions on structural or functional imaging. <u>Associated Features Supporting Diagnosis</u> Extrapyramidal features may be prominent in some cases, with an overlap with syndromes such as progressive supranuclear palsy and corticobasal degeneration. Features of motor neuron disease may be present in some cases (e.g., muscle atrophy, weakness). A subset of individuals develop visual hallucinations. <u>Diagnostic Markers</u> Computed tomography (CT) or structural magnetic resonance imaging (MRI) may show distinct patterns of atrophy. In behavioral-variant major or mild frontotemporal NCD, both frontal lobes (especially the medial frontal lobes) and the anterior temporal lobes are atrophic. In semantic language–variant major or mild frontotemporal NCD, the middle, inferior, and anterior temporal lobes are atrophic bilaterally but asymmetrically, with the left side usually being more affected. Nonfluent language–variant major or mild frontotemporal NCD is associated with predominantly left posterior frontal-insular atrophy. The logopenic variant of major or mild frontotemporal NCD is associated with predominantly left posterior perisylvian or parietal atrophy (Gorno-Tempini et al. 2011; Josephs 2008). Functional imaging demonstrates hypoperfusion and/or cortical hypometabolism in the corresponding brain regions, which may be present in the early stages in the absence of structural abnormality. Emerging biomarkers for Alzheimer’s disease (e.g., cerebrospinal fluid amyloid-beta and tau levels, and amyloid imaging) may help in the differential diagnosis, but the distinction from Alzheimer’s disease can remain difficult (the logopenic variant is in fact often a manifestation of Alzheimer’s disease). In familial cases of frontotemporal NCD, the identification of genetic mutations may help confirm the diagnosis. Mutations associated with frontotemporal NCD include the genes encoding microtubule-associated protein tau (MAPT) and granulin (GRN), C9ORF72, transactive response DNA-binding protein of 43 kDa (TDP-43, or

Condition	Diagnostic Criteria
	TARDBP), valosin-containing protein (VCP), chromatin modifying protein 2B (CHMP2B), and fused in sarcoma protein (FUS).
Dementia with Lewy bodies	-Consortium for DLB Diagnostic Criteria{McKeith, 2005 #11988} <u>Revised criteria for the clinical diagnosis of dementia with Lewy bodies (DLB)</u> 1. Central feature (essential for a diagnosis of possible or probable DLB): • Dementia defined as progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. • Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. • Deficits on tests of attention, executive function, and visuospatial ability may be especially prominent. 2. Core features (two core features are sufficient for a diagnosis of probable DLB, one for possible DLB) • Fluctuating cognition with pronounced variations in attention and alertness • Recurrent visual hallucinations that are typically well formed and detailed • Spontaneous features of parkinsonism 3. Suggestive features (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.) • REM sleep behavior disorder • Severe neuroleptic sensitivity • Low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging 4. Supportive features (commonly present but not proven to have diagnostic specificity) • Repeated falls and syncope • Transient, unexplained loss of consciousness • Severe autonomic dysfunction, e.g., orthostatic hypotension, urinary incontinence • Hallucinations in other modalities • Systematized delusions • Depression • Relative preservation of medial temporal lobe structures on CT/MRI scan • Generalized low uptake on SPECT/PET perfusion scan with reduced occipital activity • Abnormal (low uptake) MIBG myocardial scintigraphy • Prominent slow wave activity on EEG with temporal lobe transient sharp waves 5. A diagnosis of DLB is less likely • In the presence of cerebrovascular disease evident as focal neurologic signs or on brain imaging • In the presence of any other physical illness or brain disorder sufficient to account in part or in total for the clinical picture • If parkinsonism only appears for the first time at a stage of severe dementia

Condition	Diagnostic Criteria
	6. Temporal sequence of symptoms • DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism (if it is present). The term Parkinson disease dementia (PDD) should be used to describe dementia that occurs in the context of well-established Parkinson disease. In a practice setting the term that is most appropriate to the clinical situation should be used and generic terms such as LB disease are often helpful. In research studies in which distinction needs to be made between DLB and PDD, the existing 1-year rule between the onset of dementia and parkinsonism DLB continues to be recommended. Adoption of other time periods will simply confound data pooling or comparison between studies. In other research settings that may include clinicopathologic studies and clinical trials, both clinical phenotypes may be considered collectively under categories such as LB disease or alpha-synucleinopathy. _____ DSM-V{American Psychiatric Association, 2013 #19650} ***Major or Mild Neurocognitive Disorder With Lewy Bodies*** <u>Diagnostic Criteria</u> A. The criteria are met for major or mild neurocognitive disorder. B. The disorder has an insidious onset and gradual progression. C. The disorder meets a combination of core diagnostic features and suggestive diagnostic features for either probable orpossible neurocognitive disorder with Lewy bodies. For probable major or mild neurocognitive disorder with Lewy bodies: the individual has two core features, or one suggestive feature with one or more core features. For possible major or mild neurocognitive disorder with Lewy bodies, the individual has only one core feature, or one or more suggestive features. 1. Core diagnostic features: a. Fluctuating cognition with pronounced variations in attention and alertness. b. Recurrent visual hallucinations that are well formed and detailed. c. Spontaneous features of parkinsonism, with onset subsequent to the development of cognitive decline. 2. Suggestive diagnostic features: a. Meets criteria for rapid eye movement sleep behavior disorder. b. Severe neuroleptic sensitivity. D. The disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance, or another mental, neurological, or systemic disorder. <u>Diagnostic Features</u> Major or mild neurocognitive disorder with Lewy bodies (NCDLB), in the case of major neurocognitive disorder (NCD), corresponds to the condition known as dementia with Lewy bodies (DLB) (McKeith et al. 1996). The disorder includes not

Condition	Diagnostic Criteria
	only progressive cognitive impairment (with early changes in complex attention and executive function rather than learning and memory) but also recurrent complex visual hallucinations; and concurrent symptoms of rapid eye movement (REM) sleep behavior disorder (which can be a very early manifestation); as well as hallucinations in other sensory modalities, depression, and delusions. The symptoms fluctuate in a pattern that can resemble a delirium, but no adequate underlying cause can be found (McKeith et al. 1996; McKeith et al. 1999; McKeith et al. 2005). The variable presentation of NCDLB symptoms reduces the likelihood of all symptoms being observed in a brief clinic visit and necessitates a thorough assessment of caregiver observations. The use of assessment scales specifically designed to assess fluctuation may aid in diagnosis. Another core feature is spontaneous parkinsonism, which must begin after the onset of cognitive decline; by convention, major cognitive deficits are observed at least 1 year before the motor symptoms. The parkinsonism must also be distinguished from neuroleptic-induced extrapyramidal signs. Accurate diagnosis is essential to safe treatment planning, as up to 50% of individuals with NCDLB have severe sensitivity to neuroleptic drugs, and these medications should be used with extreme caution in managing the psychotic manifestations (McKeith et al. 1992). The diagnosis of mild NCDLB is appropriate for individuals who present with the core or suggestive features at a stage when cognitive or functional impairments are not of sufficient severity to fulfill criteria for major NCD. However, as for all mild NCDs, there will often be insufficient evidence to justify any single etiology, and use of the unspecified diagnosis is most appropriate. <u>Associated Features Supporting Diagnosis</u> Individuals with NCDLB frequently experience repeated falls and syncope and transient episodes of unexplained loss of consciousness. Autonomic dysfunction, such as orthostatic hypotension and urinary incontinence, may be observed. Auditory and other nonvisual hallucinations are common, as are systematized delusions, delusional misidentification, and depression (McKeith et al. 2005). <u>Diagnostic Markers</u> The underlying neurodegenerative disease is primarily a synucleinopathy due to alpha-synuclein misfolding and aggregation. Cognitive testing beyond the use of a brief screening instrument may be necessary to define deficits clearly. Assessment scales developed to measure fluctuation can be useful. The associated condition REM sleep behavior disorder may be diagnosed through a formal sleep study or identified by questioning the patient or informant about relevant symptoms. Neuroleptic sensitivity (challenge) is not recommended as a diagnostic marker but raises suspicion of NCDLB if it occurs. A diagnostically suggestive feature is low striatal dopamine transporter uptake on single photon emission computed tomography (SPECT) or positron emission tomography (PET) scan. Other clinically useful markers potentially include relative preservation of medial temporal structures on computed tomography (CT)/magnetic resonance imaging (MRI)

Condition	Diagnostic Criteria
	brain scan; reduced striatal dopamine transporter uptake on SPECT/PET scan; generalized low uptake on SPECT/PET perfusion scan with reduced occipital activity; abnormal (low uptake) MIBG myocardial scintigraphy suggesting sympathetic denervation; and prominent slow-wave activity on the electroencephalogram with temporal lobe transient waves (McKeith et al. 2000; McKeith et al. 2005). <u>Differential Diagnosis</u> *Major or mild neurocognitive disorder due to Parkinson's disease* A key differentiating feature in clinical diagnosis is the temporal sequence in which the parkinsonism and the NCD appear. For NCD due to Parkinson's disease, the individual must develop cognitive decline in the context of established Parkinson's disease; by convention, the decline should not reach the stage of major NCD until at least 1 year after Parkinson's is diagnosed. If less than a year has passed since the onset of motor symptoms, the diagnosis is NCDLB (Lippa et al. 2007; McKeith et al. 2004; McKeith et al. 2005). This distinction is clearer at the major NCD level than at the mild NCD level. The timing and sequence of parkinsonism and mild NCD may be more difficult to determine because the onset and clinical presentation can be ambiguous, and unspecified mild NCD should be diagnosed if the other core and suggestive features are absent.

APPENDIX I. FDA Approval

Manufacturer	Device/ Drug Name	NDC/NDA Number	Year of Approval	Indications for Use
GE Healthcare	DaT/ ^{123}I-FP/ DaTscan	NDC: 17156-210-01	2011	Indicated for striatal dopamine transporter visualization using SPECT brain imaging to assist in the evaluation of adult patients with suspected PS. In these patients, DaTscan may be used to help differentiate essential tremor from tremor due to PS (idiopathic Parkinson's disease, multiple system atrophy and progressive supranuclear palsy). DaTscan is an adjunct to other diagnostic evaluations.
GE Healthcare	^{99m}Technetium HMPAO/Ceretec	NDC: 17156-022-05 NDA: 19-829/S-026	2005	Indicated 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.
Citigroup Biomedical Imaging Center, Weill Medical College	18F-FDG	NDA: 21-768	2004	Indicated for assessment of abnormal glucose metabolism to assist in the evaluation of malignancy; for identification of left ventricular myocardium with residual glucose metabolism and residual loss of systolic function; and for identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.

DaT: dopamine transporter; FDG: Fludeoxyglucose; NDA: new drug application; NDC: national drug code; PS: Parkinsonian syndromes; SPECT: single photon emission computed tomography

APPENDIX J. Ongoing clinical trials

The following ongoing clinical trials were identified from a search of clinicaltrials.gov in October, 2014:

Functional Neuroimaging Modality	Condition (Estimated N)	Trial Name (Number)	Outcomes	Status (Estimated Completion)
FDG-PET vs. ASL MRI	MCI vs. normal adults (N = 120)	Arterial Spin Labeling (ASL) MRI for cognitive decline (NCT01727622)	Diagnostic accuracy, predict disease progression based on longitudinal change in hippocampal value.	Recruiting (5/2017)
FDG-PET	MCI (N = 710)	Metabolic Cerebral Imaging in Incipient Dementia (MCI-ID) (NCT00329706)	Predicting progression to AD, predicting cognitive and functional changes, utilization of healthcare resources, diagnosis before and after FDG-PET, rates of specific AD-specific therapies.	Ongoing (1/2016)
FDG-PET	AD, MCI, normal controls (N = 295)	Multi-modal neuroimaging in Alzheimer's Disease (IMAP+) (NCT01638949)	Identify predictive markers of AD. Outcomes of interest include: rate of decline as measured by cognitive tests, activities of daily living, and CDR sum of boxes, rate of change on FDG-PET, rate of change of glucose metabolism	Recruiting (12/2021)
FDG-PET	AD, DLB, FTD, VaD (N = 2500)	Imaging of Brain Amyloid Plaques in the Aging Population (NCT00950430)	Compare FDG-PET to PiB PET. Corrrelate longitundinal change in cognition in change in FDG measures.	Enrolling (4/2018)
FDG-PET	Primary progressive aphasia (N = 30)	Longitudinal Multi-Modality Imaging in Progressive Apraxia of Speech (NCT01818661)	Correlate longitudinal change in FDG-PET with change in clinical performance	Enrolling (3/2015)
DaTscan	MCI, DLB, AD, Parkinson's disease (N = 120)	DaTSCAN Imaging in Aging and Neurodegenerative Disease (NCT01453127)	Correlate findings with clinical diagnosis, safety of DaTscan	Enrolling patients (11/2015)

Functional Neuroimaging Modality	Condition (Estimated N)	Trial Name (Number)	Outcomes	Status (Estimated Completion)
DaTscan	AD, DLB, VaD (N = 214)	Co-LEsions in Alzheimer Disease and Related Disorders (CLEM) (NCT02052947)	Identify biomarkers (including DaTscan) that are most predictive of functional disability. Outcomes include: disability progression, neuropsychological inventory, Neuropsyciatric Inventory, clinical/serum markers, disability progression and cognitive decline	Not yet recruiting (10/2017)

APPENDIX K. Clinical Peer Reviewers

The following have agreed to provide clinical peer review:

Reviewer	Areas of Expertise	Peer review submitted?
Lisa Silbert, M.D., M.C.R. Oregon Health & Science University Portland, Oregon	Geriatric neurology; Aging and Alzheimer's Disease; Clinical neurophysiology	Yes
Deniz Erten Lyons, M.D. Assistant Professor of Neurology Layton Aging & Alzheimer's Disease Center Oregon Health & Science University Portland, Oregon	Geriatric neurology; Alzheimer's Disease	No (due to extenuating circumstances)
Tina Tailor, M.D. Department of Radiology University of Washington Seattle, Washington	Radiology	Yes

1. Chiou CF, Hay JW, Wallace JF, et al. Development and validation of a grading system for the quality of cost-effectiveness studies. Med Care 2003;41:32-44.

2. Ofman JJ, Sullivan SD, Neumann PJ, et al. Examining the value and quality of health economic analyses: implications of utilizing the QHES. J Manag Care Pharm 2003;9:53-61.