Methods and Review Process

A working group of the Brain Imaging Council of the Society of Nuclear Medicine, composed of five content experts, performed the review. One context expert was also a methods expert. A Medline search was performed using the main search items: Alzheimer, Autopsy, Diagnostic accuracy, Dementia, Emission computed tomography, FDG, and Prospective Study, since 2000 to reflect recent literature in this field. Eligibility of selected papers was based on the inclusion criteria as used by Patwardhan *et al.* (*1*).

a) Articles had to be written in English, include primary data, and be published in a peer-review journal.

b) Studies had to include at least 12 human subjects with the disease of interest.

c) For studies of PET operating characteristics, either clinical diagnosis (according to standard criteria of the NINCDS/ADRDA (*2*) or the Diagnostic and Statistical Manual (*3*)) or histopathologic diagnosis had to be used as the reference standard; and

d) Sufficient data had to be provided either directly or indirectly through a 2 × 2 table to be able to calculate diagnostic accuracy.

Two members of the working group reviewed each paper and final eligibility was based on a group consensus. Group consensus was also used to score eligible papers on a study quality rating scale defined also by Patwardhan *et al.* (*1*):

a) The scanner model or type and resolution of the scanner were mentioned.

b) The setting and selection of the population under investigation were clearly described.

c) The study had a representative sample of patients with an appropriate spectrum of disease.

d) The results were categorized by disease severity.

e) Standard criteria were used for image interpretation.

f) Histopathologic or clinical confirmation was performed by using standard criteria (*e.g*., NINCDS/ADRDA or Diagnostic and Statistical Manual criteria were used on the basis of long-term follow-up of 1 year or more).

g) Follow-up was completed (there was no verification bias).

h) The image reader and the person who assigned the reference standard diagnosis were blinded to clinical diagnosis.

For each of these criteria, a score of 0 or 1 was assigned. A score of 0 was assigned if the study did not adequately meet the criterion or if the data were inadequate to determine the criterion, and a score of 1 was assigned if the study met the criterion. The scores were added to give a final quality score for the study.

References:

1. Patwardhan MB, McCrory DC, Matchar DB, Samsa GP, Rutschmann OT. Alzheimer disease: operating characteristics of PET--a meta-analysis. *Radiology.* 2004;231:73-80.

2. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology.* 1984;34:939-944.

3. DSM-IV. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington DC: American Psychiatric Association; 1994.

Supplemental table 1:

Diagnostic accuracy studies of clinically diagnosed AD vs. normal control/non-AD dementia subjects of studies published since 2000 meeting review eligibility criteria

Reference; study type; diagnostic standard & quality score	**Subjects**	**TP**	**FN**	**FP**	**TN**	**Diagnosis sensitivity & specificity of AD diagnosis**
Reference: Chen et al., 2008 (*1*) **Study type:** Case-control **Diagnostic standard:** Clinical **Quality score: 4** Representative sample: 0 Setting/selection described: 1 Scanner described: 1 Standard interpretation: 1 Blinded reader: 0	Mild AD: n=52 (25M/27F); age 67(SD 9); Controls n=60 (30M/30F); age 66 (SD 8)	**47**	**5**	**9**	**51**	Sn=90%; Sp=85%.

Categorization by disease severity: 1 Follow-up complete: 0 Longitudinal clinical or post-mortem diagnosis: 0 AAN level: III						
Reference: Dobert et al., 2005 (*2*) **Study type:** Prospective cohort study **Diagnostic standard:** Longitudinal **Quality score: 7** Representative sample: 1 Setting/selection described: 1 Scanner described: 1 Standard interpretation: 1 Blinded reader: 1 Categorization by disease severity: 0 Follow-up complete: 1 Longitudinal clinical or post-mortem diagnosis: 1 AAN level: II	Mild dementia or mild cognitive impairment n=24 (11M/13F); age 69 (SD 6.8 yrs)	**4 (15)**	**5 (1)**	**3 (1)**	**12 (7)**	For pure AD diagnosis: Sn=44%; Sp=83%. For mixed AD and vascular dementia diagnosis: Sn=71%; Sp=78%. For diagnosis of AD and mixed vascular/AD dementia versus absence of dementia: Sn=91.7%; Sp=88.9% Numbers provided in brackets.
Reference: Foster et al., 2007 (*3*) **Study type:** Historical cohort **Diagnostic standard:** Post-mortem **Quality score: 7** Representative sample: 1	AD n=31 (20M/11F); age 65.6 (SD 11.1 yrs); FTD n=14 (7M/7F); age	**30**	**1**	**2**	**12**	For AD diagnosis compared to FTD: Sn=96.7%; Sp=85.7%. For FTD diagnosis compared to AD: Sn=86%; Sp=97.6%.

Setting/selection described: 1 Scanner described: 1 Standard interpretation: 1 Blinded reader: 1 Categorization by disease severity: 0 Follow-up complete: 1 Longitudinal clinical or post-mortem diagnosis: 1 AAN level: II	65.6 (SD 5.5).					Note: non-AD dementia control group.
Reference: Jagust et al., 2007 (*4*) **Study type:** Historical cohort **Diagnostic standard:** Post-mortem **Quality score: 8** Representative sample: 1 Setting/selection described: 1 Scanner described: 1 Standard interpretation: 1 Blinded reader: 1 Categorization by disease severity: 1 Follow-up complete: 1 Longitudinal clinical or post-mortem diagnosis: 1 AAN level: II	Wide spectrum 44 subjects (29M/15F); age 75 (SD 11); Post-mortem diagnosis include AD FTD, DLB, mixed, and vascular dementia. Total of 25 cases diagnosed as pure or mixed AD and 19 non-AD.	**21**	**4**	**5**	**14**	Overall group: Sn=84%; Sp=74%. Sub-set with MMSE scores > 23 (mild severity): Sn=82%; Sp=79%. Note: Non-AD controls include cases with non-AD dementia.
Reference: McMurtray et al., 2008 (*5*)	AD (young onset) n=27	**25**	**2**	**4**	**23**	Sn=92.6%; Sp=85.2%.

Study type: Case-control **Diagnostic standard:** Clinical **Quality score: 5** Representative sample: 1 Setting/selection described: 1 Scanner described: 1 Standard interpretation: 1 Blinded reader: 1 Categorization by disease severity: 0 Follow-up complete: 0 Longitudinal clinical or post-mortem diagnosis: 0 AAN level: III	(M22/F5); age 60.0 (SD 7.1) & elderly with subjective memory complaints (wide spectrum) n=27 (M22/F5); age 59.1 (SD 8.0).					Note: Controls were elderly with subjective memory complaints.
Reference: Minoshima et al., 2001 (*6*) **Study type:** Historical cohort **Diagnostic standard**: Post-mortem **Quality score: 6** Representative sample: 1 Setting/selection described: 1 Scanner described: 1 Standard interpretation: 0 Blinded reader: 1 Categorization by disease severity: 0 Follow-up complete: 1 Longitudinal clinical or post-mortem diagnosis: 1 AAN level: II	AD (wide spectrum) n=10 (9M/1F); age 69 (SD 6) & Lewy body variant AD n=7 (3M/4F); age 67 (SD 7) & diffuse Lewy body disease n=4 (3M/1F); age 70 (SD 6); Non-dementia controls n=10 (4M/6F); age 68 (SD 6).	**9**	**1**	**2**	**9**	Sn=90%; Sp=80%. Note: Non-AD dementia controls (DLB)

Reference: Mosconi et al., 2007 (*7*) **Study type:** Multi-center case-control **Diagnostic standard:** Clinical **Quality score: 5** Representative sample: 1 Setting/selection described: 0 Scanner described: 1 Standard interpretation: 1 Blinded reader: 1 Categorization by disease severity: 1 Follow-up complete: 0 Longitudinal clinical or post-mortem diagnosis: 0 AAN level: III	AD mild n=15 (7M/8F); age 69 (SD 8); AD mod-sev n=18 (6M/12F); age 65 (SD 7) & healthy controls n=19 (8M/11F); age 68 (SD 4).	**33**	**0**	**0**	**19**	Sn=100%; Sp=100%. Subset analysis mild severity age group: Sn=100%; Sp=100.
Reference: Mosconi et al., 2008 (*8*) **Study type:** Multi-center case-control **Diagnostic standard:** Clinic **Quality score: 4** Representative sample: 1 Setting/selection described: 1 Scanner described: 1 Standard interpretation: 0 Blinded reader: 1 Categorization by disease	AD n=199 (66M/133F); age 70 (SD 8); FTD n=98 (56M/46F); age 64 (SD 8); DLB n=27 (12M/15F); 66 (SD 8); MCI n=114 (46M/68F); age 68 (SD) &	**192**	**2**	**2**	**108**	AD vs normal controls: Sn=99%; Sp=98%. Also non-AD comparisons: AD vs DLB: Sn=99%; Sp=71%. AD vs FTD: Sn=99%; Sp=65%.

severity: 0 Follow-up complete: 0 Longitudinal clinical or post-mortem diagnosis: 0 AAN level: III	HC n=110 (44M/66F); age 65 (SD 8).					
Reference: Ng et al., 2007 (*9*) **Study type:** Case-control **Diagnostic standard:** Clinical **Quality score: 5** Representative sample: 1 Setting/selection described: 1 Scanner described: 1 Standard interpretation: 1 Blinded reader: 1 Categorization by disease severity: 0 Follow-up complete: 0 Longitudinal clinical or post-mortem diagnosis: 0 AAN level: III	AD (wide spectrum, possible & probable AD) n=15 (7M/8F); age 71.1 (SD 11.3) & healthy controls n=25 (14M/11F); age 71.9 (SD 6.8).	**12**	**3**	**10**	**15**	AD vs normal controls: Sn=80%; Sp=64%. Note: AD subjects may have included patients with mild cognitive impairment. Probable AD vs normal controls: Sn=77.7%; Sp=94.3%.
Reference: Panegyres et al., 2009 (*10*) **Study type:** Prospective cohort study **Diagnostic standard**: Longitudinal diagnosis **Quality score: 7** Representative sample: 1 Setting/selection described: 1	Cohort of 102 consecutively presented patients (55M/47F); age 60.1 (SD 4.3). Forty-nine patients received a final	**38**	**11**	**10**	**43**	AD versus mixed non-AD patients: Sn=78%; Sp=81%.

Scanner described: 1 Standard interpretation: 1 Blinded reader: 1 Categorization by disease severity: 0 Follow-up complete: 1 Longitudinal clinical or post-mortem diagnosis: 1 AAN level: I	clinical diagnosis of early-stage AD (24M/25F); age 62.8 (SD 9.7). There were 29 non-AD demented patients: FTD n=17; DLB n=6; primary progressive aphasia n=6, 11 depressed patients and a miscellaneous group of 13 patients (MCI, vascular dementia, progressive supranuclear palsy, corticobasal degeneration and 2 normal subjects.					
Reference: Silverman et al., 2001 (*11*) **Study type:** Multi-center historical cohort. **Diagnostic standard:** Post-mortem **Quality score: 5**	AD (n=97, including 41 with mild or questionable diagnosis at presentation); Non-AD (n=41),	**91**	**11**	**6**	**30**	AD vs. non-AD dementia and non-dementia controls: Sn=94%; Sp=73%. Subgroup analysis of very mild AD: Sn=95%;

Representative sample: 1 Setting/selection described: 0 Scanner described: 0 Standard interpretation: 1 Blinded reader: 1 Categorization by disease severity: 0 Follow-up complete: 1 Longitudinal clinical or post-mortem diagnosis: 1 AAN level: II	such as progressive supranuclear palsy, Parkinson's disease, cerebrovascular disease, or mixed.					Sp=71%. Subgroup analysis of moderate to severe AD vs. non-AD dementia and non-dementia controls: Sn=94%; Sp=73%.

References:

1. Chen WP, Samuraki M, Yanase D, et al. Effect of sample size for normal database on diagnostic performance of brain FDG PET for the detection of Alzheimer's disease using automated image analysis. *Nucl Med Commun.* 2008;29:270-276.

2. Dobert N, Pantel J, Frolich L, Hamscho N, Menzel C, Grunwald F. Diagnostic value of FDG-PET and HMPAO-SPET in patients with mild dementia and mild cognitive impairment: metabolic index and perfusion index. *Dement Geriatr Cogn Disord.* 2005;20:63-70.

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10. Panegyres PK, Rogers JM, McCarthy M, Campbell A, Wu JS. Fluorodeoxyglucose-positron emission tomography in the differential diagnosis of early-onset dementia: a prospective, community-based study. *BMC Neurol.* 2009;9:41.
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