Evidence Table

Clinical Area: **FDG PET for Alzheimer's diseases**
Keywords: **Dementia, FDG PET, Alzheimer's disease.**
Reference: **Hoffman JM, Welsh-Bohmer KA, Hanson M, et al. FDG PET in patients with pathologically verified dementia. *J Nucl Med* 2000;41:1920-1928.**

Study Type: Comparison of diagnostic tests (prospective).
Study Aim: To pathologically confirm that: 1. FDG PET metabolic findings of bilateral tempero-parietal hypometabolism are associated with Alzheimer's disease (AD), and 2. FDG PET findings allow differentiating AD from other causes of dementia.

Outcomes:

- *Primary:* Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy.

Design

- *Number of subjects:* N=22.
- *Description of study population:* The study included patients at an Alzheimer's disease research center at Duke University, NC. All patients had dementia that was difficult to determine clinically with CERAD* and NINCDS-ADRDA** criteria. There were 14 (63.6%) men, and 8(36.4%) women, with a mean age of 65.4 years at the time of FDG PET study. 10 (45.5%) patients were clinically diagnosed as probable AD, 2 (9.1%) possible AD, 8 (36.3%) non AD dementia, and 2 (9.1%) with other diseases.
- *Inclusion and exclusion criteria:* Patients with dementia that was difficult to determine clinically and who agreed to eventually undergo pathologic confirmation of their diagnosis. Exclusion criteria were not discussed.
- *Procedure:* All patients underwent standard dementia evaluations by specialized neurologists. Resting stage FGD PET scan was then performed, and visually graded by a nuclear medicine physician for the presence of bilateral tempero-parietal hypometabolism. All patients were then longitudinally followed up. 19(86.4%) patients underwent autopsy, two patients (9.1%) had biopsy, and one (4.5%) patient had both a biopsy and autopsy.

Validity

- *Independent blind comparison with a gold standard or follow-up of those not receiving the gold standard test?* The nuclear medicine physician who interpreted and graded the FDG PET results was blinded to the patients' clinical information.
- *Was "normal" defined?* Yes.

  * CERAD: Consortium to Establish a Registry for Alzheimer's disease.
** NINCDS-ADRDA: National Institute of Neurologic Communicative Disorders and Stroke-AD and related Disease Association.

- *Appropriate spectrum of disease?* No.
- *Consecutive patients?* Not specified.
- *Methods described in enough detail to enable you to replicate the test?* Yes.
- *Reproducible results?* No.

Conclusions regarding validity of methods:

This study was prospective, with histopathological confirmation (the ideal gold standard) on 100% of patients, and the interpreters of FDG PET results were blinded to the clinical diagnosis. However it had a small sample size, had no specific exclusion criteria, and included had a narrow spectrum of patients.

Results:
The interval from FDG PET study to pathological verification was 24.9+28.1 months for all patients and 30.8+19.3 for those who had an autopsy.

Sensitivity, specificity, accuracy and predictive values of FDG PET
Using pathological diagnosis as gold standard.

Results	Sensitivity	Specificity	PPV†	NPV†	Accuracy
PET grade 2 or 3* AD only	92.9% (13/14)	62.5% (5/8)	81.3% (13/16)	83.3% (5/6)	81.8% 18/22)
AD and other non- AD dementia	87.5% (14/16)	66.7% (4/6)	87.5% (14/16)	66.7% (4/6)	81.8% (18/22)

† PPV =positive predictive value, NPV= negative predictive value
* FDG PET grades 2 and 3, are interpreted as metabolically diagnostic of AD

Sensitivity, specificity, accuracy and predictive values of clinical diagnosis
Using pathological diagnosis as gold standard.

Results	Sensitivity	Specificity	PPV†	NPV†	Accuracy
Poss. or Prob.* AD clinically (AD +other on path)	75.0% (12/16)	100% (6/6)	100% (12/12)	60.0% (6/10)	81.8% 18/22)

† PPV =positive predictive value, NPV= negative predictive value
* Possible or probable

Authors' Conclusions:
The authors concluded that the study confirms that the bilateral tempero-parietal hypometabolism findings on FDG PET scan are associated with AD. They also concluded that FDG PET, combined with the clinical evaluation and neuropsychological tests, would improve the diagnosis of AD and its differentiation from other causes of dementia.

Reviewer's Conclusions:
The study had the advantage of using the ideal gold standard of pathological confirmation, on a cohort of patients, and blinding the interpreters of FDG PET to the clinical information. However, it has some threats that may limit generalization or usefulness of the results. It had a small sample size, with a narrow spectrum of patients, and no specific exclusion criteria.

In this study FDG PET scan, had a sensitivity of 92.9% and 87.5% in diagnosing AD alone or with concurrent non-AD dementias, and a specificity of only 62.2% and 66.7% respectively i.e. more than one third of the patients may be falsely diagnosed with AD.
The authors did not report confidence intervals, and the number of patients who were histopathologically negative for AD was too small (6 patients) to provide sufficient power to assess the specificity of the test. Moreover, the impact of FGD PET on the disease management and health outcome was not studied. The interpretation of the test results was visual and made by only one reader, and not confirmed by another. It also appears that the patients included in the study had a rapidly progressive disease, the mean age at entry was 65 years, and the mean follow-up to the autopsy was 2.5 years. At a progressive stage of the disease there will be sufficient cortical degeneration to increase the sensitivity of the scan at the expense of the specificity.