Evidence Table

Clinical Area: **FDG PET for Alzheimer's diseases**
Keywords: **Dementia, FDG PET.**
Reference: **Silverman DH, Small GW, Chang CY, et al. Positron Emission Tomography in Evaluation of Dementia. *JAMA* 2001;286:2120- 2127.**

Study Type: Comparison of diagnostic tests (prospective).
Study Aim: To assess the value of PET scans in predicting the progression of cognitive impairment.

Outcomes:
- *Primary:* Sensitivity and specificity.

Design
- *Number of subjects:* N=284. (n=146 UCLA patients, and n=138 from other institutions)
- *Description of study population:* The study included: (1): 146 patients (with symptoms of cognitive deficit or behavior changes) referred to the Nuclear Medicine Clinic at UCLA for PET evaluation between 1991 and 1998, and (2) 138 patients from 8 different centers in USA and Europe who underwent PET scans between 1984 and 1998, and had a subsequent neuropathologic examination. The UCLA group included 75 men (51.4%), and 71 women (48.6%), 22% were 55 years old or younger, 24.7% were 56-65 years old and the rest were 66 years of age or older. The group with pathological confirmation had a mean age of 67±10 years, and 59% were men.
- *Inclusion and exclusion criteria:* UCLA group included patients who were followed up for at least 2 years after their FDG PET scan. The second group included patients who underwent a PET scan and had neuropathologic verification of their diagnosis. Other inclusion/exclusion criteria were not specified.
- *Procedure:* Different protocols were followed in each center. All patients underwent neurological, psychiatric and PET evaluations. UCLA group: A resting stage FGD PET scan was performed, and visually interpreted at the same day by a nuclear medicine physician. Patients were then longitudinally followed up for 2-9 years (mean 3.2 years). Demographic, personal and clinical data were obtained from UCLA medical records, and follow-up data were obtained through questionnaires sent to the treating physicians. Pathologically confirmed group: Each center had its own protocol, instruments, and scanning procedures as well as methods and criteria for pathological examination and establishing a diagnosis. Patients' demographic, clinical, and pathological data were obtained through questionnaires sent to the centers. All patients underwent autopsy between 1984 and 2000 (0.1-9.5 years after PET with a mean of 2.9 years).

Validity
- *Independent blind comparison with a gold standard or follow-up of those not receiving the gold standard test?* For all cases, the nuclear medicine physicians who interpreted PET scan results were blinded to the patients' clinical and pathological data except for age, sex, and any MRI or CT scan reports. In the UCLA cohort, the outcome data were independently reviewed by two internists blinded to the PET findings.
- *Was "normal" defined?* Yes.
- *Appropriate spectrum of disease?* Not discussed.
- *Consecutive patients?* Not discussed.
- *Methods described in enough detail to enable you to replicate the test?* Only for the UCLA group.
- *Reproducible results?* No.

Conclusions regarding validity of methods:
The study included two populations: A prospective cohort with a clinical follow-up, and a retrospective cohort with pathological confirmation from 8 different centers in the USA and Europe. Each center had its own study protocol, instruments and criteria of diagnosis and interpretation of test results. Details on the PET scan instrument, and procedure used, were only delineated for the UCLA group, but not for the other centers. Patients with pathological confirmation underwent PET scans between 1984-1998, in eight different centers in the US and Europe. Different scans, may have different resolutions, and more recent scans may give better resolutions. This may be a potential source of bias. In addition, the PET scan readers were not totally blinded as they had access to patients' information on age, sex, and any MRI or CT scan findings. This could be a potential source of bias. Moreover, the inclusion and exclusion criteria were not specified, and not all data on patients' demographics and health conditions were available. The mean age the patients with

pathological confirmation was 67 years at the time of PET scanning and their mean survival after PET was 2.9 years. This may indicate that this group of patients had a progressive disease, which in turn may yield to a higher PET sensitivity. In the UCLA group, the clinical follow-up period might have been insufficient to achieve an accurate diagnose.

Results:

Clinical follow-up group: (N= 146)

After clinical follow-up period of 2-9 years (mean 3.2 years) the course of the cognitive impairment was observed to be progressive* in 86 (59%) patients, and non-progressive** in 60 (41%) patients.

Sensitivity and specificity of FDG PET in predicting progress of cognitive impairment:

		95% CI
Sensitivity	92% (78/86)	85%-97%
Specificity	75% (45/60)	64%-86%

* Memory, language, and functional ability progressed at a rare faster than that expected with normal aging
** Mild short-term memory deficit typical for patient's age and general health

Pathologically confirmed group: (N= 138):

Alzheimer's disease (AD) was pathologically identified in 97 (70.28%) of the 138 patients.

Sensitivity and specificity of PET scans in the group with neuropathologic confirmation (N=138)

Results	*Sensitivity (95%CI)*	*Specificity (95%CI)*
Alzheimer's disease (n=97)	93.81% (91/97) (89%-99%)	73.17% (30/41) (60%-87%)
Neurodegenerative disease of any kind* (n=120)	94.17% (113/120) (90%-98%)	77.78% (14/18) (59%-97%)

*Includes AD, frontotemporal dementia, dementia with Lewy bodies, Creutzfeldt-Jacob disease, and other dementias.

Clinical follow-up group plus the pathologically confirmed group: (N=284)

Sensitivity and specificity of PET in predicting progressive dementia:

		95% CI
Sensitivity	92.72% (191/206)	89%-96%
Specificity	75.64% (59/78)	66%-85%

Authors' Conclusions:
The authors concluded, "The use of PET for evaluation of an appropriate population permits sensitive identification of future decline associated with AD and other neurodegenerative disease."

Reviewer's Conclusions:
The study does not provide sufficient evidence to determine the value of FDG PET in evaluating dementia, and predicting its progression. The study had the advantage of including a larger number of patients compared to the other studies conducted to evaluate FDG PET, yet it had several methodological problems that limit generalization of its results.

The study encompassed two different studies with different protocols, and unclear inclusion and exclusion criteria. For the group of patients with histopathological confirmation, data were pooled from 8 centers over 14 years. The available data were incomplete, and each center had its own study protocol. It is also most probable that different instruments of PET scans with different resolutions were used in the different institutes and along the time. The clinical follow-up group only included patients referred to UCLA Nuclear Medicine department for a PET evaluation of their cognitive impairment. These patients might not represent the all those who undergo dementia evaluation. In this group, the performance of FDG PET scan was not compared to the standard clinical criteria, and the mean follow-up duration was 3.2 years, which might not be sufficient to study the progress of dementia.