



**TITLE:** Positron Emission Tomography (PET) for the Evaluation of Alzheimer's Disease/Dementia

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**PUBLISHER NAME:** California Technology Assessment Forum

**DATE OF PUBLICATION:** February 11, 2004

**PLACE OF PUBLICATION:** San Francisco, CA



## POSITRON EMISSION TOMOGRAPHY (PET) FOR THE EVALUATION OF ALZHEIMER'S DISEASE / DEMENTIA

### INTRODUCTION

The California Technology Assessment Forum has been asked to review the evidence for whether the addition of positron emission tomography (PET) to the current standard evaluation improves the diagnosis and management of Alzheimer's Disease and dementia.

### BACKGROUND

Dementia is defined as an acquired, persistent, and usually progressive impairment in intellectual function, with compromise in multiple cognitive domains at least one of which is memory. The deficits must represent a significant decline in function, and must be severe enough to interfere with work or social life (Lyons and Yaffe, 2003).

Dementia is an increasingly common disorder affecting about 1% of individuals aged 60 years and older with a doubling of prevalence every 5 years thereafter (Cummings *et al*, 2002). Direct and indirect costs secondary to dementia are also increasing at a rapid rate. By 2010, Medicare spending on Alzheimer's disease will rise to \$49.3 billion, a 54% increase over costs in the year 2000 (Prigerson, 2003).

Alzheimer's Disease (AD) is the most common form of dementia, accounting for about two-thirds of all cases (Mayeux and Sano 1999). Other causes of dementia include Dementia with Lewy Bodies (DLB), vascular dementia, fronto-temporal dementias, advanced Parkinson's disease, chronic alcohol abuse and HIV-1 associated dementia. Recent estimates indicate that AD is increasing at a dramatic rate in the U.S. In 2000, 4.5 million Americans were diagnosed with AD; the prevalence is expected to increase by 70% by the year 2030 (Prigerson, 2003). The age of onset of AD varies considerably. While many cases present between the ages of 50-60, symptoms are most common after age 70. AD presenting prior to age 60 is often associated with autosomal dominant inherited mutations of the amyloid precursor polypeptide genes and polymorphisms of the apolipoprotein E gene. These mutations account for less than 5% of all cases of AD (Cummings and Cole, 2002).

AD usually follows a progressive and insidious course. Memory deficits are prominent in all dementias and are typically the first and most obvious manifestation of the disorder. The typical clinical syndrome of AD includes an amnesic type of memory defect with difficulty learning and recalling new information, progressive language disorder beginning with anomia and progressing to fluent aphasia, and disturbances of visuo-spatial skills manifested by disorientation and difficulty copying figures. Neuropsychiatric symptoms are common in AD and agitation and depressive symptoms are frequently present particularly later in the course of disease (Cummings and Cole, 2002).

Life expectancy following the first appearance of the disorder is generally 3-15 years, but survival up to 20 years has been reported (Lyons and Yaffe, 2003).

Current clinical diagnosis of dementia is based on a careful history and physical exam, neurological and mental status examinations, and directed laboratory testing and possible neuro-imaging with either a non-contrast CT or MR scan (Knopman *et al*, 2001). Screening for depression (with an instrument such as the Geriatric Depression Scale) is appropriate, as depression may mimic or more frequently co-exists with dementia (Kawas, 2003). In patients with dementia, the likelihood of Alzheimer's disease is assessed largely on the basis of the history. The DSM-IV criteria for the diagnosis of Alzheimer's dementia include the following: 1) The gradual onset and continuing decline of cognitive function from a previously higher level, resulting in impairment in social or occupational function; 2) Impairment of recent memory (inability to learn new information) and at least one of the following: disturbance of language; inability to execute skilled motor activities in the absence of weakness; disturbances of visual processing; or disturbances of executive function (including abstract reasoning and concentration; 3) The cognitive deficits are not due to other psychiatric, neurologic, or systemic diseases; and 4) The deficits do not occur exclusively in the setting of delirium (APA Press 1994). The sensitivity and specificity of the DSM-IV criteria are 76% and 80%, respectively (Kukull *et al* 1990).

The diagnosis of dementia has recently been the subject of an evidence-based review by the quality standards subcommittee of the American Academy of Neurology (Knopman *et al*, 2001). They concluded that the current clinical criteria for the diagnosis of dementia are reliable and should be used routinely. Clinical studies suggest that the accuracy of diagnosis of AD varies from about 50%-60% among general practitioners in community settings to approximately 80%-90% among dementia specialists in referral centers (Bowler *et al*, 1998; Corey-Bloom *et al*, 1995).

The definitive diagnosis of AD is made by pathological examination of brain tissue at post-mortem. The current criteria for the pathologic diagnosis requires the presence of both neuritic plaques and neurofibrillary tangles in excess of the abundance anticipated for age-matched healthy controls. In addition, AD is characterized by reductions in synaptic density, loss of neurons and others processes that lead to deficits in cholinergic, noradrenergic, and serotonergic transmitters (Cummings and Cole, 2002).

Treatment of AD ranges from addressing safety issues, to the pharmacological treatment of memory and behavioral problems. Patients with AD have reduced cerebral production of choline acetyl transferase, which leads to a decrease in acetylcholine synthesis and impaired cortical cholinergic function. There are currently four cholinesterase inhibitors approved by the FDA for use in mild to moderate AD (tacrine, donepezil, rivastigmine and galantamine). These drugs have been found to improve cognitive function in patients with mild to moderate AD (Doody *et al*, 2001). Cholinesterase inhibitors have been shown to offer symptomatic, not disease-modifying, treatment and overall have modest benefit, though they have been shown to positively impact significant outcomes such as the need for admission to a nursing home (Lopez *et al* 2002). The choice of agents (with the exception of tacrine which is rarely

used due to reports of hepatotoxicity) is largely based upon cost, individual patient tolerability, and physician experience, as efficacy appears to be similar (Trinh *et al* 2003).

In addition to the cholinesterase inhibitors, there is growing interest in a number of agents that may help slow the progression of AD. One such agent recently approved by the FDA is memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist which appears to be effective in reducing clinical deterioration in patients with moderate to severe AD (Reisberg *et al*, 2003). Other potential disease modifying agents in AD include alpha-tocopherol (vitamin E) and seligiline (because of their antioxidant properties), NSAIDS, ginkgo biloba, and estrogen replacement therapy. There is currently no evidence from RCT's for initiating any of these therapies in patients with established dementia. In addition, preliminary studies in human have found that immunization with amyloid beta peptide reduces the amyloid plaque burden and may play a role in the prevention and treatment of AD in the future. (Hock *et al*, 2002).

### **Positron Emission Scanning in Dementia**

Positron Emission Tomography (PET) is a minimally invasive nuclear medicine imaging modality that uses radiopharmaceuticals to capture and measure biochemical processes within tissues. PET may complement other imaging modalities, such as radiography, computed tomography (CT), or other magnetic resonance imaging. Like other nuclear medicine techniques, PET defines disease in terms of quantifiably abnormal regional chemistry. PET imaging employs radioactive isotopes that decay by emitting a positively charged electron (called a positron) from the nucleus. The positron collides with a negatively charged electron resulting in two high-energy photons that travel in opposite directions. PET uses the principle of coincidence detection to form the raw image. Radiation detectors are arranged in a ring around the patient to allow for simultaneous (or coincident) detection of the two photons (Berger, 2003).

The most widely used radiopharmaceutical in PET is FDG (Fluro 2-deoxy D-glucose), the D-glucose analog used to study cellular glucose metabolism. (Cerebral glucose metabolism as measured by FDG-PET is the preferred PET technique for evaluation of dementia). For FDG-PET the patient should be fasting for at least 30 minutes prior to the evaluation to allow brain accumulation of the radio-tracer (Frisoni *et al*, 2003). Typical findings on FDG-PET seen in AD are bilateral temporo-parietal hypo-metabolism and hypo-perfusion (Hoffman *et al*, 2000).

**TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies.**

There are several manufacturers of PET scanners that have received FDA clearance for marketing. Fluro2-deoxyD-glucose (FDG) is considered by the FDA as a drug that is safe and effective for the evaluation of glucose metabolism. Due to the short half-life of this radiotracer it is frequently produced in the clinical setting. The FDA intends to regulate PET centers for production of FDG and other radiotracers.

TA criterion 1 is met.

**TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.**

Frisoni *et al* (2003) assert that a clinical test ideally should answer 4 questions before entering clinical practice: 1) Do test results in patients with the target disorder differ from those with normal people? 2) Are patients with certain test results more likely to have the target disorder than patients with other test results? 3) Does the test result distinguish patients with and without the target disorder among patients in whom it is clinically reasonable to suspect that the disease is present? 4) Do patients who undergo this diagnostic test fare better in their ultimate health outcomes than similar patients who are not tested? They correctly point out that diagnostic tests are rarely able to answer questions 3 and 4 and may have difficulty addressing question 2 satisfactorily. As a result, the use of diagnostic tests is often based on extrapolation and likelihood rather than on direct evidence. In this regard, the current literature on FDG-PET in the evaluation of AD and dementia is no exception.

More than 30 published studies have examined the use of PET in the evaluation of dementia and AD. None of these to date are randomized trials. The literature consists of level 3 evidence (nonrandomized concurrent cohort comparisons between contemporaneous patients) and level 5 evidence (case series without control subjects). Few of the cohort studies enrolled patients from more than one institution.

The main outcome of interest would be that the enhanced diagnostic capability offered by PET leads to improved health outcomes and quality of life for persons with AD. Ultimately, earlier and more accurate diagnosis may lead to the prevention of AD in vulnerable individuals. A randomized clinical trial would be the ideal way to address these outcomes with patients randomized to receive a conventional evaluation for dementia vs. an evaluation that includes PET (and possibly a third arm with a competing neuro-imaging technique).

In the absence of level 1-evidence, studies of PET in dementia (as with studies of many other diagnostic technologies) must rely on intermediate outcomes to support its use. The main intermediate outcome of interest is the diagnostic accuracy of PET in the differential diagnosis of the underlying cause of dementia relative to defined reference standards. Diagnostic accuracy is most commonly reported in studies as the sensitivity, specificity, positive and negative predictive values receiver operating curves (ROC's). The ideal comparison outcome of interest would be histopathological confirmation of AD. Most studies instead use clinical correlates of AD/dementia obtained by a variety of methods.

The clinical value of PET depends upon its ability to improve diagnostic accuracy beyond that provided by clinical criteria. To date, the scientific evidence does not permit conclusions concerning the effectiveness of FDG-PET regarding health outcomes.

Level of evidence: 3, 5

TA criterion 2 is not met.

### **TA Criterion 3: The technology must improve the net health outcomes.**

There is a large amount of literature reporting on the use of PET scans in the evaluation of patients with dementia. Much of the literature consists of case reports or small, single institution case series. This review has adapted the structure suggested by Matchar *et al*, 2001 in their review for AHRQ to only include studies that had at least 12 subjects with AD and in which either clinical or histo-pathological diagnosis was used as the reference standard. They organized the literature into 3 scenarios in which PET could be a useful addition to the diagnostic work-up: A) Studies that use PET scans of patients with mild to moderate dementia; B) Patients with mild cognitive impairment; and C) Asymptomatic patients but with a first-degree relative with AD.

#### **A) PET scans in patients with mild-moderate dementia**

Twenty-three studies report on the use of FDG-PET in patients with mild to moderate dementia. Of these, 8 studies aimed to differentiate patients with AD from those with dementia from other etiologies (Salmon *et al*, 1994; Hoffman *et al*, 2000; Silverman *et al*, 2001; Duara *et al*, 1989; Mielke *et al*, 1994; Szelies *et al*, 1994; Ishi *et al*, 1998; Higuchi, 2000) and 16 studies compared patients with AD to normal controls (Alexander *et al*, 2002; Azari *et al*, 1993; Burdette *et al*, 1996; Duara *et al*, 1989; Fazekas *et al*, 1989; Grady *et al*, 1990; Herholz, 1990; Herholz, 1993; Higuchi *et al*, 2000; Ishi *et al*, 1998; Kippenhan *et al*, 1992; Messa *et al*, 1994; Mielke *et al*, 1994; Minoshima *et al*, 1995; Ohyama, 2000; Szelies *et al*, 1994; Mishina, 2000).

##### **1) PET in patients with AD compared with non-AD dementia**

Eight studies report on the sensitivity and specificity of PET in patients with AD as compared with other causes of dementia. Three of the larger studies are discussed below. Salmon *et al*, (1994) analyzed PET studies obtained from 129 patients referred for evaluation of dementia rated as mild, moderate or severe. Probable AD was diagnosed in 65 patients using the NINCDS/ADRDA criteria. PET images were classified according to 9 different patterns and were initially read with the reader blind to clinical data (though not subsequently) and CT scans were also used, particularly to exclude cerebral infarct. Overall, 43 of 65 patients with AD had the classic pattern of bilateral temporo-parietal hypometabolism on FDG-PET. Other patients with a bilateral TP pattern included 11 of 13 patients with Parkinson's disease, 5 of 9 with mixed dementia, and 1 of 3 with CJ disease. In the overall study population, which included patients with severe dementia, operating characteristics of FDG-PET for distinguishing AD from vascular dementia included sensitivity of 86% and specificity of 61%. In addition, they found a sensitivity of FDG-PET of 75% for patients with mild AD, 88% for moderate AD and 92% for patients with severe AD. Only 12 of 129 subjects had neuropathological verification of a diagnosis. Normal control patients were not included.

Hoffman *et al*, (2000) report on 22 patients of the Memory Disorder Clinic at Duke (8 women and 14 men) for whom the etiology of their memory loss was considered diagnostically challenging and who agreed to eventually have pathological confirmation of their diagnosis. The clinical diagnosis of probable or possible AD was determined as the

primary cause of dementia in 12 of 22 patients; the pathologic diagnosis of AD was found in 16 of the 22 patients. The sensitivity (% of patients with pathologic AD who had the classic imaging pattern of bilateral temporo-parietal hypometabolism) and specificity (% of pathological non-AD patients who were negative for the pattern) were 93% and 63% respectively.

In the largest study to date, Silverman *et al*, (2001) recruited 284 patients presenting with symptoms of dementia at neurology, psychiatry, and PET facilities at 8 academic medical centers in the US and Europe. Of these patients, two groups of patients were included in the analysis: 1) 146 patients studied with FDG-PET and followed for at least 2 years at UCLA and 2) 138 patients from all institutions who later underwent histopathological determination of disease status. Group 1 patients were followed for an average of 3.2 years after PET. Clinical data on these patients was obtained from questionnaires sent to the patient's referring physician and from UCLA medical records. The mean Mini-Mental State Examination (MMSE) measured near the time of PET was 24 (SD=6). A progressive clinical course was documented in 59% of these patients. Of these, sensitivity of PET for predicting an ensuing progressive course of disease was 91% (78/86; 95% CI, 85%-97%) and correctly predicted a non-progressive course with a specificity of 75% (45/60; 95% CI, 64%-86%). In Group 2 (with pathologically confirmed diagnoses) PET correctly identified the presence or absence of AD in 88% (95% CI, 82%-93%) of the cases with a sensitivity of 94% (91/97; 95% CI; 89%-99%) and a specificity of 73% (30/41; 95% CI, 60%-87%). Autopsies were performed on average 2.9 years after the PET scan was obtained, suggesting that these patients were, on average, further advanced in their disease than would be suggested by their age or baseline MMSE scores. The sensitivity and specificity of PET in patients with mild dementia was similar (sensitivity 95%; CI, 89%-100%; specificity 71%; (48%-95%).

In the five additional studies that compared the operating characteristics of PET in patients with AD as compared with other etiologies of dementia (Duara, 1989; Mielke, 1994; Szelies, 1994; Ishi, 1998; Higuchi, 2000), the sensitivity of PET ranged from 88%-90% and the specificity ranged from 18%-86% (Matchar *et al*, 2001).

## 2. PET in patients with AD compared with normal controls

Sixteen studies examined the operating characteristics of PET in the diagnosis of AD compared to normal controls. Overall, the sensitivity of these studies ranged from 61% to 100% and the specificity from 17% to 100%. The large range in results is indicative of the variability in patients and in PET technique in these studies. The most recent study (Alexander *et al*, 2002) of PET in patients with AD and normal controls enrolled 14 patients with AD (mean MMSE scores of 20/30) and 34 controls to investigate cross-sectional reductions in regional cerebral glucose metabolism and the decline in regional cerebral glucose metabolism over 1 year. They found that at 1-year follow-up, the patients with AD showed significant declines in glucose metabolism from baseline in the expected parietal, temporal, frontal, and posterior cingulate regions. Similarly, MMSE scores declined on average 2.9 points over this period. Unfortunately, they did not measure changes in FDG-PET in the normal healthy controls over this same period of time so it is impossible to conclude that the observed changes were not a consequence of normal aging.

## **B. PET in patients with mild cognitive impairment**

Mild cognitive impairment (MCI) is considered a pre-clinical AD present in some older persons without functional impairment that do not satisfy established clinical criteria for dementia or probable AD (Jelic and Nordberg, 2000). One clinical tool used to define MCI, the Clinical Dementia Rating scale (CDR), assesses subjects according to six categories: memory, orientation, judgment/problem solving, community affairs, home/hobbies, and personal care. Scores range from 0.0 (normal) to 0.5 (questionable) up to 2.0 (moderate) and 5.0 (terminal). Persons with scores of 0.5 are characterized as meeting criteria for MCI. These individuals have a memory complaint corroborated by friends or family but have normal cognition and ADL's (Albert, 2003). The conversion rate to AD for patients with MCI is thought to be around 15% per year (Petersen *et al*, 2001). Future studies hope to establish rigorous diagnostic measures that can identify persons with MCI that will progress to AD so that they can be offered enrollment in clinical trials or considered for treatment.

Several studies included patients with mild dementia, but only two studies included formal sub-group analysis of patients by degree of dementia (Burdette *et al*, 1996; Fazekas *et al*, 1989). Burdette *et al* (1996) obtained FDG-PET images in 39 patients with probable AD according to the NINCDS-ADRDA criteria. Of these, 28 patients had a CDR of 0.5 or 1.0 (questionable or mild dementia). In this group, the sensitivity of PET was 79% (as compared with a sensitivity of 100% in the patients with moderate to severe dementia).

## **C. PET in asymptomatic patients with a family history of AD**

A gene on chromosome 19, apolipoprotein E-4 (APOE) has been found to increase risk and decrease age of onset of AD. However, APOE-4 genotyping is not currently recommended for at-risk individuals, as the allele is neither necessary nor sufficient for a diagnosis of dementia (Small and Leiter, 1998). No research to date directly addressed the operating characteristics of PET in asymptomatic patients with a family history of AD. One study addressed the use of PET in non-demented relatives with the APOE-4 allele (Small *et al*, 2000) <http://www.pnas.org/cgi/doi/10.1073/pnas.090106797>. They studied 31 at-risk subjects with MCI and at least 2 relatives with AD and found that parietal metabolism was significantly lower and left-right parietal asymmetry higher in at-risk subjects with the APOE-4 allele. These investigators concluded that PET imaging twice within 2 years could identify pathologically affected but not demented subjects at risk for AD. This study has been critiqued for the fact that they did not indicate whether their APOE-4 subjects were hypertensive in spite of the fact that HTN and APOE-4 are risk factors for vascular dementia and that vascular dementia can produce an AD like brain metabolic pattern (Rapoport, 2000).

It is not possible to conclude from the current literature that use of PET leads to improved health outcomes for patients with dementia, with MCI or persons at risk for AD.

TA Criterion 3 is not met.

**TA Criterion 4: The technology must be as beneficial as any established alternatives.**

Alternatives to PET for the evaluation of dementia include clinical evaluation (complete history and physical exam, MMSE, appropriate laboratory testing) and structural neuro-imaging with CT or MR. Clinical accuracy for AD is consistently above 85% and has been reported to achieve levels of accuracy above 90%, although this figure may be somewhat lower in community settings and in early stages of AD (DeCarli, 2001). The Quality Standards Subcommittee of the American Academy of Neurology reviewed the evidence for the diagnostic accuracy of the clinical diagnosis of AD using neuropathological confirmation as the 'gold standard'. They concluded that the DSMIIIR "Dementia of the Alzheimer Type (DAT)" and the NINCDS-ADRDA "probable" AD definitions achieved either good sensitivity (average across 13 studies was = 81%, range 49% to 100%) for with less specificity (average = 70%, range 47% to 100%) or less sensitivity with a higher specificity. A diagnosis of "possible AD" achieved very high sensitivity (average 93%) with lower sensitivity (average 48%) (Knopman, 2000).

Structural brain imaging with CT or MR is often used in the evaluation of persons with dementia. MR imaging and CT indices of hippocampal atrophy are associated with AD, but specificity is not well established (Jagust, 2000). In general, structural imaging is primarily used to exclude non-AD causes of dementia rather than to diagnose AD. CT imaging has the advantage of general availability, brief time requirements, and low cost. The advantages of MR are the lack of ionizing radiation, excellent spatial resolution, and the ability to modify imaging pulse sequences to enhance imaging of specific tissue characteristics (DeCarli, 2001). Long imaging times in an enclosed space and the problems created by metal objects such as prostheses may rule out use of MR in some older persons. The Quality Standards Subcommittee of the American Academy of Neurology now recommends the use of either a non-contrast CT or MR scan generally at the time of the initial dementia assessment to identify pathology such as brain neoplasms or subdural hematomas (Knopman, 2001).

In addition to the structural brain imaging provided by CT or MR, functional brain imaging can be accomplished with PET scans and with single photon emission CT (SPECT) scans. Both PET and SPECT are based on the same principle of imaging, in which a molecule of interest, generally used to trace either blood flow or glucose metabolism, is tagged with a radioactive atom and detected with external radiation detectors (Jagust, 2000). Unlike PET, which generates two photons at 180-degree opposition, SPECT uses direct photon emitting isotopes. This simplifies image reconstruction (and means that SPECT is significantly less expensive than PET) but also means a generally lower spatial resolution than with PET. Overall, SPECT is not consistently better than established clinical criteria in the diagnosis of AD.

The available evidence does not currently support the conclusion that PET is as beneficial as the established alternatives (diagnostic criteria with appropriate laboratory testing and structural imaging with CT or MR) in the evaluation of AD/dementia.

TA Criterion 4 is not met.

**TA Criterion 5: The improvement must be attainable outside of the investigational setting.**

Studies have not yet demonstrated the efficacy of Positron Emission Tomography in improving net health outcomes in the investigational setting. Whether PET will be effective in improving health outcomes when used to evaluate patients with AD and dementia in the community setting under conditions of usual medical practice remains to be demonstrated.

TA criterion 5 is met

## **RECOMMENDATION OF OTHERS**

### **Blue Cross Blue Shield Association (BCBSA)**

The BCBSA Technology Evaluation Center has not conducted a review of this specific indication for PET.

### **USPSTF**

"The U.S. Preventive Services Task Force (USPSTF) concludes that the evidence is insufficient to recommend for or against routine screening for dementia in older adults."

### **American Academy of Neurology (Knopman *et al*/2001)**

"PET scanning appears to have promise for use as an adjunct to clinical diagnosis, but further prospective studies with PET are needed to establish the value that it brings to diagnosis over and above a competent clinical diagnosis".

### **Neuroimaging Working Group of the European Alzheimer's Disease Consortium (EADC):**

"Of the tools presented here (CT, MR, SPET and PET), evidence of added diagnostic value (that is the diagnostic accuracy compared to current clinical accuracy for the diagnosis) was available for only two (visual rating of the medial temporal lobe on MR and visual rating of color coded hard copies on SPET images)."

### **Centers for Medicare and Medicaid Services (CMS)**

"On April 16, 2003 CMS released a Decision Memorandum stating that it would retain the previous noncoverage decision of PET for AD. The analysis concluded that the addition of an FDG-PET scan to the standard evaluation of AD does not result in improved patient outcomes. It was determined that the available evidence was adequate to conclude that an FDG-PET scan is not reasonable and necessary when used in the patients for whom the differential diagnosis includes one or more kinds of neurodegenerative disease."

CMS has received a request from UCLA regarding a more restrictive coverage determination. The expected completion date for review of this request is January 7, 2004.

### **Association of California Neurologists (ACN)**

The Association of California Neurologists does not have a formal opinion on the use of PET for the evaluation of Alzheimer's Disease/Dementia and did not send a representative to the meeting.

### **California Psychiatric Association (CPA)**

The California Psychiatric Association does not have an official opinion regarding the use of PET in the evaluation of Alzheimer's Disease/Dementia and did not send a representative to the meeting.

### **California Radiological Society (CRS)**

The California Radiological Society sent a representative to the meeting and provided an opinion in favor of the use of PET.

### **Alzheimer's Association**

The Alzheimer's Association provided a statement in support of the use of PET under specific circumstances.

## CONCLUSION

There is no effective treatment to cure or prevent AD. Current treatment with cholinesterase inhibitors and other drugs provide modest benefits for some patients who usually eventually progress to end-stage disease. Recently, memantine, an NMDA receptor antagonist was found to be effective in reducing clinical deterioration in patients with moderate to severe AD (Reisberg *et al*, 2003). In the near future, patients may be treated with a combination of therapies that aim to ameliorate their symptoms, improve their function and slow or reverse the course of their disease. It is imperative that we make progress in the early detection of dementia if patients are to fully benefit from these therapeutic advances.

There is no question that early dementia usually goes unrecognized. One author puts the estimate of unrecognized dementia in the U.S. at 1.8 million cases (Doraiswamy, 1998). But there is no convincing evidence to date that PET can significantly help to address this gap. Studies to date demonstrate a high sensitivity of PET in AD somewhat at the expense of specificity. For example, in one of the largest studies to date of PET in the evaluation of dementia, PET studies in 146 patients presenting with cognitive symptoms of dementia were sensitive indicators of the presence of Alzheimer's disease and of neurodegenerative disease in general (Silverman *et al*, 2001). These investigators found that when compared with pathologically confirmed diagnoses, PET correctly identified the presence or absence of AD in 88% (95% CI, 82%-93%) of the cases with a sensitivity of 94% (91/97; 95% CI; 89%-99%) and a specificity of 73% (30/41; 95% CI, 60%-87%). A negative PET scan indicated that pathologic progression of cognitive impairment was unlikely to occur over the next three years.

As impressive as these results appear, the clinical application of PET scanning remains to be determined. The critical question that remains unanswered by this and the other studies of PET in the evaluation of AD/dementia is: To what extent does PET improve diagnostic accuracy beyond what can be obtained with a thorough clinical evaluation? Given that the sensitivity of clinical criteria are reported to be about 80%-90% (Knopman *et al* 2001), it is difficult for any diagnostic test to significantly improve diagnostic accuracy. And given the fact that treatment of the most common non-AD dementias (e.g. Dementia of Lewy Bodies or vascular dementias) with cholinesterase inhibitor drugs is not likely to be harmful and in fact may be beneficial to these patients (Silverman and Small, 2002), it may be that an empirical approach of ruling out reversible causes of dementia and treating all others with cholinesterase inhibitor drugs is appropriate and cost effective. In fact, a recently published cost-effectiveness analysis of PET in the diagnosis of AD concluded that adding PET to the standard diagnostic regimen at AD clinics would "yield limited, if any, benefits at very high costs" (McMahon *et al*, 2003).

The greatest promise of current and future neuroimaging techniques is likely to be in improving our ability to identify at-risk patients and to offer them treatment before they are significantly affected by AD. Few studies enrolled patients with mild symptoms or MCI so it is unclear what role PET is destined to play in identifying this subgroup of patients most likely to benefit from current and emerging therapies for AD. While Silverman *et al* (2001) report that the

sensitivity and specificity of PET in patients with mild dementia was similar (sensitivity 95%; CI, 89%-100%; specificity 71%; (48%-95%) to those with more advanced disease, the fact that average survival after PET was relatively brief (2.9 years) suggests that these patients were referred into the study because their presentation was atypical; this limits the generalizability of the results presented.

The diagnosis and management of dementia is challenging for clinicians, patients and family members and often requires considerable time and expense. Never before have so many promising avenues of treatment been available, and these agents will push clinicians to make earlier and more accurate diagnoses in patients at risk. Whether treatment of AD will require multiple medications like coronary heart disease, or will yield to a single treatment, remains unclear. What is clear is that while current and emerging neuroimaging techniques offer the promise of earlier and more accurate diagnosis of AD for at-risk and affected persons, more definitive data is needed before any of these technologies can be recommended as part of the evaluation of persons with AD and dementia.

#### **RECOMMENDATION**

It is recommended that Positron Emission for the evaluation of patients with AD and dementia does not meet Blue Shield TA Criteria.

*The California Technology Assessment Forum approved the recommendation as presented.*

February 11, 2004

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