Beta Amyloid Imaging with Positron Emission Tomography (PET) for Evaluation of Suspected Alzheimer’s Disease or Other Causes of Cognitive Decline

Executive Summary

Background
Alzheimer’s disease (AD) is the most common cause of dementia in the U.S., and is responsible for a considerable and increasing burden of morbidity and mortality. Currently an estimated 5.3 million individuals in the U.S. suffer from AD; this prevalence is expected to increase to 11–16 million by 2050. The most recent classification of AD in clinical settings includes “Possible AD dementia” or “Probable AD dementia.” The category of “Pathophysiologically proved AD dementia” requires neuropathologic examination documenting the presence of extracellular beta amyloid plaques and neurofibrillary tangles in the cerebral cortex. Probable and possible AD are primarily clinical diagnoses. An estimated 10% to 20% of individuals diagnosed with clinical AD do not meet the histopathologic criteria for AD on autopsy, which is the reference standard, and thus the clinical diagnosis was incorrect. The presence of beta amyloid deposition in the brain is a necessary but not sufficient condition for AD. Conversely, the absence of beta amyloid deposition rules out AD at that time. The precise role of beta amyloid in AD initiation and progression has long been a subject for research and debate and continues to be so. Treatment with cholinesterase inhibitors or memantine for people with mild to severe dementia due to AD produces statistically significant, but clinically marginal, improvement at 6 months and 1 year in measures of cognitive function when compared to placebo, despite higher rates of study discontinuation and adverse effects. These medications may also be used in patients with other types of dementia.

Objective
To determine whether evaluating patients with suspected Alzheimer’s disease (AD) or other causes of cognitive decline using beta amyloid imaging by positron emission tomography (PET) results in improved health outcomes compared to no testing.

Search Strategy
A MEDLINE® (via PubMed) literature search using the term “florbetapir” performed in January 2013 identified 55 publications. EMBASE was also searched. Bibliographies of included studies were examined for additional citations. Selective searches were conducted for the background sections of the report on, for example, treatments for AD.

Selection Criteria
- Use of florbetapir F18 with PET imaging to detect beta amyloid deposition in the human brain.
- Other beta amyloid radiotracers were not included because they are not approved by the U.S. Food and Drug Administration (FDA) (e.g., 18F-florbetaben, 11F-flutemetamol).
- Study populations include subjects with possible or probable AD, mild cognitive impairment (MCI), or other cognitive decline.
- Reference standard is clinical diagnosis and/or postmortem histopathologic findings.

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Main Results
Evidence on technical performance is mainly from a study by Clark et al. submitted for FDA approval. This was a Phase III multicenter trial with an autopsy cohort (n=29) and a young, cognitively intact cohort (n=47). The autopsy cohort included 9 subjects (31%) who were not cognitively impaired, 2 (7%) who were mildly impaired, 15 (45%) with a clinical diagnosis of AD, and 5 (17%) with a clinical diagnosis of a non-AD dementia. Histopathologic amyloid burden was assessed in all patients, with 52% meeting pathologic criteria for AD. A significant correlation of 0.78 was found between amyloid burden in the brain measured by florbetapir F18 and histopathology. Of 15 subjects who met pathologic criteria for AD, 14 had positive florbetapir scans (sensitivity of 93%). In the specificity cohort to evaluate false positives, the primary endpoint was the exclusion of amyloid in 47 young subjects who were negative for the apolipoprotein E ε4 (APOE4) allele, randomly interspersed with PET scans of 40 subjects in the autopsy cohort. The study achieved specificity of 100% in this cohort, although the young controls who formed a majority of the specificity cohort are outside of the intended use population.

Reproducibility of the readings was assessed by 3 trained readers blinded to the clinical information. Using a binary scale (positive or negative for amyloid), sensitivity ranged from 55% to 90% for the 3 readers. Subsequent reanalysis for publication used the majority rating of 3 nuclear medicine physicians as the primary outcome variable, resulting in 96% agreement between florbetapir-PET images and histopathologic results in the 29 subjects in the primary analysis cohort.

A strength of this study is the comparison of florbetapir F18 imaging with the reference standard of post-mortem histopathology. Limitations include the small sample size, a majority rating for assessing diagnostic accuracy, and only 2 patients in the mildly impaired category, which is the population in whom the test is most likely to be used. There is evidence for inter-observer variability in reading the test; using a majority of 2/3 readers leads to a high agreement with histopathology. Further high-quality studies from patient populations representing those presenting in clinical care are needed to better define the diagnostic performance of this test.

A small independent study (Avid Radiopharmaceuticals only provided the Amyvid) reported the diagnostic performance of florbetapir F18 PET in a clinical setting. Included were 15 subjects with AD, 12 with MCI, and 21 older unimpaired controls. Agreement in visual analysis between the 2 readers had a kappa value of 0.71. Comparing visual assessment with the initial clinical diagnosis, 11 of 13 AD patients (85%), 6 subjects with MCI (50%) and 13 of 21 control subjects (60%) had positive scans, resulting in a sensitivity of 84.6% and a specificity of 38.1% for discriminating AD patients from control subjects. Although study conclusions are limited by the small number of subjects and the use of clinical diagnosis as a reference standard, these results suggest a high number of false positives with visual image assessment. In addition, quantitative analysis could not differentiate subjects with MCI from unimpaired controls.

There is no direct evidence for clinical utility of beta amyloid imaging. Additional research is needed on the sensitivity and specificity of beta amyloid testing. It is not possible to link an indirect chain with existing evidence to convincingly argue health outcomes are improved. Furthermore several factors make it difficult to ascertain the potential net benefit associated with use of florbetapir F18 PET:

- The limited effectiveness of pharmacologic treatments for AD, as well as for other types of dementia that may be difficult to distinguish from AD
- Pharmacologic treatment efficacy has been demonstrated in patients with clinically diagnosed AD, which may or may not be equivalent to patients with positive florbetapir F18 results.
- The generally modest adverse effects of medications used for AD, with some evidence of effectiveness in non-AD dementia, so that these medications are used widely in patients with dementia
- The coexistence of AD with other types of dementia
Author’s Conclusions and Comment

In general, evidence of a health benefit or clinical utility from testing requires demonstration of:

- incremental improvement in diagnostic or prognostic accuracy over current practice and
- that incremental improvements lead to improved health outcomes (e.g., by informing clinical management decisions), and
- that these outcomes may be obtained (i.e., are generalizable) outside of the investigational setting.

The use of florbetapir F18 PET in individuals with suspected AD, other causes of dementia, or cognitive decline does meet any of these criteria. Studies have shown that florbetapir F18 PET results correlate with histopathologic findings at autopsy. This finding is important. Studies have also suggested that florbetapir F18 PET has some ability to differentiate between cognitively normal adults and patients with AD. However, the studies are limited by small sample sizes, differences in determining outcomes (e.g., qualitative versus quantitative, unknown impact of training for physicians inexperienced with this modality), and the lack of evidence obtained from populations encountered in clinical practice. No information is available on the impact of this test on clinical outcomes, and few data are available on whether it can accurately identify patients with MCI who will develop AD.

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) made the following judgments about whether beta amyloid imaging with positron emission tomography (PET) meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria to evaluate suspected Alzheimer’s disease (AD) and other causes of cognitive decline.

1. The technology must have final approval from the appropriate governmental regulatory bodies.

In 2012, the U.S. Food and Drug Administration (FDA) approved the use of one beta amyloid radioactive diagnostic agent, florbetapir F18 (Amyvid™, Avid Radiopharmaceuticals, Inc., a subsidiary of Eli Lilly), for use with PET. Florbetapir F18 is indicated to estimate beta-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer’s disease and other causes of cognitive decline, as an adjunct to other diagnostic evaluations.

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

The available evidence is insufficient to permit conclusions concerning the impact of beta amyloid PET imaging with florbetapir F18 on health outcomes. The evidence to date focuses solely on the correlation between the results of beta amyloid PET imaging and other indicators of cognitive decline, clinical diagnoses, and histopathologic results. Studies are needed to define the accuracy of beta amyloid imaging according to age (since beta amyloid deposition increases with age in cognitively normal individuals). Further evidence is also needed on the link between the test results and improving health outcomes.

3. The technology must improve the net health outcome.

Because evidence is insufficient to permit conclusions on the effect of beta amyloid PET imaging on health outcomes, any improvement cannot be established.

4. The technology must be as beneficial as any established alternatives.

Comparative benefit cannot be established lacking sufficient evidence.
5. The improvement must be attainable outside the investigational setting.

Improved health outcomes following beta amyloid PET imaging have not been demonstrated in the investigational setting.

Based on the above, beta amyloid imaging with positron emission tomography (PET) to evaluate suspected Alzheimer’s disease (AD) and other causes of cognitive decline does not meet the TEC criteria.
Assessment Objective

The objective of this Assessment is to determine whether evaluating patients with suspected Alzheimer’s disease (AD) or other causes of cognitive decline using beta amyloid imaging by positron emission tomography (PET) results in improved health outcomes compared to no testing. The test may also be used in patients with mild cognitive impairment (MCI), which is an AD precursor in some patients. Beta-amyloid plaques found in the cerebral cortex, as well as neurofibrillary tangles, characterize AD pathologically. Pharmacologic treatments are available, but their effectiveness is limited to small improvements and delaying symptomatic decline for some patients; they do not alter disease progression. Diagnostic tests used to identify other potentially treatable forms of dementia with better prognoses (e.g., vitamin B12 deficiency) are likely to precede beta amyloid PET imaging.

Background

Alzheimer’s Disease. AD is the most common cause of dementia in the U.S., and is responsible for a considerable and increasing burden of morbidity and mortality. Currently, an estimated 5.3 million individuals in the U.S. suffer from AD; this prevalence is expected to increase to 11–16 million by 2050. It is the sixth leading cause of death in the U.S. Mortality from AD is increasing rapidly—between years 2000 and 2006, the number of deaths attributable to AD rose 47% (Anonymous 2009). It is also associated with multiple medical and psychiatric morbidities, caregiver burden, and need for long-term care. These factors lead to a marked decrease in quality of life for afflicted patients and their caregivers.

The primary risk factor for AD is age. The disease is rare before the age of 65 and has an estimated annual incidence of 0.6% in patients aged 65 to 69. Incidence rises rapidly with increasing age over 65. Genetic factors and family history play a smaller role, except for a small group of individuals with early onset familial AD (less than 5% of AD patients). Having a first-degree relative with sporadic AD (i.e., nonfamilial) increases the risk of developing disease by 10% to 50%. Other concomitant medical diseases, particularly atherosclerotic disorders, appear to hasten the onset and progression of AD.

A typical clinical course is defined as an insidious onset with inexorable progression over the course of years, from mild cognitive deficits early in the course of disease to advanced dementia and complete functional dependence late in the course of disease.

Diagnosis of AD. The most recent classification of AD in clinical settings includes “Possible AD dementia” or “Probable AD dementia.” The category of “Pathophysiologically proved AD dementia” requires neuropathologic examination documenting the presence of extracellular beta amyloid plaques and neurofibrillary tangles in the cerebral cortex (McKhann et al. 2011). Probable and possible AD are primarily clinical diagnoses (Hyman et al. 2012). An estimated 10% to 20% of individuals diagnosed with clinical AD do not meet the histopathologic criteria for AD on autopsy, and thus the clinical diagnosis was incorrect.

Criteria for diagnosis of probable AD were recently updated by the National Institute on Aging and the Alzheimer’s Association (NIA-AA) (McKhann et al. 2011). These criteria require evidence of a specific pattern of cognitive impairment, a typical clinical course, and exclusion of other potential etiologies, as follows:

- Cognitive impairment
  - Cognitive impairment established by history from patient and a knowledgeable informant, plus objective assessment by bedside mental status examination or neuropsychological testing
  - Cognitive impairment involving a minimum of two of the following domains:
    - Impaired ability to acquire and remember new information
    - Impaired reasoning and handling of complex tasks, poor judgment
    - Impaired visuospatial abilities
    - Impaired language functions
    - Changes in personality, behavior, or comportment
  - Initial and most prominent cognitive deficits are one of the following:
    - Amnestic presentation
    - Nonamnestic presentations, either a language presentation with prominent word-finding deficits; a visuospatial presentation with visual cognitive defects; or a dysexecutive presentation with prominent impairment of reasoning, judgment, and/or problem solving
Mild cognitive impairment (MCI) typically precedes dementia due to AD. MCI may be diagnosed when there is a change in cognition, but not sufficient impairment for the diagnosis of dementia (Albert et al. 2011). Features of MCI include impairment in one or more cognitive domains, and preserved functional independence. Patients with MCI may undergo testing (e.g., neuroimaging, laboratory studies, and neuropsychological assessment) to identify vascular, traumatic, and medical causes of cognitive decline and to evaluate genetic factors. While laboratory tests such as vitamin B12 and thyroid-stimulating hormone are performed to identify potentially reversible or contributory causes of dementia, elevated levels of plasma apoE and apoE4 may have some predictive value in AD, as do some biochemical markers in cerebrospinal fluid such as tau protein and beta amyloid protein. However, these markers are not part of the standard evaluation of patients suspected to have AD, and their role in clinical care has not been established. Similarly, genetic testing for apoE may have limited predictive value for the diagnosis of AD, but it is not considered useful in the diagnosis of AD for most patients. Recently revised NIA-AA diagnostic guidelines for AD discuss the use of biomarkers in patients with MCI to establish the etiology of cognitive impairment, increasing or decreasing the probability that AD is responsible. However, general clinical use is currently not recommended (McKhann et al. 2011). These guidelines were developed before the FDA approval of florbetapir F18.

Standard neuroimaging lacks sensitivity and specificity to identify the cerebral accompaniments of AD (Knopman et al. 2001). However, computed tomography or magnetic resonance imaging (MRI) is generally performed in the workup of suspected AD to identify cerebrovascular disease, structural abnormalities (e.g., tumor, subdural hematoma), or normal pressure hydrocephalus. In patients with AD, imaging typically reveals nonspecific abnormalities including atrophy (loss of hippocampal volume) and white matter lesions. Functional MRI or PET scanning reveals distinct areas of hypoperfusion and low metabolism in the hippocampus, parietal lobes, and lateral parietotemporal cortex. However, MRI and PET testing is rarely indicated and not part of diagnostic criteria.

Clinical course

- Insidious onset
- Clear-cut history of worsening over time
- Interference with ability to function at work or usual activities
- Decline from previous level of functioning and performing

Exclusion of other disorders

- Cognitive decline not explained by delirium or major psychiatric disorder
- No evidence of other active neurologic disease, including substantial cerebrovascular disease or dementia with Lewy bodies
- Lack of prominent features of variant frontotemporal dementia or primary progressive aphasia
- No medication use with substantial effects on cognition

A diagnosis of possible AD dementia is made when the patient meets most of the AD criteria, but has an atypical course or an etiologically mixed presentation (McKhann et al. 1984). This may consist of an atypical (e.g., sudden) onset or atypical progression. A diagnosis of possible AD is also made when there is another potentially causative systemic or neurologic disorder that is not thought to be the primary etiology of dementia. AD and other causes of dementia often occur concurrently, e.g., cerebrovascular disease, dementia with Lewy bodies. In a study of 141 consecutive deceased and autopsied community-dwelling older adults from the Rush Memory and Aging Project, 59 had a clinical diagnosis of probable AD; 8, possible AD; and 5, dementia from other causes (Schneider et al. 2007). Neuropathologic diagnoses were: 19 AD and infarcts, 15 pure AD, 6 vascular dementia, 6 AD with Parkinson’s disease/Lewy body disease, and 4 other diagnoses. Over 50% of these individuals had multiple diagnoses. Among those without a premortem dementia diagnosis, the following neuropathologic diagnoses were determined: 26 had no chronic diagnostic abnormalities, 22 had pure AD, and 16 had infarctions; the remainder had other diagnoses, including 16 with AD and another diagnosis. Over 80% of individuals without a clinical diagnosis of dementia had one or no neuropathologic diagnosis. After accounting for age, individuals with multiple pathological diagnoses were more likely (OR=2.8; 95% CI: 1.2, 6.7) to have been diagnosed clinically with dementia compared to those with a single pathologic diagnosis.
Beta Amyloid Imaging with PET for Evaluation of Suspected AD or Other Causes of Cognitive Decline

Beta Amyloid and AD. The accumulation of beta amyloid in the brain is a necessary but not sufficient condition for a diagnosis of definitive AD; the presence of neurofibrillary tangles, composed primarily of tau protein, is also required. In 1906, Alois Alzheimer first described extracellular plaques composed primarily of beta amyloid (Teich and Arancio 2012). All genetic mutations associated with AD involve the amyloid precursor protein (APP) or subsequent APP processing. The “amyloid hypothesis” (also called the “amyloid cascade hypothesis”) posits that beta amyloid deposition is a central event in the etiology of AD, with beta amyloid deposition leading to tau pathology and cell death. Understanding of beta amyloid has progressed, including the recognition that soluble beta amyloid is neurotoxic and may play a role in disease development and progression. Soluble Aβ can be found in blood plasma, cerebrospinal fluid, and in the intracellular and extracellular spaces. Certain forms of Aβ are also thought to be more toxic (e.g., Aβ1-42 peptide). Florbetapir F18 PET does not detect soluble Aβ.

The precise role of beta amyloid accumulation in the initiation and progression of AD is an area of active research (for reviews, see Di Carlo M et al. 2012; Honjo et al. 2012; Teich & Arancio 2012; Murphy & LeVine 2010; Skaper 2012; Tam & Pasternak 2012). Among factors that may challenge the beta amyloid hypothesis are the following:

- Clinical trials to date of pharmaceuticals targeting beta amyloid have failed.
- Many cognitively normal adults also have beta amyloid plaques on the brain, particularly as they age.
- Beta amyloid plaques do not correlate strongly with disease progression or cognitive function, particularly later in the disease course.

Several studies have failed to detect an association between amyloid burden in cognitively intact individuals and memory impairment or clinical symptoms (Jack et al. 2008; Jack et al. 2009; Mormino et al. 2009), while others have observed such an association (Pike et al. 2007; Villemagne et al. 2008; Hedden et al. 2009; Kennedy et al. 2012). A number of studies suggest beta amyloid deposition, hippocampal atrophy (observed by MRI), and memory and cognitive decline occur sequentially in the elderly, with beta amyloid deposition being just the first event in this sequence, with possibly minimal impact on cognitive decline (Aizenstein et al. 2008; Jack et al. 2008; Villemagne et al. 2008; Jack et al. 2009; Mormino et al. 2009; Mormino et al. 2009; Rodrigue et al. 2009; Rowe et al. 2010; Pike et al. 2011; Quigley et al. 2011).

Hypotheses concerning the causes and mechanisms of AD initiation and development continue to be proposed and explored (see, for example, Honjo et al. 2012, Skaper 2012).

Treatment of AD. There is neither a cure for AD nor a means of reversing its pathologic processes. At best, the available medications may slow the clinical decline, thereby reducing the rate at which symptoms worsen (Farlow and Cummings 2007; Sadowsky and Galvin 2012). The potential impact of earlier diagnosis and treatment in patients with uncertain AD is accompanied by considerable uncertainty.

There are currently five drugs approved by the U.S. Food and Drug Administration (FDA) to treat the cognitive symptoms of AD. Four of the approved drugs, donepezil (Aricept®), galantamine (Razadyne®), rivastigmine (Exelon®), and tacrine (Cognex®), are cholinesterase inhibitors. They function by blocking the activity of the enzyme acetylcholinesterase and may help compensate for the loss of functioning brain cells due to AD. Donepezil is the only cholinesterase inhibitor approved for all stages of AD (mild, moderate, severe); the other three are approved for mild to moderate disease. The first of the approved cholinesterase inhibitors, tacrine, is rarely used today due to its associated adverse effects, including possible liver damage (Seltzer 2006). The fifth FDA-approved drug, memantine (Namenda), a N-methyl-D-aspartate (NMDA) antagonist, is approved for moderate to severe AD. Memantine has not been approved for mild AD.

The efficacy and safety of cholinesterase inhibitors and memantine for the treatment of AD has been examined in numerous reviews and meta-analyses of randomized clinical trials and open-label studies. Efficacy results have been generally consistent across this evidence, concluding that treatment with cholinesterase inhibitors or memantine, for people with mild to severe dementia due to AD, produced statistically significant, but clinically marginal improvement at 6 months and 1 year in measures of cognitive function when compared to placebo, despite higher rates of study discontinuation and adverse effects (Dooley...
Because their underlying mechanisms differ, memantine can be combined with a cholinesterase inhibitor. Reviews examining the impact of combination therapy with memantine and donepezil have reported that such treatment improved cognitive outcomes more than donepezil plus placebo in patients with moderate to severe AD (McKeage 2009; Riverol et al. 2011). A recent systematic review by Farrimond et al. (Farrimond et al. 2012) suggests a small, but significant benefit of memantine combination therapy on cognitive measures. In contrast, the findings of another report found no evidence of additional benefit of combination therapy (Bond et al. 2012). Other treatments for AD are largely supportive.

Several Phase III trials have evaluated the use of pharmaceuticals that target beta amyloid, such as bapineuzumab and solanezumab without demonstrable clinical improvement (Callaway 2012). Some researchers hypothesize that such treatments need to be started in patients earlier in the disease process, before beta amyloid deposits have damaged the brain beyond repair. They hypothesize that administration earlier in the disease would be more effective and that beta amyloid PET imaging might be used to assess whether the agents are effective. Although this is a commonly expressed argument, both the role of beta amyloid accumulation in the initiation and progression of AD and the impact of these pharmaceuticals on disease progression remain topics for research.

Other treatments for AD are largely supportive. Behavioral disturbances including delusions or hallucinations and concomitant depression are common in AD. These often require treatment with pharmacologic and nonpharmacologic measures and sometimes referral to a specialist. As dementia becomes more advanced, safety issues such as driving and the ability to handle financial matters become increasingly important. The capacity to live independently is often lost, and placement with other family members or in a nursing facility needs to be considered.

Nonpharmacologic interventions are sometimes used for patients with AD dementia—e.g., exercise, music, psychotherapy, reminiscence therapy, and stimulation-oriented interventions such as exercise or dance. Guidance on proper sleep hygiene, occupational therapy, and environmental modification may also be helpful.
Beta-amyloid Imaging. The purpose of beta amyloid PET imaging is to detect the presence of beta amyloid plaques in the brain, concentrated in certain areas such as the cortex. Beta amyloid refers to the radiotracer to be used in PET imaging, as an alternative to FDG ([F-18]-2-fluoro-2-deoxy-D-glucose) or other commonly used radiotracers. A number of radiotracers have been developed and have or are being tested to detect the accumulation of beta amyloid. Florbetapir (Amyvid), a fluorine-18 (¹⁸F) tracer, is the only one approved by the FDA (in April 2012), and it is intended for use in adults being evaluated for AD or other cognitive decline. (See Appendix A for practice guidelines and position statements on its use.) Florbetapir F18 binds to amyloid aggregates in the brain, and the florbetapir F18 PET image is used to estimate the density of β-amyloid neuritic plaque (Yang et al. 2012).

Another beta amyloid radiotracer called Pittsburgh compound B (PiB), a carbon-11-labeled tracer, has been used in AD research since 2002. Studies in AD have reported high (90% or greater) PiB sensitivity, in a pattern similar to the distribution of beta amyloid plaques found at autopsy (Ikonomovic et al. 2008; Rowe et al. 2010). Patients with MCI and positive PiB scans (beta amyloid deposition) have a high risk of progressing to AD dementia; whereas, MCI patients with negative PiB scans rarely develop dementia (Forsberg et al. 2008; Okello et al. 2009; Jack et al. 2010). Access to PiB is limited because the isotope’s very short, 20-minute half-life restricts use to centers able to produce it on-site, and it is not FDA approved.

Fluorine-18 has a longer half-life of about 110 minutes, making F18-labeled amyloid tracers, such as florbetapir F18, more viable options for commercial distribution to other PET scanning facilities. There are a number of F18 amyloid tracers besides florbetapir F18 being tested in clinical trials. Those currently in contention for FDA approval include FDDNP, flutemetamol, florbetaben, and AZD4694. For additional details on these other radiotracers, see Appendix B.

Generally, the data on PiB and F18-labeled beta amyloid-targeted PET tracers provide evidence of preliminary information on their capacity for in vivo detection of beta amyloid plaques. The prognostic potential of beta amyloid PET tracers to predict AD in MCI patients or other cohorts remains to be established.

A recently published study (Fleisher et al. 2012a) reported florbetapir F18 PET results among 50 members of a Colombian family with familial AD. These individuals have a 100% probability of developing AD if they carry the PSEN1 E280A mutation, usually at an earlier age than other AD patients, and 0% of developing the familial form otherwise. Results were compared among 11 symptomatic individuals, 19 presymptomatic mutation carriers, and 20 asymptomatic noncarriers who ranged in age from 26 to 50 years. Age-matched carriers demonstrated greater beta amyloid deposition than noncarriers. Fibrillar beta amyloid began to accumulate in carriers about 16 years before the predicted median age at MCI and 21 years before the onset of dementia. It is not known whether this pattern would be seen in other types of AD patients. Beta amyloid PET imaging could have different utility in individuals at risk for familial AD.

Beta Amyloid Deposition in the Brains of Cognitively Normal Individuals. While beta amyloid deposition in the brain is considered a marker of AD, its presence is not exclusive to AD patients. There is no true baseline estimate of amyloid positivity in the general population because there is no clinical reason for amyloid testing in cognitively normal individuals. Available data are based primarily on highly selected convenience samples of normal controls participating in AD studies (Laforce Jr and Rabinovici 2011). Estimates vary in the literature, but PET scans have shown that between 10% and 50% of cognitively normal controls have elevated beta amyloid (Pike et al. 2007; Aizenstein et al. 2008; Hedden et al. 2009; Rodrigue et al. 2009; Rowe et al. 2010; Sojkova et al. 2011). This range is consistent with rates of amyloid pathology observed in autopsy studies of normal aging (Dickson et al. 1992; Knopman et al. 2005; Aizenstein et al. 2008; Wolk and Klunk 2009). From a diagnostic perspective, increased brain beta amyloid is a necessary but not sufficient condition for a diagnosis of AD. The absence of beta amyloid deposition in the brain excludes AD at that time.

The significance of a positive amyloid scan in a cognitively normal individual is not clear. One hypothesis is that the pathologic process of AD may operate for a number of years before
clinical symptoms become evident. Therefore, it is believed that amyloid-positive normal control patients are in a preclinical phase of AD, and as time passes these individuals will begin to display cognitive decline associated with the disease (Sperling et al. 2011). A longitudinal study of this hypothesis by Morris et al. (2009) reported that 25 of 159 participants with a Clinical Dementia Rating (CDR) of zero at baseline progressed to a CDR of 0.5 (very mild dementia) at follow-up (0.8 to 5.5 years), and that 9 of those 25 were subsequently diagnosed with very mild dementia of the Alzheimer type. They also found higher levels of PiB binding and older age predicted progression from cognitive normality to mild AD.

While the process of progression from amyloid-positivity in cognitively normal individuals to AD remains unclear, there are several factors that have been identified as major predictors of amyloid deposition in normal controls, including increasing age (Pike et al. 2007; Aizenstein et al. 2008; Jack et al. 2009; Sojkova et al. 2011; Rodrigue et al. 2012), the presence of the ApoE4 allele (Reiman et al. 2009; Mosconi et al. 2010; Rowe et al. 2010), a family history of AD (Mosconi et al. 2010), and decreased subjective cognition (Perrotin et al. 2012). An examination of amyloid deposition across regions of the brain showed linear increases with age, with the greatest age-related increase being in the precuneus, an area involved with episodic memory, visuospatial processing, and reflections upon self (Pike et al. 2007; Rodrigue et al. 2012). In addition, individuals with higher initial amyloid burden tend to have greater deposition with age, providing evidence for differential rates of amyloid deposition (Sojkova et al. 2011). These findings suggest that beta amyloid slowly accumulates over an asymptomatic stage as individuals age, but the rapidity of the increase remains undetermined (Aizenstein et al. 2008; Jack et al. 2009).

Types of Dementia without Beta Amyloid Deposition. As mentioned above, a negative beta amyloid scan (i.e., the absence of beta amyloid deposition) in a person with dementia excludes AD at that time. Such a patient may have one of several other types of dementia, as listed in Table 1. As noted in the treatment column, the same pharmaceuticals currently used to treat AD may be prescribed for other types of dementia, based on varying strength of evidence (see also Table 1). Patients may also have more than one type of dementia concurrently, which makes the diagnostic task more difficult.

**FDA Status.** In 2012, the FDA approved florbetapir F18 (Amyvid™, Avid Radiopharmaceuticals, Inc., a subsidiary of Eli Lilly) as a radioactive diagnostic agent for visualization of amyloid plaque in the brain. The FDA document prepared for the advisory committee meeting indicated that while florbetapir F18 may detect pathology, there could be no claim of disease detection, since beta amyloid aggregates can be found in cognitively normal elderly individuals, as well as in patients with AD (U.S. Food and Drug Administration 2011). The label indicates that “the safety and effectiveness of Amyvid have not been established for:

- Predicting development of dementia or other neurologic condition;
- Monitoring responses to therapy.”

Furthermore, the label indicates that Amyvid is an adjunct to other diagnostic evaluations.

Amyvid™ is indicated “for PET [positron emission tomography] imaging of the brain to estimate beta-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer’s disease and other causes of cognitive decline.”

The FDA also required two postmarketing studies, to be completed by November or December 2014:

**1887-1:** To conduct a clinical study that will compare the results of Amyvid scan interpretations at local clinical sites to interpretations performed by an expert(s) at a central reading facility. The main objectives of this study are to assess the impact of different reader training methods on the reliability of Amyvid scan interpretations as they are performed in clinical practice and to help determine the performance of the reader training processes as compared to the experts at the central reading facility.

**1887-2:** To conduct a clinical study that will explore the use of standard uptake value ratio (SUVR) and/or other quantitative outcomes as an alternative or an adjunct to qualitative Amyvid scan interpretations. The main objective of this study is to assess the feasibility of implementing a quantitative process for Amyvid scan interpretation by clinical sites, and to measure the resulting reliability of scan interpretations.
Table 1. Causes and Treatment of Dementia without Beta Amyloid Deposition

<table>
<thead>
<tr>
<th>Dementias</th>
<th>Description</th>
<th>Incidence &amp; Detection</th>
<th>Treatment</th>
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<tr>
<td>Frontotemporal Dementia (FTD)</td>
<td>Group of disorders caused by progressive cell degeneration in the frontal and/or temporal lobes of the brain, causing tissue shrinkage and reduced functioning in areas that control judgment and planning, emotions, speaking and understanding speech, and certain types of movements (Rabinovici and Miller 2010).</td>
<td>FTD accounts for around 10–15% of all dementia cases. May account for 20–50% of dementia cases in people &lt;65 yrs. There are no tests that can conclusively diagnose FTD. MRI can detect shrinkage in the frontal and temporal lobes. Frontotemporal dementia (FTD) is distinguishable from AD because of the lack of beta amyloid plaque formation (Wolk and Klunk 2009; Laforce Jr and Rabinovici 2011).</td>
<td>Focuses on treatment of behavioral and motor symptoms using medications to manipulate serotonergic or dopaminergic neurotransmitter systems. Anticholinesterase inhibitors have been used, but without much benefit and, in some cases, worsening of symptoms (Moretti et al. 2004; Mendez et al. 2007; Kertesz et al. 2008). While open-label studies of memantine for the treatment of FTD have shown some success (Swanberg 2007; Diehl-Schmid et al. 2008; Boxer et al. 2009), a Phase III placebo-controlled study presented at the 2012 Alzheimer’s Association International Conference (AAIC) by Boxer et al. (Boxer et al. 2012) showed that memantine treatment was associated with greater functional and cognitive decline in frontotemporal dementia.</td>
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<tr>
<td>Dementia with Lewy Bodies (DLB)</td>
<td>Caused by abnormal aggregation of the synaptic protein alpha-synuclein. Similar clinical and pathological characteristics of the dementia associated with Parkinson’s Disease. Characterized by confusion, changes in thinking and reasoning, visual hallucinations, REM sleep disorder, memory loss, Parkinson’s-type symptoms such as balance problems, muscle rigidity (McKeith et al. 2004; Ferman and Boeve 2007; Graff-Radford et al. 2012).</td>
<td>Lewy bodies found in about 20–35% of dementia cases. Not found in normal brains. Diagnosis is clinical judgment based on symptoms. Confirmed diagnosis only through autopsy. DLB tends to coexist with Alzheimer’s disease (AD) (Schneider et al. 2007).</td>
<td>Treatment with cholinesterase inhibitors is well-tolerated and substantially improves cognitive and neuropsychiatric symptoms (McKeith et al. 2004; Ferman and Boeve 2007; Graff-Radford et al. 2012). Some evidence that cholinesterase inhibitors are more effective in DLB than in AD (Samuel et al. 2000). A recent study reported that patients with DLB who do not have the imaging features of coexistent AD-related pathology are more likely show cognitive improvement with cholinesterase inhibitor treatment (Graff-Radford et al. 2012).</td>
</tr>
<tr>
<td>Dementias</td>
<td>Description</td>
<td>Incidence &amp; Detection</td>
<td>Treatment</td>
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<td>Huntington’s Disease (HD)</td>
<td>A progressive, incurable, brain disorder caused by a defective dominant gene on Chromosome 4 which affects a protein called huntington. Defective huntington leads to brain changes that cause abnormal involuntary movements, a severe decline in thinking and reasoning skills, uncharacteristic anger and irritability, depression (Walker 2007).</td>
<td>Symptoms usually develop between 30 and 50 years of age. Juvenile HD has an onset ≤20 years. A meta-analysis of 62 studies of HD reported a Juvenile HD prevalence of 4.9 percent (Quarrell et al. 2012). A genetic test is available to confirm the cause of symptoms in people suspected of having HD, and also to detect the gene in those who are at risk because a parent has HD (Walker 2007).</td>
<td>Treatment focuses on managing symptoms and includes antipsychotic drugs to control involuntary movements and selective serotonin reuptake inhibitors for mood changes and for obsessive-compulsive symptoms. Tetrabenazine is an FDA-approved drug specifically for chorea, the uncontrolled movements associated with HD (Huntington Study Group 2006). Cholinesterase inhibitors, galantamine and rivastigmine, have resulted in improvement of symptoms (Petrikis et al. 2004; de Tommaso et al. 2007).</td>
</tr>
<tr>
<td>Normal Pressure Hydrocephalus (NPH)</td>
<td>Excess cerebrospinal fluid (CFS) accumulates in the brain ventricles causing enlargement, which can disrupt and damage nearby brain tissue. Decline in thinking skills, impaired planning and decision-making, reduced concentration, and changes in personality and behavior.</td>
<td>Primarily affects people in the 60s &amp; 70s. No single test to confirm diagnosis. MRI plays key role in diagnosis. Unlike AD, which results in brain shrinkage, making the ventricles look larger, in NPH the ventricles are enlarged, but brain tissue may not be shrunken.</td>
<td>If symptoms and MRI suggest NPH, a large-volume spinal tap may identify those who would benefit from a shunt to drain excess CFS. Shunting is associated with an approximately 29% rate of significant improvement and a 6% significant complication rate (Hebb and Cusimano 2001). There are no effective nonsurgical treatments for NPH.</td>
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### Table 1. Causes and Treatment of Dementia without Beta Amyloid Deposition (cont’d)

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<td>Vascular Dementia</td>
<td>Typically associated with mild to severe damage due to stroke, which blocks major blood vessels, leading to inadequate blood flow to the brain. Symptoms vary based on severity of blood vessel damage and the part of the brain affected, and include memory loss, confusion, disorientation, trouble speaking or understanding speech, vision loss.</td>
<td>Accounts for 20–30% of dementia cases. Traditionally distinguished from AD as a purely neurodegenerative form of dementia. Recent evidence suggests there is a spectrum, ranging from patients with pure vascular dementia to patients with pure AD and including a large majority of patients with contributions from both pathologies (Viswanathan et al. 2009). Diagnosis of vascular dementia is typically confirmed by neurocognitive testing and MRI for evidence of recent stroke.</td>
<td>No FDA-approved drugs specifically to treat symptoms of vascular dementia. A meta-analysis of randomized controlled trials of cholinesterase inhibitors and memantine reported small benefits in cognition of uncertain clinical significance in patients with mild to moderate vascular dementia (Kavirajan and Schneider 2007).</td>
</tr>
<tr>
<td>Korsakoff Syndrome</td>
<td>Often, but not always, preceded by Wernicke encephalopathy, an acute brain reaction to severe lack of thiamine (vitamin B1). Symptoms include confusion, staggering, lack of coordination, abnormal eye movement, memory lapses, problems learning new information, and possibly confabulation (Kopelman et al. 2009).</td>
<td>Commonly caused by alcoholism, but also associated with AIDS, chronic infection, and poor nutrition. There are no specific tests or brain scan procedures to confirm the disorder. Diagnosis is a clinical judgment based on symptoms.</td>
<td>Extended treatment with thiamine is usual; however, recovery is usually incomplete, suggesting some irreversible damage (Zubaran et al. 1997). Improvements in function have been reported with clonidine and fluvoxamine (Zubaran et al. 1997). Case reports of treatment with cholinesterase inhibitor, donepezil, reported progressive partial cognitive improvement during treatment, some of which continued after treatment discontinuation (Cochrane et al. 2005).</td>
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<td>Creutzfeldt-Jakob Disease (CJD)</td>
<td>A rapidly progressing, incurable disease that occurs when prion protein in the brain folds into abnormal 3-D shape, destroying brain cells. Rapid decline in thinking and reasoning, involuntary movements, confusion, difficulty walking, mood changes. Those with sporadic CJD eventually experience loss of movement and/or speech, and 90% die within one year. Early clinical symptoms of sporadic CJD may overlap with other neurodegenerative diseases like AD and FTD.</td>
<td>Sporadic CJD (no known cause) accounts for 85% cases; on average appears between 60 and 65 yrs. Familial CJD, Gerstmann-Strassler-Scheinker (GSS) syndrome, and fatal familial insomnia (FFI) represent the core phenotypes of genetic prion disease. Genetic prion disease is inherited as an autosomal dominant disorder. PPNP is the only gene known to cause genetic prion disease. The genetic forms represent about 10% of the prion disease cases. Infectious CJD is rare, from external exposure to abnormal prion protein (i.e., mad cow disease). No tests exist to conclusively diagnose sporadic CJD, but rapid decline, EEG or MRI to detect heart and brain changes, and spinal tap to detect certain proteins, may help to diagnose CJD. The P-tau/total tau ratio in CSF has been shown to differentiate CJD patients from AD and FTD (Riemenschneider et al. 2003).</td>
<td>There is no treatment that can slow or stop the brain cell destruction caused by CJD. Treatment is primarily supportive (i.e., pain-killers, muscle-relaxers, antiseizure medication).</td>
</tr>
</tbody>
</table>
Formulation of the Assessment

Patient Indications
- Evaluation for possible or probable Alzheimer's disease, following clinical examination
- Evaluation for cognitive decline

Technologies to be Evaluated and Compared
PET imaging using florbetapir F18, also known as "18F-AV-45 or by its brand name, Amyvid".

Health Outcomes
- Cognition
- Institutionalization
- Quality of life (QOL)
- Function (e.g., Activities of Daily Living and Instrumental Activities of Daily Living)
- Medication side effects
- Diagnostic errors and consequences
- Potential harms of beta amyloid PET (radiation exposure of about 7 mSv).

Specific Assessment Questions
How accurate is florbetapir F18, a beta amyloid radiotracer used with PET imaging, in either
- ruling out AD in patients with suspected Alzheimer's disease or other causes of cognitive decline or
- increasing the probability of a correct diagnosis of AD?

What is the accuracy of florbetapir F18, a beta amyloid radiotracer used with PET imaging, to
- exclude AD in patients with suspected Alzheimer's disease or other causes of cognitive decline or
- increase the probability of a correct diagnosis of AD?

What is the incremental value of florbetapir F18 PET imaging, when added to existing methods such as clinical evaluation, in identifying individuals with MCI who are most likely to progress to AD?

What is the incremental value of florbetapir F18 PET imaging, when added to existing methods such as clinical evaluation, in ruling out AD in individuals with dementia?

Balance Table
The following balance table (Table 2) summarizes the evidence on the potential benefits and harms of pharmacologic treatments for AD and MCI among several groups of patients with cognitive decline.
The usual approach in clinical care when encountering an individual with dementia or cognitive impairment is to perform a clinical evaluation for AD and to assess the patient for reversible causes. The benefits of earlier diagnosis of AD or another type of dementia are limited, because of the lack of effective treatments for AD and for many other types of dementia that fundamentally alter the course of the diseases. As described above, two types of pharmaceuticals have been approved by the FDA for use with AD, but their effects are limited and are only seen in a minority of patients. Furthermore, the clinical trials to test the efficacy of these drugs were performed in patients with a clinical diagnosis of probable or possible AD, not among those with a definitive diagnosis of AD, which can only be assigned at autopsy, nor among patients with a clinical diagnosis of AD and a positive beta amyloid scan. Whether effectiveness of these medications differs in the latter population has not been studied. Furthermore, these medications are used in some other types of dementia, so the potential benefits of “more accurate” prescribing of these medications cannot be ascertained at this point. Therefore, regardless of the accuracy of beta amyloid PET in detecting beta amyloid deposition in the brain, which will be discussed below, how the use of this procedure might affect outcomes is unclear. One can envision a number of promising avenues for research using this test, some of which are underway (e.g., sequential imaging of individuals who may or may not develop AD); but the potential benefits and harms in clinical practice are much less clear, given the current state of knowledge about and treatments for AD. At best, positive beta amyloid imaging results may increase the probability that an individual has AD (with or without concurrent forms of dementia), while negative results may exclude the possibility that the individual has AD at that time. What is less clear is the impact on subsequent decision making, treatments, and clinical outcomes.

Also, beta amyloid PET imaging exposes patients to low doses of radiation, which might be taken into account particularly if the test is repeated several times or if the individual is also undergoing a number of other imaging tests that require the use of radiation (e.g., CT). The issue of radiation exposure through diagnostic imaging is of less concern for older patients, however, given the substantial lag time between exposure and any cancers that might develop as a result.

**Review of Evidence**

**Methodological Issues**

Assessment of a diagnostic technology typically focuses on the following three domains: 1) technical performance; 2) diagnostic performance (sensitivity, specificity, and positive and negative predictive value) in relevant populations of patients, such as those with mild cognitive impairment or suspected AD; and
5) demonstration that the diagnostic information can be used to inform decisions and treatments leading to improved patient outcomes. The reference standard for the diagnosis of AD is post-mortem neuropathologic examination. In the absence of comparisons with the reference standard, long-term clinical follow-up (e.g., conversion from MCI to probable AD) may be used as a surrogate standard to evaluate the diagnostic performance of beta amyloid imaging with PET in MCI.

Literature Review

Technical Performance. Evidence on technical performance of this test should demonstrate that the test measures what it is intended to, i.e., beta amyloid plaque. The best evidence on this would be direct comparison with the reference standard for measuring amyloid plaque, which is histopathologic examination of tissue. Other important measures of technical performance are the reliability of testing, including both test-retest reliability and inter-observer reliability in reading test results.

Interpreting beta amyloid PET images requires different skills than commonly used in nuclear medicine. “For example, the image reader must be proficient in distinguishing white from gray matter, a distinction that may be particularly challenging in patients with cortical atrophy. Unique ‘gray-white contrast’ characteristics of florbetapir F18 images must be recognized as signals of normal or abnormal isotope distribution” (Yang et al. 2012). The images are also intended to be read independently of other information on the patient. As a result of these challenges, the FDA required the developer of florbetapir F18 to create a training program and to assess readers’ performance in clinical practice compared to that of experts at a central facility as part of a postmarketing study.

Two methods are used to interpret PET results. The first is qualitative. Physicians, typically nuclear medicine specialists, review the images, identify particular patterns of enhancement, and make a determination. The outcome is usually binary, i.e., PET positive (beta amyloid deposition) or PET negative (little or no beta amyloid deposition). The second is a quantitative assessment performed by the imaging equipment estimating the amount of radiotracer uptake in each area of the brain. The metric used is called the standardized uptake value (SUV), and SUVs are compared in different parts of the brain to determine whether the pattern is consistent with AD. The resulting statistic for AD, the SUV ratio, usually compares the intensity of the PET signal (i.e., uptake) in the parts of the brain prone to beta amyloid accumulation in AD, such as the cortex, to the cerebellum, where there is little beta amyloid deposition. SUV ratios are often reported in research, but the primary focus has remained on the qualitative evaluation by readers. A challenge in using the SUV is determining and validating the cutoff value, since the SUV is a continuous variable. One of the post-marketing studies required by the FDA is to assess the feasibility and reliability of using a quantitative process for interpreting PET scans using florbetapir F 18.

Wong et al. (2010) reported on the first study of PET using florbetapir F 18 in humans (see Table 3). They compared results between 16 cognitively normal adults older than 50 years to 16 adults with AD. The SUV was 1.25±0.18 for cognitively normal adults and 1.67±0.18 for individuals with AD. Two of the cognitively normal individuals who were older than 80 years old had positive scans (i.e., indication of beta amyloid deposition), while two others had borderline results.

Data on technical performance of the test was included in the study submitted to the FDA (Clark et al. 2011; U.S. Food and Drug Administration 2011) (see Table 5 for an evidence table summarizing all study results). The study was a Phase III multicenter trial with two separate cohorts: an autopsy cohort and a young, cognitively intact cohort. The autopsy cohort was drawn from 152 subjects with a projected life expectancy of 6 months or less. Thirty-five individuals died and were autopsied within 12 months of PET imaging; 29 were included in the primary analysis. This cohort was composed of 9 subjects (51%) who were not cognitively impaired, 2 (7%) who were mildly impaired, 15 (45%) with a clinical diagnosis of AD, and 5 (17%) with a clinical diagnosis of a non-AD dementia.

All patients had direct measurement of amyloid burden by histopathologic examination, and 52% met the pathologic criteria for AD. A significant correlation of 0.78 was found between amyloid burden in the brain measured by florbetapir F18 and histopathology. The correlation between quantitative whole-brain florbetapir image scores and post-mortem silver stain was 0.71. In the young controls (specificity cohort
### Table 3. Florbetapir F18 PET Imaging Evidence Table

<table>
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<tr>
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<tr>
<td><strong>Technical Performance</strong></td>
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</tr>
<tr>
<td>Wong et al. 2010</td>
<td>16 HC &gt;50 yrs&lt;br&gt;16 AD&lt;br&gt;(funded in part by Avid; some authors are Avid employees)&lt;br&gt;Drop-out=6&lt;br&gt;(1 withdrew consent; 5 technical failures)</td>
<td>None</td>
<td>None</td>
<td>SUVR</td>
<td>1.25±0.18 HC&lt;br&gt;1.67±0.18 AD</td>
<td>First study in humans&lt;br&gt;2 HCs &gt;80 yrs old had positive scans; 2 other HCs &gt;80 yrs old had borderline uptake</td>
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<tr>
<td><strong>Technical and Diagnostic Performance</strong></td>
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<tr>
<td>Clark et al. 2011, 2012</td>
<td>152 subjects had PET scan&lt;br&gt;Drop-out=14; 5 due to poor quality scans, consent withdrawn for 9</td>
<td>Autopsy results (12 to 24 months after beta amyloid PET) for “moderate or frequent neuritic plaques,” i.e., positive for beta amyloid.&lt;br&gt;Autopsy results for 59 subjects: 15 No AD&lt;br&gt;5 possible AD&lt;br&gt;9 probable AD&lt;br&gt;30 definite AD</td>
<td>5 board-certified nuclear medicine physicians masked to clinical and neuropathological data. Result from majority of readers used in calculated sensitivity and specificity.&lt;br&gt;Fleiss’ kappa for all inter-reader comparisons = 0.75 (95% CI: 0.67-0.83)</td>
<td>Readers Sensitivity</td>
<td>92% for beta amyloid&lt;br&gt;100% for beta amyloid</td>
<td>Of 30 subjects with definite AD post-mortem, the % positive beta amyloid scans for the 5 readers was 100%, 100%, 100%, 93%, 73%. Of 9 subjects with probable AD post-mortem, the % positive beta amyloid scans for the 5 readers is 78%, 67%, 67%, 67%, 67%. Of 15 subjects with no AD post-mortem, the % negative beta amyloid scans for the 5 readers was 93%, 93%, 87%, 87%, 80%.</td>
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<tr>
<td>Fleisher et al. 2011 (Fleisher et al. 2011)</td>
<td>82 HC 60 MCI 68 probable AD</td>
<td>None</td>
<td>None</td>
<td>Mean SUVR (SD)</td>
<td>1.05 (0.16) HC 1.17 (0.27) MCI 1.39 (0.24) probable AD (p=2.9 × 10⁻¹⁴)</td>
<td>Of those with positive visual ratings, 76% were APOE carriers and 24% were noncarriers. AD vs. HC 84.6% (55–98) MCI patients significantly older.</td>
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<td>Clinical diagnosis</td>
<td>2 readers blinded to clinical info and SUVRs</td>
<td>SUVR (median, Q1–Q3)</td>
<td>1.05, 1.04–1.08 HC 1.20, 1.16–1.30 AD p=0.0001</td>
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<tr>
<td>Wolk et al. 2012 (Wolk et al. 2012)</td>
<td>14 HC</td>
<td>Compared florbetapir F18 with PiB performed within 28 days</td>
<td>None</td>
<td>SUVR (SD)</td>
<td>Florbetapir F18 1.06 (0.17) HC</td>
<td>Pearson correlation = 0.78 (p&lt;0.0001)</td>
</tr>
<tr>
<td>(some authors Avid employees; funded by Pennsylvania Dept. Health)</td>
<td>12 AD</td>
<td></td>
<td></td>
<td></td>
<td>1.38 (0.15) AD</td>
<td>Uptake for both radiotracers higher in AD group than HC group (p&lt;0.05).</td>
</tr>
</tbody>
</table>

**Clinical Performance:** No Studies

AD=Alzheimer’s disease; HC=healthy cognitively; MCI=mild cognitive impairment; Q=quartile; ROC=receiver operating curve; SUVR=standardized update value ratios (cortex to cerebellum unless otherwise indicated)

*All diagnoses in this column were established clinically, unless otherwise specified.

**Comparison of posterior cingulate cortex to cerebellum.
to evaluate false positives), the primary efficacy endpoint was the exclusion of amyloid in 47 young subjects who were negative for the apolipoprotein E ε4 (APOE4) allele, randomly interspersed with PET scans of 40 subjects in the autopsy cohort. The study achieved specificity of 100% in this cohort, although it is noted that the young controls are outside of the intended use population.

Reproducibility of the readings was assessed using 5 trained readers who were blinded to the clinical information. Using a binary scale (positive or negative for amyloid), sensitivity ranged from 55% to 90% for the 5 readers. In 24% to 45% of the images (depending on the sample), at least one reader would have had a different interpretation of amyloid status from the other readers (U.S. Food and Drug Administration 2011). Subsequent reanalysis for publication used the majority rating of 5 nuclear medicine physicians as the primary outcome variable, resulting in 96% agreement between florbetapir-PET images and histopathologic results in the 29 subjects in the primary analysis cohort (Clark et al. 2011).

**Diagnostic Performance.** Using the majority consensus of three independent reviewers as the final test reading, also in the FDA-approval study, sensitivity and specificity were calculated compared to the reference standard of histopathology (Clark et al. 2011). Of 15 subjects who met pathologic criteria for AD, 14 had positive florbetapir scans (sensitivity of 93%). Of the 14 subjects who did not meet pathologic criteria for AD, all 14 had negative scans (specificity of 100%; 95% CI: 76.8 to 100). Scans from all of the young subjects (27 APOE4+ and 47 APOE-) were negative. Exploratory analysis indicated that in 5 subjects (20%), the clinical diagnosis did not match the final autopsy diagnosis. These measures of diagnostic accuracy are limited by the patient population, which is unrepresentative of the target population, and the use of a majority reading based on 5 independent experts, which is not likely to be used in clinical care.

In a follow-up of the Clark studies (2011, 2012) including 151 patients, not just those who had died and undergone an autopsy, Doraiswamy et al. (2012) compared changes in cognition and diagnostic status over 18 months among individuals with beta amyloid positive versus beta amyloid negative results using florbetapir F18 PET. At baseline, 51 individuals had recently diagnosed MCI (19 or 57% were beta amyloid positive using the majority of the readers’ results), 69 were cognitively normal controls (10 or 14% were beta amyloid positive), and 31 had clinically diagnosed AD dementia (21 or 68% were beta amyloid positive) (p<0.0001 in an exploratory analysis unadjusted for multiple comparisons). Individuals with MCI and positive beta amyloid results experienced greater cognitive decline over the next 18 months than those with negative beta amyloid results. Individuals with AD or cognitively normal who had positive beta amyloid results experienced greater cognitive decline on some measures over the next 18 months than those with negative beta amyloid results. Among MCI subjects, 5 of 17 subjects with beta amyloid positive results converted to AD dementia during the 18 month period, while 5 of 29 beta amyloid negative subjects did so (p=0.0996).

A multicenter (n=51) study by Fleisher et al. pooled data from 4 Phase I and II trials of florbetapir-PET imaging from 210 participants, including 68 subjects with probable AD, 60 subjects with MCI, and 82 older unimpaired controls (Fleisher et al. 2011). The thresholds for a diagnosis of AD using SUVRs were determined from the Phase III trial described above. Although there were significant differences in mean standard uptake value ratio thresholds across groups, there was considerable overlap in the range of values. The percentages of subjects meeting threshold levels of amyloid (i.e., beta amyloid PET positive results) with clinical AD, MCI and cognitively healthy controls were 80.9%, 40.0%, and 20.7%, respectively. The percentages of subjects with any identifiable florbetapir F 18 signal were 85.3%, 46.6%, and 28.1%, respectively. Among healthy controls, the percentage of subjects with any florbetapir positivity increased linearly by age, ranging from 11.8% for subjects 55 to 60 years of age to 41.7% for subjects 81 years of age or older. APOE4 carriers in the control group had about twice the percentage of florbetapir positivity as noncarriers, although this comparison did not reach statistical significance.

In a subsequent paper, Fleisher et al. (2012b) pooled data from five registered trials of florbetapir F18 PET to investigate the impact of the APOE4 gene and aging on the PET results. They found that individuals with AD or MCI or who were cognitively healthy and who had the
APOE4 gene had greater amyloid beta deposition (measured by SUVR) than those did not have the gene.

Both of the Clark et al. articles (2011, 2012), the Doraiswamy study (2012), and both Fleisher et al. articles (2011, 2012b) were conducted by overlapping groups of authors, including individuals from Avid Radiopharmaceuticals.

An independent study by Camus et al. reported the diagnostic performance of florbetapir F18 PET in a clinical setting (Camus et al. 2012). Included were 15 subjects with AD, 12 with MCI, and 21 older unimpaired controls. PET images were assessed visually by two readers blinded to any clinical information and quantitatively by the standard uptake value ratio thresholds of cortical regions compared to the cerebellum. Sensitivity and specificity were calculated based on clinical diagnosis as the reference standard. Agreement in visual analysis between the two readers had a kappa of 0.71 (95% CI: 0.50 to 0.95). Comparing visual assessment with the initial clinical diagnosis, 11 of 13 AD patients (85%), 6 subjects with MCI (50%) and 15 of 21 control subjects (60%) had positive scans, resulting in a sensitivity of 84.6% (95% CI: 54.6 to 98.1) and a specificity of 38.1% (95% CI: 18.1 to 61.6) for discriminating AD patients from control subjects. A quantitative assessment of the global cortex standard uptake value ratio thresholds showed a sensitivity of 92.5% and specificity of 90.5% at a cut-off value of 1.12 (ROC [receiver operating characteristics] area under the curve=0.89). Although the study is limited by the small number of subjects and the use of clinical diagnosis as a reference standard, these results suggest a high number of false positives with visual assessment of the images. In addition, quantitative analysis was not able to differentiate subjects with MCI from unimpaired controls.

Wolk et al. (2012) compared the performance of florbetapir F18 with PiB, a beta amyloid radiotracer developed earlier that is not FDA approved, among 26 patients. PiB has a larger evidence base than other beta amyloid radiotracers for use with PET in AD. Wolk et al. compared quantitative results (SUVR) between 14 cognitively healthy adults and 12 individuals with AD. The Pearson correlation coefficient was 0.78 (p<0.0001), and uptake for both radiotracers was higher in the AD group than in the cognitively healthy group (p<0.05).

Evidence estimating sensitivity and specificity of florbetapir F18 PET for detecting beta amyloid is limited by the small number of studies with generally small sample sizes; differences in the reference standards (clinical or histopathologic diagnosis); variations in interpreting the images, whether qualitative or quantitative or a single reader or the mean of readers’ decisions; and the composition of the population, since test accuracy may vary across the disease spectrum. Clark et al. (2011, 2012) report a sensitivity of 92% and a specificity of 100%, but the specificity cohort includes a substantial number of younger, cognitively healthy adults, and results were averaged over three readers, among other limitations. Camus et al. (2012) reported sensitivity of 84.6% (95% CI: 55% to 98%) and specificity of 38.1% (95% CI: 18% to 62%), but the sample was small and the reference standard was the known to be imperfect clinical diagnosis.

Clinical Outcomes. No studies were identified that reported health outcomes following florbetapir F18 PET imaging.

Additional research is needed on the sensitivity and specificity of beta amyloid testing. It is not possible to link an indirect chain with existing evidence to convincingly argue that health outcomes are improved. Furthermore, discussed in the section “Formulation of the Assessment,” several factors make it difficult to ascertain the potential net benefit associated with use of florbetapir F18 PET:

- The limited effectiveness of pharmacologic treatments for AD, as well as for other types of dementia that may be difficult to distinguish from AD
- Pharmacologic treatment efficacy has been demonstrated in patients with clinically diagnosed AD, which may or may not be equivalent to patients with positive florbetapir results
- The generally modest adverse effects of medications used for AD, with some evidence of effectiveness in non-AD dementia, so that these medications are used widely in patients with dementia
- The coexistence of AD with other types of dementia
Ongoing Clinical Trials
A search of the online site www.clinicaltrials.gov in May 2012 identified a number of trials on amyloid imaging with PET. Of particular interest are the following:

- An industry-sponsored Phase III open-label study to evaluate the efficacy and safety of florbetaben (BAY94-9172) PET imaging for detection/exclusion of cerebral beta amyloid compared to postmortem histopathology (NCT01020858). This study has an estimated enrollment of 216 subjects with completion of the primary outcome measure in 2011 and final study completion in 2014.
- An industry-sponsored Phase III open-label study to compare the brain uptake of flutemetamol with brain amyloid levels determined post-mortem (NCT01165554). The study has an estimated enrollment of 100 subjects with completion in 2012.
- An industry-sponsored Phase III open-label study to assess the prognostic usefulness of flutemetamol for identifying subjects with amnestic MCI who will convert to clinically probable AD (NCT01028053). The study has an estimated enrollment of 225 subjects with completion estimated for January 2015.

Discussion
In general, evidence of a health benefit or clinical utility from testing requires demonstration of:

- incremental improvement in diagnostic or prognostic accuracy over current practice and
- that incremental improvements lead to improved health outcomes (e.g., by informing clinical management decisions), and
- that these outcomes may be obtained (i.e., are generalizable) outside of the investigational setting.

The use of florbetapir F18 PET in individuals who may have AD or other causes of cognitive decline does meet any of these criteria. The studies to date have shown that florbetapir F18 PET results are correlated with histopathological findings at autopsy. This finding is important. Studies have also suggested that florbetapir F18 PET has some ability to differentiate between cognitively healthy adults and patients with AD. However, the studies are limited by small sample sizes, differences in determining outcomes (e.g., qualitative versus quantitative, unknown impact of training for physicians inexperienced with this modality), and the lack of evidence on its use in populations encountered in clinical practice. No information is available on the impact of this test on clinical outcomes.

Reading florbetapir F18 PET images requires different skills than are usually needed to read other PET images, because of the need to distinguish between white matter and gray matter, which can be particularly challenging in patients with cortical atrophy. Unique “gray-white contrast” characteristics of the florbetapir F18 images must be recognized as indications of normal or abnormal distributions (Yang et al. 2012). While the median sensitivity and specificity among readers in the trials submitted to the FDA were quite high, there was variability across readers. Avid Pharmaceuticals, Inc., has created a training module for readers of these images. The FDA has also required two post-marketing studies, which are due to be completed by the end of 2014. One focuses on comparing the results of Amyvid scan interpretations at local clinical sites to interpretations performed by an expert(s) at a central reading facility. The other investigates whether use of SUVRs or other quantitative outcomes can serve as an alternative or adjunct to qualitative scan interpretations.

Another issue that needs to be resolved regarding the use of beta amyloid PET is where this test fits relative to other biomarkers that may be used to diagnose or exclude AD. Existing data on levels in CSF suggests a lower sensitivity and specificity. Further research on the same population with head-to-head comparison might be warranted if clinical utility can be demonstrated.

Furthermore, what is the incremental value of beta amyloid imaging results compared to a clinical diagnosis alone? It would be useful to compare results from patients with possible or probable AD to both florbetapir F18 PET and to autopsy results, to determine whether the use of florbetapir F18 PET increases the accuracy of clinical diagnosis compared to histopathology. Also, beta amyloid deposition is one of the two requirements for a post-mortem diagnosis of AD; the other is neurofibrillary tangles in the cerebral cortex. In terms of biomarkers, the NIA-AA working groups have identified two categories: beta amyloid accumulation and neuronal degeneration or injury.
Linking PET detected beta amyloid to improved health outcomes requires demonstrating a number of premises. These might include, but are not limited to, the following:

1. Beta amyloid PET has sufficiently high sensitivity and specificity in the relevant patient populations, so that test results alter disease probability to a degree that would change clinical decision-making. Given the pretest probability of AD for a patient with a clinically determined, probable diagnosis, the test specificity must be high (e.g., exceeding 80% or even 90%). Achieving this degree of specificity will be difficult, given the prevalence of amyloid in the absence of disease as well as challenges in interpreting test results. For possible AD, a lower specificity might be sufficient. To exclude AD, sensitivity must be exceedingly high.

2. Interventions must have a clinically meaningful impact on outcomes and for a majority of patients. Cholinesterase inhibitors may provide a modest benefit for 50% of patients with possible or probable AD. Therefore, improving the proportion of true positive results by 10% might affect only 3% (other assumptions being met).

3. Plaque burden is a predictor of pharmacologic treatment benefit/response.

4. If used in patients with MCI, beta amyloid PET imaging will provide incremental prognostic information over clinical evaluation and will affect treatment outcomes.

Conclusions. Evidence on technical performance is mainly from the FDA-sponsored study (Clark et al. 2011, 2012). A strength of this study is the comparison of florbetapir F18 imaging with the reference standard of post-mortem histopathology. Limitations include the small sample size, a majority rating for assessing diagnostic accuracy, and having only 2 patients in the mildly impaired category, which is the population for whom the test is most likely to be used. There is evidence for inter-observer variability in reading the test; using a majority of 2/3 readers leads to a high agreement with histopathology. Further high-quality studies using populations of patients that represent those presenting in clinical care are needed to better define the diagnostic performance of this test.

Evidence for clinical utility, i.e., that testing improves health outcomes, is lacking. Few data are available on whether it can accurately identify patients with MCI who will develop AD. Literature on the use of florbetapir F18 PET imaging to aid in the diagnosis of patients with suspected Alzheimer’s disease is limited.

Summary of Application of the Technology Evaluation Criteria

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) made the following judgments about whether beta amyloid imaging with positron emission tomography (PET) meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria to evaluate suspected Alzheimer’s disease (AD) and other causes of cognitive decline.

1. The technology must have final approval from the appropriate governmental regulatory bodies.

In 2012, the U.S. Food and Drug Administration (FDA) approved the use of one beta amyloid radioactive diagnostic agent, florbetapir F18 (Amyvid™, Avid Radiopharmaceuticals, Inc., a subsidiary of Eli Lilly), for use with PET. Florbetapir F18 is indicated to estimate beta-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer’s disease and other causes of cognitive decline, as an adjunct to other diagnostic evaluations.

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

The available evidence is insufficient to permit conclusions concerning the impact of beta amyloid PET imaging with florbetapir F18 on health outcomes. The evidence to date focuses solely on the correlation between the results of beta amyloid PET imaging and other indicators of cognitive decline, clinical diagnoses, and histopathologic results. Studies are needed to define the accuracy of beta amyloid imaging according to age (since beta amyloid deposition increases with age in cognitively normal individuals). Further evidence is also needed on the link between the test results and improving health outcomes.
5. The technology must improve the net health outcome.

Because evidence is insufficient to permit conclusions on the effect of beta amyloid PET imaging on health outcomes, any improvement cannot be established.

4. The technology must be as beneficial as any established alternatives.

Comparative benefit cannot be established lacking sufficient evidence.

5. The improvement must be attainable outside the investigational setting.

Improved health outcomes following beta amyloid PET imaging have not been demonstrated in the investigational setting.

Based on the above, beta amyloid imaging with positron emission tomography (PET) to evaluate suspected Alzheimer's disease (AD) and other causes of cognitive decline does not meet the TEC criteria.
References


Beta Amyloid Imaging with PET for Evaluation of Suspected AD or Other Causes of Cognitive Decline


Beta Amyloid Imaging with PET for Evaluation of Suspected AD or Other Causes of Cognitive Decline


Appendices

**Appendix A**

**Practice Guidelines and Position Statements Regarding Florbetapir F-18**

2011 Guidelines from the National Institute on Aging and Alzheimer’s Association on the diagnosis of mild cognitive impairment and dementia due to Alzheimer’s disease recommend the use of biomarkers, including beta amyloid imaging with PET, only in research settings (McKhann et al. 2011; Albert et al. 2011). Reasons for this recommendation are that more research needs to be done to ensure that the criteria that include the use of biomarkers have been appropriately designed, there is limited standardization of biomarkers from one locale to another; and access to biomarkers may be limited in community settings.

The Alzheimer’s Association has indicated qualified support for the availability of florbetapir (Alzheimer’s Association 2012). The statement includes the following: “On one hand, FDA approval of this product will expand the clinical and research opportunities for amyloid imaging by making this brain imaging tool more widely available to the field. On the other hand, the fact that all of the potential uses of this product are not crystal clear tempers our enthusiasm. Again, additional research is needed to clarify the role of florbetapir-PET imaging in Alzheimer’s.” The Alzheimer’s Association has convened a task force with the Society of Nuclear Medicine to develop recommendations for the use of amyloid imaging.

**Medicare National Coverage**

No national coverage determination was identified. However, the Medicare Evidence Development and Coverage Advisory Committee (MedCAC) is holding a meeting on Beta Amyloid Positron Emission Tomography (PET) in Dementia and Neurodegenerative Disease on January 30, 2015.

**Appendix B**

**Description of F-18 Radiotracers other than Florbetapir F18**

F18-FDDNP [2-(1-(6-[(2-[(18)F]fluoroethyl)(methyl)amino]-2-naphthyl)ethylidene]malono-nitrile], developed at UCLA in 2002, is a molecular imaging probe that binds to beta amyloid plaques and neurofibrillary tangles, although it binds to beta amyloid with less affinity than PiB and related tracers (Agdeppa et al. 2001). It was the first of the F18 tracers to be used for in vivo imaging of beta amyloid in patients with AD and healthy controls (Klunk and Mathis 2008; Vallabhajosula 2011). FDDNP–PET scanning is currently the only available brain-imaging technique that can assess tau tangles. Autopsy findings have shown that tangles tend to correlate with AD progression better than plaques. In a recent study at UCLA (Small et al. 2012), researchers performed brain scans and cognitive assessments at baseline and again 2 years later on 43 volunteer participants, with an average age of 64, who did not have dementia. At the start of the study, 22 of the participants had normal aging and the other 21 had MCI. They found that for both groups at the 2-year follow-up, increased FDDNP binding to beta amyloid and tau in the areas of the brain involved in decision-making, complex reasoning, memory and emotions correlated with progression of cognitive decline. Among the subjects with MCI, the amount of initial binding provided the greatest accuracy in identifying those who developed AD after 2 years.

F18-Flutemetamol, also known as GE-067, 5’-fluoro-PiB, is the fluorine-18 version of PiB, and is under development by GE Healthcare. In a 2010 Phase II study of patients with MCI versus healthy volunteers, flutemetamol demonstrated rates of sensitivity and specificity similar to its PiB parent tracer, and also provided high test–retest reliability (Vandenbergh et al. 2010). At the Alzheimer’s Association International Conference 2012 (AAIC 2012), GE Healthcare presented results of its Phase III study of 68 terminally ill patients who had
agreed to undergo postmortem brain autopsy. The data showed concordance (sensitivity, 86%; specificity, 92%) between flutemetamol PET images and beta amyloid brain histopathology. Flutemetamol PET images reflected fibrillar beta amyloid levels as detected later in post-mortem analyses (http://www.news-medical.net/news/20120718/GE-Healthcare-announces-final-results-from-18Fflutemetamol-phase-3-study-on-AD.aspx). GE Healthcare planned to submit their application for FDA approval of F18-Flutemetamol by the end of 2012.

F18-Florbetaben (Bayer Schering Pharma AG) is a stilbene compound also known as BAY94-9172 or AV-1. It differs from florbetapir only by a carbon-to-nitrogen substitution in one position, and because of this, florbetaben has similar imaging properties to florbetapir (Herholz 2011). A Phase II, multicenter trial to determine the diagnostic efficacy of florbetaben in differentiating probable AD subjects (n=81) and age-matched healthy controls (n=69) was recently published (Sabri et al. 2010; Barthel et al. 2011). According to the study, florbetaben had a sensitivity of 80% and a specificity of 90% in discriminating AD patients from healthy controls, with high inter-reader agreement. In addition, for the AD subjects, a positive PET scan was associated with the number of APOE4 alleles.

F18-AZD4694 is the latest of the F18 tracers and is under development by AstraZeneca. A clinical validation study by Cselenyi et al. (Cselenyi et al. 2012) determined that AZD4694 combines the convenience of a fluorine-18 label and the sensitivity and selectivity similar to that seen with PiB. They reported that AZD4694 demonstrates decreased white matter binding, which offers improved image clarity.
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