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Conference Insights:

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A Continuing Medical Education Series

IN THIS ISSUE: **New Developments in Molecular Imaging for the Differential Diagnosis of Alzheimer's Disease and Other Dementias***

SUMMARY HIGHLIGHTS

Key points of longitudinal studies and clinical trials of potentially disease-modifying agents, studies addressing molecular imaging in neurodegenerative disorders as presented at the Radiological Society of North America 98th Scientific Assembly and Annual Meeting (November 25–30, 2012; Chicago, Illinois), and recent news relevant to clinical practice:

- ^{18}F-florbetapir (Amyvid™; Eli Lilly & Co., Indianapolis, Indiana) is the only FDA-approved amyloid-positron emission tomography (amyloid-PET) tracer indicated for brain imaging of ß-amyloid plaques in patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) and other causes of cognitive decline. Three ^{18}F-amyloid PET tracers are in clinical development. Phase 3 trials were completed, and FDA and EMA regulatory applications recently submitted, for flutemetamol (GE Healthcare, Waukesha, Wisconsin) and florbetaben (Piramal Healthcare, Mumbai, India); NAV4694 (Navidea Biopharmaceuticals, Dublin, Ohio) is in phase 2
- Appropriate use criteria for amyloid-PET were published recently by the Amyloid Imaging Taskforce, an expert panel convened by the Alzheimer's Association and the Society of Nuclear Medicine and Molecular Imaging
- Best practices for the use of fluorodeoxyglucose (FDG)-PET are not yet available
- Results from longitudinal studies suggest that amyloid-PET and FDG-PET may enable physicians to identify patients in the earliest stages of memory loss who will eventually develop AD
- The first PET tracer for imaging tau protein—found in the hallmark neurofibrillary tangles of AD—is in early-stage clinical development. Its potential utility and timing of availability to clinicians have not been established
- All phase 3 and most phase 2b clinical trials of anti-amyloid agents incorporate amyloid-PET imaging as a trial endpoint; this technique is included in the 3 prominent anti-amyloid trials planned for 2013 by the Collaboration for Alzheimer's Prevention

Current and Emerging PET Brain Imaging Applications in Dementia

Several sessions at the Radiological Society of North America's 98th Scientific Assembly and Annual Meeting addressed clinical practice and research applications of amyloid-positron emission tomography (amyloid-PET) and fluorodeoxyglucose (FDG)-PET imaging.

Limited Use of Imaging in Dementia Clinical Practice

Alexander Drzezga, MD, from the University of Cologne in Germany, discussed the clinical practice and research aspects of the ^{18}F-florbetapir amyloid-PET imaging workup.

^{18}F-florbetapir Image Interpretation

- Clinical information not a component
- Binary
  - Compare cortical GM to WM in cortex (not cerebellum)
- Negative
  - WM > GM, good contrast
- Positive
  - ≥2 areas GM = WM (loss of contrast)
  - ≥1 area GM > WM

GM, gray matter; **WM**, white matter.

A positive amyloid-PET scan does not predict or establish a diagnosis of Alzheimer's disease (AD) or other disorder; however, recent longitudinal studies (see *sidebar, page 5*) suggest that amyloid-PET imaging might eventually play a wider role in the evaluation of patients with memory loss.

Amyloid-PET imaging with ^{18}F-florbetapir has been available since June 2012 to US clinicians who complete a training program. Centers for Medicare & Medicaid Services (CMS) reimbursement is not yet available for this agent, however, which limits its use.

Satoshi Minoshima, MD, PhD, from the University of Washington in Seattle, reviewed the use of FDG-PET imaging in the differential diagnosis of dementia. In addition to clinical utility, Dr. Minoshima described practical advantages, including the following:

- Wide accessibility across the US because of well-established use in oncology
- Inexpensive tracer
- CMS reimbursement for use in differentiation of AD from frontotemporal dementia (FTD)

Despite these factors, at least one physician in attendance observed that FDG-PET imaging is not performed widely for the differentia diagnosis of dementia, but rather is

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Also in This Issue:

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*This program's educational content is based, in part, on various abstracts, posters, presentations, and interviews from the Radiological Society of North America (RSNA) 98th Scientific Assembly and Annual Meeting, which took place November 25–30, 2012 in Chicago, Illinois. This publication was prepared under the design and production supervision of Dothen Healthcare Press. It is not sanctioned by RSNA, nor is it an official publication of the RSNA 2012 Annual Meeting.

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Conference Insights: New Developments in Molecular Imaging for the Differential Diagnosis of Alzheimer's Disease and Other Dementias

CME ACCREDITATION

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Dr. Fleisher reports that he serves as a consultant for Siemens, Avid, Eli Lilly, and Merck & Co.

Dr. Tankosic, Bill Jacobs, and Erika Gettings have nothing to disclose.

Needs Statement/Overview

Alzheimer's disease (AD), the most common form of dementia, accounts for approximately 60% of all cases and affects an estimated 5.4 million Americans. AD represents a growing epidemic in the US (and other developed nations) because of the aging population and lack of effective treatments for preventing, halting, or reversing the disease. In the absence of significant advances, by 2050 the US incidence of AD will reach nearly 1 million new cases per year and prevalence will reach 11–16 million [Alzheimer's Association. *Alzheimers Dement.* 2012;8(2):131–168]. Although criteria for the clinical diagnosis of AD have been established, an AD diagnosis remains only "probable" until confirmed at autopsy by the presence of the hallmark neuropathologic findings of AD—senile plaques (containing ß-amyloid peptides) and neurofibrillary tangles (containing phosphorylated tau protein). Differentiating AD from dementia of other causes, such as frontotemporal dementias and others, can be challenging even in established disease, and it is difficult and often not possible in the early stages of memory loss. New molecular-based imaging neuroimaging probes can aid the diagnosis of dementia, particularly when memory symptoms are mild or the clinical disease is uncertain. A new agent for the imaging of ß-amyloid depositions in the brain was recently approved by FDA and is having an impact on the management of patients in current clinical practice. The research implications are also great, holding promise for the development of effective disease-modifying agents for the prevention and treatment of AD.

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Learning Objectives

This is a **knowledge and comprehension** type of activity. At the end of this activity, participants should be able to:

1. Identify the various pathological processes that take place during the onset and course of Alzheimer's disease, and how these can be visualized and quantified using molecular imaging.
2. Describe new methods, such as amyloid-positron emission tomography (amyloid-PET) imaging, in dementia workup.
3. Discuss the use and interpretation of different PET probes (fluorodeoxyglucose [FDG], amyloid, neurotransmitter) to aid in the differential diagnosis of clinical dementia.

Target Audience

This educational program is intended for neurologists involved with the detection and treatment of Alzheimer's disease.

Estimated Time of Completion

This activity should take approximately 1.0 hour to complete.

Method of Participation

There are no fees for participating in and receiving credit for this activity. Participants should read the objectives and meeting report, then go online to answer the questions on the multiple-choice post-test and complete the online evaluation. Participants may then claim credit for participation.

Dear Reader:

The use of molecular imaging biomarkers for the differential diagnosis of Alzheimer's disease (AD) and other dementias continues to advance in clinical practice and research applications. In addition to structural–functional imaging techniques such as magnetic resonance imaging and computed tomography, newer strategies, including amyloid-positron emission tomography (amyloid-PET) and fluorodeoxyglucose (FDG)-PET, are available to practicing clinicians for the evaluation of cognitive impairment in cases of suspected dementia.

The roles of these techniques remain unclear, as do the functions of novel AD biomarkers and genetic risk factors such as the presence of apolipoprotein E4 and levels of amyloid and tau proteins in cerebral spinal fluid.

More research is needed to determine the optimal application of individual biomarkers and combinations of biomarkers in various stages of dementia. However, recent results from longitudinal studies suggest that amyloid-PET and FDG-PET may enable physicians to identify patients in the earliest stages of memory loss (prodromal AD or mild cognitive impairment) who may eventually develop AD.

This CME program focuses on the use of amyloid-PET and FDG-PET imaging techniques in the clinical evaluation of memory loss and dementia. Highlights from the Radiological Society of North America's 98th Scientific Assembly and Annual Meeting are provided along with recent findings from key longitudinal studies and clinical trials of novel agents in development for the treatment of AD.

Warm regards,

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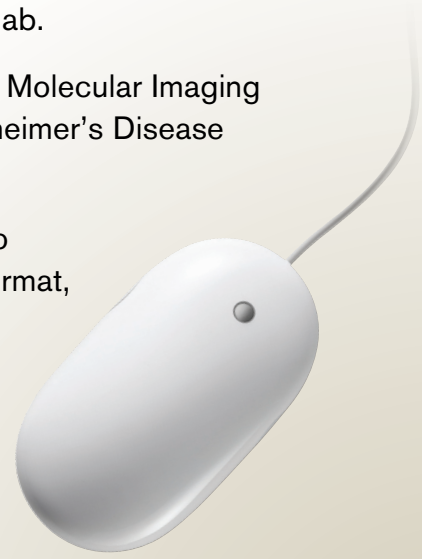


CURRENT VIEWS ON DEMENTIA
Pathophysiology, Population, Burden, *and more*

In a "Hot Topic" session, *New Approaches in Imaging Evaluation of Alzheimer's Disease*, Daniel Press, MD, from Beth Israel Deaconess Medical Center in Boston, Massachusetts, discussed hypotheses in the pathophysiology underlying various types of dementia, reviewed clinical features, and summarized current treatments.

Alzheimer's disease (AD) is well recognized as the most prevalent cause of dementia, occurring in more than 75% of cases (**Table 1**). Less well appreciated is the relatively high frequency of Lewy body pathology—found in slightly more than a quarter of cases—and mixed dementia, which is marked by features of AD combined with those of various other dementia types. Also of note, disease frequency exhibits age-related variance, with vascular dementia more common in advancing age, and vascular and Lewy body disease less common.[1]

Table 1. Relative Frequencies of Various Dementia Types[1]

Cause of dementia	Frequency, %
AD	77
LBD	26
VaD	18
HS	13
FTD	5
Mixed dementia*	39

AD, Alzheimer's disease; **HS**, hippocampal sclerosis; **FTD**, frontotemporal dementia; **LBD**, Lewy body disease; **VaD**, vascular dementia.

*Individual causes add to 139%, reflecting more than one cause in about 40% of cases (mixed dementia); AD+LBD and AD+VaD are two of the most common co-occurring causes of dementia.

Table 2. Alzheimer's Disease: Population, Risk Factors, Treatment, and Prevention[2-5]

Patient population, millions	United States, 2011	5.4[2]
	Worldwide, 2010	35.6[3]
	Worldwide (estimated), 2050	115[3] (1 in 85)[5]
Risk factors	Greatest	Age[2]
	Genetic	ApoE4,[2] TREM2, rare dominant genetic Alzheimer's disease, others
	Preventable/reversible	Physical inactivity, high cholesterol (especially in midlife), diabetes, smoking, obesity[2]
	Protective	Cognitive reserve
Treatment	Currently, symptomatic only	• Approved (cognitive): AChEIs (donepezil, galantamine, rivastigmine, tacrine), NMDA receptor inhibitor (memantine) • Not approved (behavioral): atypical antipsychotics ("Black Box" warning for use in the elderly)
Prevention	Drug trials, to date	All have failed: estrogen replacement, vitamin E, donepezil, statins, NSAIDs, B12, others
	Exercise training	Increases size of hippocampus and improves memory[4]
	Benefit of modestly effective preventive (ie, delay onset and progression by 1 year)	Would reduce estimated number of cases in 2050 by 9.2 million[5]

AChEI, acetylcholinesterase inhibitor; **ApoE4,** apolipoprotein E4; **NMDA,** N-methyl-D-aspartate; **NSAID,** nonsteroidal anti-inflammatory drug; **TREM2,** triggering receptor expressed on myeloid cells 2.

Dr. Press also shared current perspectives on the size of the AD patient population, which is estimated at 5.4 million individuals in the United States[2] and 35 million worldwide.[3] Aging populations, especially in Western nations, are expected to drive that number to 115 million and possibly higher by 2050.[3]

Current treatment strategies for AD are inadequate. Limited to symptomatic approaches, existing therapies are effective for only some patients[2] and for only a limited period of time (usually ranging from months to 1–2 years), and they may cause side effects that lead to discontinuation of treatment. All of the many clinical trials undertaken to identify a disease-modifying molecule that slows, halts, or reverses AD have failed.

Together, the lack of an effective disease-modifying agent for AD and the burgeoning patient population present one of the most important health care and drug development challenges of our time (**Table 2**).[2-5] In addition to the suffering of an increasing number of patients and families, the economic cost is great. An estimated 43% of cases require a high level of care (ie, equivalent to that provided by a nursing home).[5]

The successful development of even a modestly effective disease-modifying drug is expected to reduce the prevalence of AD and attendant costs greatly. An intervention that would delay both disease onset and progression by 1 year would result in approximately 9.2 million fewer cases of AD in 2050—nearly all among those needing a high level of care.[5]

Interestingly, a non-drug approach, exercise training, has been shown to improve memory and increase brain volume. A 1-year aerobic exercise training program increased hippocampal volume by 2%, which effectively reversed age-related volume loss by 1 to 2 years. Although the implications for preventing AD are not entirely clear, this study found that aerobic exercise is neuroprotective and that starting an exercise regimen later in life is not futile for improving cognition or increasing brain volume.[4]

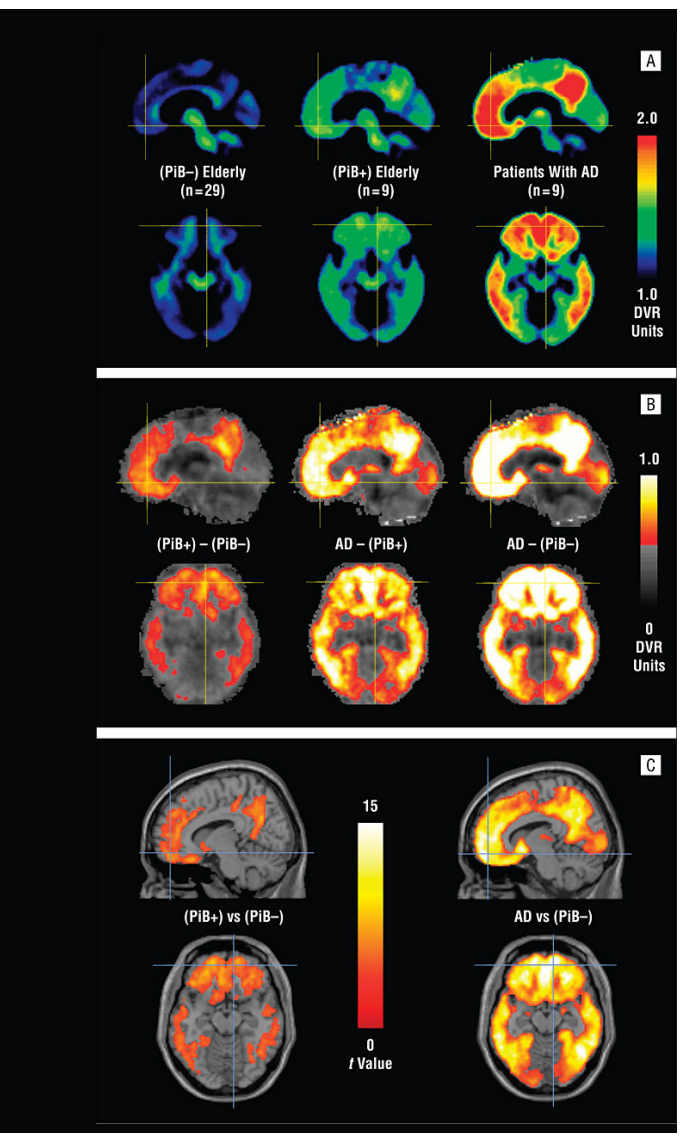
continued from page 1

Table 3. Correct Diagnosis Informs Appropriate Treatment

Drug Treatment	Alzheimer's Disease	Frontotemporal Dementia	Dementia with Lewy Bodies
AChEIs	Effective	No role; adverse effects on behavior	Data suggest effectiveness
NMDA receptor inhibitor	Effective	Insufficient data	Insufficient data
Antipsychotic agents ("Black Box" warning for use in the elderly)	Risk assessment required	Effective	Potentially lethal adverse reactions
Antiparkinsonian agents (excluding dopamine agonists)	No role	No role	Data suggest effectiveness

AChEI, acetylcholinesterase inhibitor; **NMDA**, N-methyl-D-aspartate.

Figure 1.
Amyloid Imaging in Clinically Unimpaired Participants and Patients with Alzheimer's disease (AD)



Amyloid-PET imaging was performed with the Pittsburgh Compound B (PiB) tracer.

A: Mean distribution volume ratio (DVR) images for: (left) 29 amyloid-negative clinically unimpaired participants, (center) 9 amyloid-positive clinically unimpaired participants, and (right) 9 patients with AD.

B: Images obtained by subtracting the amyloid-negative mean image from the mean of: (left) amyloid-positive elderly participants and (right) the mean of patients with AD. Center: the amyloid-positive mean image was subtracted from the mean image of patients with AD. The gray background is not a magnetic resonance image; it represents PiB retention differences of less than 0.5 DVR units and is shown for orientation.

C: Statistical parametric mapping software image of *t* values was determined by comparing the amyloid-negative group with: (left) the amyloid-positive clinically unimpaired group and (right) patients with AD.

Aizenstein HJ, Nebes RD, Saxton JA, et al. *Arch Neurol.* 2008;65:1509-1517.

limited principally to "academic centers in several regions of the United States." Even in the absence of a disease-modifying treatment for AD, the results of molecular imaging modalities can have immediate therapeutic implications and psycho-social-economic implications for patients and their families by helping to direct drug therapy selection (**Table 3**).

^{18}F-Florbetapir Clinical Use Update

^{18}F-florbetapir is currently the only amyloid-PET tracer that has been approved by FDA (in April 2012). The first guidelines for its appropriate clinical use were published recently by the Amyloid Imaging Taskforce (AIT), an expert panel convened by the Alzheimer's Association and the Society of Nuclear Medicine and Molecular Imaging.[6] The guidelines set out 3 required characteristics that all patients must demonstrate and 3 appropriate clinical situations (patients must fit one of 3) in order to qualify for appropriate use of florbetapir imaging. According to AIT, appropriate use is in patients with cognitive symptoms possibly caused by AD but with an uncertain diagnosis after comprehensive workup by a dementia expert, and when knowledge of Aß pathology would probably increase diagnostic certainty and alter management (**Table 4**).

CMS reimbursement for florbetapir imaging is not currently available. After receiving a request from its manufacturer, Eli Lilly & Co. (Indianapolis, Indiana), CMS announced that it would consider reimbursement for β-amyloid imaging agents for use in diagnosing dementia this summer. In making its analysis, CMS will consider evidence provided by the Medicare Evidence Development and Coverage Advisory Committee (MEDCAC), which met early this year to assess the data supporting the benefit of amyloid-PET imaging in improving patient outcomes.[7]

Among the reports available to MEDCAC was a white paper released in December 2012 by the Institute for Clinical and Economic Review.[8] In it, interim results are reviewed from an ongoing Level-III study of more than 200 patients who received ^{18}F-florbetapir PET scans at 19 sites.[9] Selected findings include the following:

- After scanning, physicians changed their diagnoses in more than 50% of cases
- After scanning, physicians altered their proposed treatment plans in 85% of cases, including discontinuation of further diagnostic testing and changing drug treatment

On January 30, MEDCAC concluded that, currently, there is insufficient evidence to determine whether the use of the FDA-approved amyloid-PET diagnostic-imaging test improves health outcomes in patients with early signs of cognitive dysfunction, including AD. Advisory Committee recommendations are not binding; CMS may consider additional evidence before making its final coverage decision this summer.

Development Update: ^{18}F Amyloid and Tau Imaging Agents

Kirk Frey, MD, PhD, from the University of Michigan, discussed new radiotracers for amyloid imaging. **Table 5** summarizes the current development status of amyloid-PET tracers and includes the first available tau-PET tracer, which is in early-stage clinical development.

Of the 3 developmental amyloid-PET agents, flutemetamol appears closest to market entry; its manufacturer, GE Healthcare (Waukesha, Wisconsin), announced the acceptance of its submissions to US and EU regulatory agencies for approval in the visual detection of beta amyloid in the brains of adult patients who are being evaluated for AD.[10] Flutemetamol amyloid scans will be performed on subjects in Merck's (Whitehouse Station, New Jersey) phase 2/3 trial of MK-8931, a novel investigational oral β-amyloid precursor protein site-cleaving enzyme inhibitor, which is being studied in the 78-week placebo-controlled, randomized, parallel-group, double-blind trial.[11]

More recently, Piramal Healthcare (Mumbai, India) announced the acceptance of its submissions to US and EU regulatory agencies for florbetaben. Navidea Biopharmaceuticals' (Dublin, Ohio) NAV4694, in phase 2, might have advantages over other agents (high signal-to-noise ratio/less white matter interference).

Recent Research Highlights

A biomarker is any identifiable indicator that accurately represents underlying disease pathology, as detected via blood, cerebrospinal fluid, or imaging. Recent research findings are helping to elucidate the roles of amyloid-PET, FDG-PET, and other biomarkers in the diagnostic workup of the patient exhibiting cognitive decline.

β-amyloid plaque deposition is thought to be the first biomarker to appear in the AD brain, preceding cognitive impairment by many years. **Figure 1** shows amyloid-PET imaging results in clinically unimpaired participants and patients with AD. Compared to the amyloid-negative group, the amyloid-positive clinically unimpaired subjects showed increased PiB retention in the same cortical areas (and striatum) in which PiB retention among AD patients greatly exceeded that of controls. Recent research implicates elevated β-amyloid load in cognitively normal elderly subjects with significantly greater decline in memory (over 18 months), compared to the cognitively normal elderly with a low β-amyloid load.[12]

Table 4. Guidelines for Appropriate Use of Amyloid-PET Imaging[6]

APPROPRIATE USE of amyloid imaging	INAPPROPRIATE USE of amyloid imaging
Patient meets ALL of the following 3 characteristics:	• In patients with core clinical criteria for probable AD with typical age of onset
• A cognitive complaint with objectively confirmed impairment	• To determine dementia severity
• AD as a possible diagnosis, but when the diagnosis is uncertain after a comprehensive evaluation by a dementia expert	• Based solely on a positive family history of dementia or presence of ApoE4
• Knowledge of the presence or absence of Aß pathology is expected to increase diagnostic certainty and alter management	• In patients with a cognitive complaint that is unconfirmed on clinical examination
AND	• In lieu of genotyping for suspected autosomal mutation carriers
Patient fits ONE of the following clinical situations:	• In asymptomatic individuals
• Persistent or progressive unexplained MCI	• Nonmedical use (eg, legal, insurance coverage, or employment screening)
• Satisfies core clinical criteria for possible AD because of unclear clinical presentation (either an atypical clinical course or an etiologically mixed presentation)	
• Progressive dementia and atypically early age of onset (usually defined as 65 years or less in age)	

Aß, ß-amyloid; **AD**, Alzheimer's disease; **ApoE4**, apolipoprotein E4; **MCI**, mild cognitive impairment.

Adapted by permission of the Society of Nuclear Medicine and Molecular Imaging from: Johnson KA, Minoshima S, Bohnen NI, et al. Appropriate use criteria for amyloid PET: A report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association. *J Nucl Med.* 2013; 54(3): 476-490. Section 6.1.

Table 5. Development of ^{18}F Amyloid and Tau Imaging Agents

Agent	Company	Status	Notes
Amyloid-PET			
Florbetapir	Eli Lilly & Co. (Indianapolis, Indiana)	US: approved EU: approval recommended	Only FDA/EMA approved amyloid-PET tracer
Flutemetamol	GE Healthcare (Waukesha, Wisconsin)	US: NDA accepted EU: MAA accepted	Demonstrated consistent performance in visual detection of ß-amyloid compared with histopathology data
Florbetaben	Piramal Healthcare (Mumbai, India)	US: NDA accepted EU: MAA accepted	Data suggest effectiveness
NAV4694	Navidea Biopharmaceuticals (Dublin, Ohio)	Phase 2	May demonstrate superior signal-to-noise ratio
Tau-PET			
^{18}F-T807 ^{18}F-T808	Siemens Molecular Imaging (Erlangen, Germany)	Phase 0	2 trials (each, N=12)

MAA, Marketing Authorisation Application; **NDA**, New Drug Application.

RECENT FINDINGS IN THE LITERATURE RELATIVE TO AMYLOID-PET AND FDG-PET

Findings from longitudinal studies of amyloid-positron emission tomography (amyloid-PET) and fluorodeoxyglucose (FDG)-PET are emerging and may contribute to a deeper understanding of the natural histories of normal cognitive aging, memory loss, and dementia, as well as support more effective differential diagnosis and patient management in the clinic.

Effects of Amyloid-PET Imaging Data on Diagnostic and Treatment Decisions[9]

One of the greatest challenges in defining a role for amyloid-PET in clinical practice is to demonstrate that the information obtained from the imaging study will enhance physician decision making relative to patient care. This study examined the effects of the use of florbetapir imaging on diagnosis and intended patient management in 229 individuals with progressive cognitive decline. Before receiving results of florbetapir-PET imaging, treating physicians recorded a provisional diagnosis, an estimation of their confidence in that diagnosis, and their plan for diagnostic evaluation and management. They recorded the same information after receiving florbetapir-PET results. Comparison of "before and after" data, after reviewing florbetapir-PET results, found that:

- Physicians changed diagnosis in 125 of 229 of cases (54.6%; 95% confidence interval [CI], 48.1%-60.9%)
- Physicians' diagnostic confidence increased by an average of 21.6% (95% CI, 18.3%-24.8%)
- Physicians changed at least one aspect of their management plans in 199 of 229 cases (86.9%; 95% CI, 81.9%-90.7%)
- Changes included increased intention to treat with an acetylcholinesterase inhibitor (AChEI) or memantine in cases with positive scans and decreased intent for negative scans. In patients whose workups were not yet completed, planned use of structural imaging with computed tomography or magnetic resonance imaging (MRI), and neuropsychological testing, was reduced

Combined Amyloid-PET and FDG-PET Increased Diagnostic Confidence and Predicted Disease Progression[13]

In this study, 154 patients who had completed standard dementia screening underwent amyloid-PET imaging with Pittsburgh compound B (PiB) and FDG-PET imaging. Two-year clinical follow-up data were available for 39 patients. Outcome measures were (change in) clinical diagnosis and confidence in that diagnosis before and after disclosing PET results. Amyloid

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(PiB)-PET scans were positive in 40 of 66 patients (61%) with a clinical diagnosis of Alzheimer's disease (AD), 5 of 18 (28%) with frontotemporal dementia (FTD), 4 of 5 (80%) with Lewy body disease (LBD), and 3 of 10 (30%) patients with other dementias. FDG-PET uptake patterns matched the clinical diagnosis in 38 of 66 patients (58%) with AD and 6 of 18 (33%) with FTD.

- PET results led to a change in diagnosis in 35 patients (23%) and only when prior diagnostic certainty was lower than 90%
- Diagnostic confidence increased from 71%±17% before to 87%±16% after PET ($P<0.001$)
- The diagnosis of dementia established after PET remained unchanged in 96% of patients
- Two-year clinical follow-up (n=39) showed that amyloid (PiB)-PET and FDG-PET predicted progression to AD for patients with mild cognitive impairment (MCI)

Florbetapir-PET May Help Clarify Risk for Progressive Cognitive Decline[14,15]

This prospective, longitudinal (18-month) study evaluated the prognostic utility of florbetapir-PET in 151 subjects at risk for progressive cognitive decline. Participants included 51 patients with recently diagnosed MCI, 69 cognitively normal (CN) controls, and 31 with clinically diagnosed AD.

- In both the MCI and CN groups, positive baseline ß-amyloid scans were associated with greater clinical worsening on the AD Assessment Scale–Cognitive subscale (ADAS-Cog; $P<0.01$) and Clinical Dementia Rating–Sum of Boxes ($P<.02$)
- In the MCI group, positive baseline ß-amyloid scans were associated with greater decline in memory as measured by the Digit Symbol Substitution test and Mini-Mental State Examination ($P<0.05$)
- ß-amyloid–positive MCI tended to convert to AD at a higher rate than ß-amyloid–negative MCI ($P<0.10$)

The researchers concluded that florbetapir PET may help identify individuals at increased risk for progressive cognitive decline.

FDG-PET + CSF Biomarkers Predicted MCI-to-AD Conversion[16]

A study of 97 subjects with MCI from the Alzheimer's Disease Neuroimaging Initiative (ADNI) compared multiple AD biomarkers with clinical parameters alone for the ability to predict future cognitive decline. Biomarkers included FDG-PET, MRI-derived gray matter probability maps and cerebrospinal fluid (CSF) proteins; and covariates included age, education, apolipoprotein E (ApoE) genotype, and ADAS-Cog score. The conversion to AD within 4 years was assessed.

- Combined data obtained from MRI, FDG-PET, CSF analysis, and clinical assessment were significantly more accurate in predicting conversion to AD compared with clinical assessment alone
- With combined data, the misclassification rate decreased from 41.3% to 28.4% ($P<0.00001$)
- FDG-PET contributed more information to routine tests ($P<0.00001$) than CSF analysis or MRI

New Evidence for Prodromal AD[17]

The Australian Imaging, Biomarker, and Lifestyle (AIBL) study used amyloid-PET imaging to compare cognitive decline in healthy older adults exhibiting low ß-amyloid levels with that of adults who had amnestic MCI (aMCI) and high or low levels of ß-amyloid.

- Relative to healthy older adults with low ß-amyloid, adults with aMCI and high ß-amyloid showed greater decline in working memory and verbal and visual episodic memory at 18 months
- Adults with aMCI and low ß-amyloid also showed greater decline in working memory but not episodic memory at 18 months
- In adults with aMCI and high levels of Aß, the rate of decline on measures of episodic memory over 18 months was approximately twice that observed previously for healthy older adults with high ß-amyloid levels

ApoE4 Associated with Reduced Cerebral Glucose Metabolism in Normal Aging[18]

The ApoE4 gene is a known risk factor for AD, deposition of ß-amyloid, and decreased cerebral glucose metabolism in asymptomatic individuals. However, whether its effect on glucose metabolism is related to ß-amyloid is unclear. Data were examined for 175 CN older subjects enrolled in the ADNI who were studied concurrently with FDG-PET and florbetapir-PET. Based on a threshold value of florbetapir uptake, subjects were categorized as florbetapir-positive or -negative. In this sample, 29% of subjects were florbetapir-positive, and 23% were ApoE4 carriers.

- As expected, a significant association between ApoE4 genotype and florbetapir positivity was observed
- Florbetapir status was not significantly associated with glucose metabolism
- ApoE4 genotype was associated with glucose hypometabolism

The researchers concluded that ApoE genotype (but not ß-amyloid) contributes to reduced glucose metabolism in aging, "and adds to a growing list of neural consequences of ApoE that do not appear to be related to Aß (sic)."

Effect of ß-Amyloid Load on Cognitive Decline in Healthy Older Adults[12]

This study examined the significance of elevated cerebral ß-amyloid load for longitudinal changes in cognition over time. As participants in the AIBL study, 141 healthy CN older adults underwent amyloid-PET imaging, ApoE genotyping, and cognitive baseline assessment. Reassessment 18 months later found the following:

- Relative to individuals with low cerebral ß-amyloid, those with high ß-amyloid showed significantly greater decline in working, verbal, and visual episodic memory
- Compared with noncarriers, ApoE4 carriers showed a greater decline in visual memory
- No interaction between ApoE4 and cerebral ß-amyloid load was observed for any measure of cognitive function

The researchers concluded that cerebral ß-amyloid load had a greater negative effect on cognitive decline than the presence of ApoE4.

REFERENCES & FURTHER READING

1. Barker WW, Luis CA, Kashuba A, et al. Relative frequencies of Alzheimer disease, Lewy body, vascular and frontotemporal dementia, and hippocampal sclerosis in the State of Florida Brain Bank. *Alzheimer Dis Assoc Disord.* 2002;16(4):203-212.
2. Alzheimer's Association. 2012 Alzheimer's disease facts and figures. *Alzheimer's Dement.* 2012;8:131-168.
3. Batsch NL, Mittelman MS. World Alzheimer Report 2012: Overcoming the stigma of dementia. London, UK: *Alzheimer's Disease International*; 2009.
4. Erickson KI, Voss MW, Prakash RS, et al. Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci USA*. 2011;108(7):3017-3022.
5. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. *Alzheimers Dement*. 2007;3(3):186-191.
6. Johnson KA, Minoshima S, Bohnen NI, et al. Appropriate use criteria for amyloid PET: a report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association. *Alzheimer's Dement*. 2013 Jan 26 [Epub ahead of print] and *J Nucl Med.* 2013 Jan 28 [Epub ahead of print]
7. Alzheimer Research Forum. Insurance coverage of AD diagnostics? not without better data. www.alzforum.org/new/detailprint.asp?id=3350. Accessed January 7, 2013.
8. Pearson SD, Ollendorf DA, Colby JA. Diagnostic Tests for Alzheimer's Disease: Generating and Evaluating Evidence to Inform Insurance Coverage Policy [white paper]. Boston, MA: Institute for Clinical and Economic Review; 2012.
9. Grundman M, Pontecorvo MJ, Salloway SP, et al. Potential impact of amyloid imaging on diagnosis and intended Mmanagement in patients with progressive cognitive decline. *Alzheimer Dis Assoc Disord*. 2012 Nov 29. [Epub ahead of print]
10. GE Healthcare. GE Healthcare Announces Acceptance of Applications for Review of Investigational Imaging Agent [18F]Flutemetamol in the United States and Europe [press release]. January 8, 2013. http://www.businesswire.com/news/topix/20130108005396/en. Accessed January 9, 2012.
11. US National Institutes of Health. An Efficacy and Safety Trial of MK-8931 in Mild to Moderate Alzheimer's Disease (P07738 AM3) (EPOCH). http://www.clinicaltrials.gov/ct2/show/NCT01739348?term=NCT01739348&rank=1. Accessed January 9, 2013.
12. Lim YY, Ellis KA, Pietrzak RH, et al. Stronger effect of amyloid load than APOE genotype on cognitive decline in healthy older adults. *Neurology*. 2012;79:1645-1652.
13. Ossenkoppele R, Prins ND, Pijnenburg YA, et al. Impact of molecular imaging on the diagnostic process in a memory clinic. *Alzheimers Dement*. 2012 Nov 16. [Epub ahead of print]
14. Doraiswamy PM, Sperling RA, Coleman RE, et al. Amyloid-ß assessed by florbetapir F 18 PET and 18-month cognitive decline: A multicenter study. *Neurology*. 2012;79:1636-1644.
15. Furst AJ, Kerchner GA. From Alois to Amyvid: Seeing Alzheimer disease. *Neurology*. 2012;79:1628-1629.
16. Shaffer JL, Petrella JR, Sheldon FC, et al. Predicting cognitive decline in subjects at risk for Alzheimer disease by using combined cerebrospinal fluid, MR imaging, and PET biomarkers. *Radiology*. 2012 Dec 11. [Epub ahead of print]
17. Lim YY, Ellis KA, Harrington K, et al. Cognitive decline in adults with amnestic mild cognitive impairment and high amyloid-ß: prodromal Alzheimer's disease? *J Alzheimers Dis*. 2012 Nov 16. [Epub ahead of print]
18. Jagust WJ, Landau SM. Apolipoprotein E, not fibrillar ß-amyloid, reduces cerebral glucose metabolism in normal aging. *J Neurosci*. 2012;32(50):18227-18233.
19. Alzheimer's Research Forum. Collaborative umbrella CAPs three prevention trial initiatives. http://www.alzforum.org/new/detail.asp?id=3232. Accessed January 9, 2013.
20. US National Institutes of Health. A Study of Gantenerumab in Patients With Prodromal Alzheimer's Disease. http://clinicaltrials.gov/ct2/show/NCT01224106. Accessed January 9, 2013.
21. US National Institutes of Health. Safety and Efficacy Study Evaluating TRx0237 in Subjects With Mild Alzheimer's Disease. http://clinicaltrials.gov/ct2/show/NCT01689233. Accessed January 9, 2013.
22. US National Institutes of Health. An Efficacy and Safety Trial of MK-8931 in Mild to Moderate Alzheimer's Disease (P07738 AM3) (EPOCH). http://clinicaltrials.gov/ct2/show/NCT01739348. Accessed January 9, 2013.
23. US National Institutes of Health. A Study to Evaluate the Impact of MABT5102A on Brain Amyloid Load and Related Biomarkers in Patients With Mild to Moderate Alzheimer's Disease. http://clinicaltrials.gov/show/NCT01397578. Accessed January 9, 2013.
24. US National Institutes of Health. Riluzole in Mild Alzheimer's Disease. http://clinicaltrials.gov/ct2/show/NCT01703117. Accessed January 9, 2013.
25. US National Institutes of Health. Identifying Potential Effects of Liraglutide on Degenerative Changes. http://clinicaltrials.gov/ct2/show/NCT01469351. Accessed January 9, 2013.
26. US National Institutes of Health. Multiple Dose Study of BIIB037 in Subjects With Prodromal or Mild Alzheimer's Disease. http://clinicaltrials.gov/ct2/show/NCT01677572. Accessed January 9, 2013.

MOLECULAR IMAGING IN CLINICAL TRIALS OF EMERGING THERAPIES

Amyloid-positron emission tomography (amyloid-PET) and fluorodeoxyglucose (FDG)-PET imaging techniques are fulfilling important functions in clinical trials of novel drugs for the treatment of Alzheimer's disease (AD). AD drug development has been slowed by the need for large, long, and costly clinical trials. Molecular imaging techniques may enable researchers to parse individual subject information more closely and allow for selection of the purest possible study populations for more efficient trials, particularly for trials of potential disease-modifying therapeutics in very-early-stage (prodromal) AD or mild cognitive impairment. Amyloid-PET and FDG-PET are also contributing to new clinical trial designs, to allow enrollment of the smallest number of subjects and for the shortest trial periods required to answer the clinical science questions posed.

Amyloid-PET imaging is already commonly included as an endpoint in clinical trials of anti-amyloid drugs in development. All Phase 3 and most Phase 2b studies of anti-amyloid agents incorporate an amyloid-PET endpoint, and amyloid-PET imaging will be included in the 3 prominent anti-amyloid AD prevention trials planned for 2013 by the Collaboration for Alzheimer's Prevention **(Table 6)**. FDG-PET imaging also plays a role in current AD drug development; many late-stage AD treatment trials incorporate FDG-PET endpoints **(Table 7)**. Emerging data suggests that, eventually, amyloid-PET and FDG-PET imaging biomarkers might serve as principal, primary surrogate endpoints to monitor treatment effectiveness.

Table 6. 2013 CAP Trials of Amyloid-PET Imaging[19]

Trial	Description
A4 (ACDS)	• Treatment trial in asymptomatic cognitively normal older adults • Biomarker evidence of disease used to enroll high-risk individuals, follow treatment effects
DIAN Treatment Trial	• Pre-symptomatic autosomal dominant Alzheimer's disease • Multisite, mulitmutation families, 3 different drugs • Biomarkers as primary endpoints • Leading to phase 3 clinical outcome trials
API Crenezumab Trial	• Autosomal dominant pre-symptomatic treatment in a single mutation family (90%) plus mixed mutation safety cohort (10%) • 5-year clinical outcomes

A4, Anti-Amyloid treatment of Asymptomatic Alzheimer's disease; **ACDS**, Alzheimer's Disease Cooperative Study; **API**, Alzheimer's Prevention Initiative; **CAP**, Collaboration for Alzheimer's Prevention; **DIAN**, Dominantly Inherited Alzheimer Network.

Table 7. Molecular Imaging Biomarkers in Trials for Alzheimer's Disease[11, 20-26]

Drug (NCT#)	Sponsor	Indication	MOA	Phase	Imaging Modality
Gantenerumab[20] (NCT01224106)	Roche Basel, Switzerland	Prodromal AD	Anti-amyloid MAb	3	Amyloid-PET (1°)
TRx0237[21] (NCT01689233)	TauRx Therapeutics Singapore	Mild AD	Anti-tau aggregation	3	FDG-PET (1°)
MK-8931[11,22] (NCT01739348)	Merck Whitehouse Station, New Jersey	Mild to moderate AD	Anti-amyloid BACEi	2/3	Amyloid-PET (2°)
MABT5102A[23] (NCT01397578)	Genentech San Francisco, California	Mild to moderate AD	Anti-amyloid MAb	2	Amyloid-PET (1°) FDG-PET (2°)
Riluzole[24] (NCT01703117)	Rockefeller University New York, New York	Mild AD	Glutamate modulation	2	FDG-PET (1°) MRS-NAA (1°) MRS-NAA (2°)
Liraglutide[25] (NCT01469351)	Aarhus University Aarhus, Denmark	Mild to moderate AD	Anti-amyloid (GLP-1)	n/a	PiB-PET (1°) FDG-PET (2°)
BIIB037[26] (NCT01677572)	Biogen Idec Weston, Massachusetts	Prodromal or mild AD	Anti-amyloid MAb	1	Amyloid-PET (2°)

AD, Alzheimer's disease; **BACEi**, ß-secretase (1) inhibitor; **GLP-1**, glucagon-like peptide-1; **MAb**, monoclonal antibody; **MOA**, mechanism of action; **MRS**, magnetic resonance spectroscopy; **NAA**, N-acetylaspartate; **PiB**, Pittsburgh compound B.

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