a closer look into the diagnosis of Alzheimer's disease:
A CASE-BASED APPROACH TO UTILIZING AMYLOID-PET IMAGING IN CLINICAL PRACTICE

March 6, 2014
Houston, TX
1:00 PM – 2:00 PM

FACULTY
Michael S. Rafii, MD, PhD
Assistant Professor
Neurosciences
UC San Diego School of Medicine
Director
Memory Disorders Clinic
UC San Diego Medical Center
La Jolla, CA

This activity is sponsored by Med Learning Group.
This activity was co-provided by Ultimate Medical Academy/CCM.

Supported by an Educational Grant from Lilly USA, LLC.
AGENDA

I. Alzheimer’s Disease: Amyloid and Beyond
   - Brief Overview of Disease Pathophysiology and Risk Factors

II. Challenges in the Diagnosis of Alzheimer’s Disease
   - Impact of the 2011 guidelines on clinical practice
   - Role of different biomarkers across the stages of Alzheimer’s disease

III. Amyloid Imaging as a Diagnostic Tool in Alzheimer’s Disease
   - Update on data from clinical trials of F-18 Radiotracers
   - Appropriate use of amyloid-PET: Recent Recommendations

IV. Review of Treatment Landscape and Emerging Therapies

V. Conclusions

VI. Questions and Answers

March 6, 2014 ● Houston, TX
A Closer Look into the Diagnosis of Alzheimer’s Disease: A Case-based Approach to Utilizing Amyloid-PET Imaging in Clinical Practice

PROGRAM OVERVIEW
This case-based live activity will cover the diagnosis, treatment and management of patients with Alzheimer’s disease (AD).

TARGET AUDIENCE
This activity is designed to meet the educational needs of neurologists, imaging technologists, radiologists, internal medicine physicians, nurses and other healthcare practitioners involved in the diagnosis and management of patients with cognitive impairment and AD.

LEARNING OBJECTIVES
Upon completion of the program, attendees should be able to:

- Discuss the diagnostic criteria for AD and the current use of biomarkers
- Review data supporting the clinical utility of new radiotracers and amyloid-PET imaging as tools for improving diagnostic accuracy in mild cognitive impairment and AD
- Analyze the challenges of diagnosis of AD in clinical practice and the appropriate application of amyloid-PET imaging across the spectrum of AD
- Discuss current clinical trial data regarding the treatment of AD

ACCREDITATION STATEMENT
Med Learning Group is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

This CME activity was planned and produced in accordance with the ACCME Essentials. For CME questions, please contact: Med Learning Group at info@medlearninggroup.com
Contact this CME provider at Med Learning Group for privacy and confidentiality policy statement information at: http://www.medlearninggroup.com/privacy-policy/
CREDIT DESIGNATION STATEMENT
Med Learning Group designates this live activity for a maximum of 1.0 AMA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the live activity.

ADDITIONAL ACCREDITATIONS
This program is in process of approval by the American Society of Radiological Technologists (ASRT) for Category A+ credits.

NURSING CREDIT INFORMATION
Purpose: This program would be beneficial for nurses involved in the diagnosis and management of patients with cognitive impairment and Alzheimer’s disease.

Credits: 1.00 ANCC Contact Hour(s).

CE ACCREDITATION STATEMENT
Ultimate Medical Academy/CCM is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center’s Commission on Accreditation.

Awarded 1.00 contact hour(s) of continuing nursing education of RNs and APNs.
FACULTY

Course Chair
Adam S. Fleisher, MD, MAS
Associate Professor, Department of Neurosciences
University of California San Diego
San Diego, California
Director of Brain Imaging
Banner Alzheimer’s Institute
Phoenix, Arizona

Presenter
Michael S. Rafii, MD, PhD
Assistant Professor
Neurosciences
UC San Diego School of Medicine
Director
Memory Disorders Clinic
UC San Diego Medical Center
La Jolla, CA

Course Reviewer
Katherine Galluzzi, DO, CMD, FACOFP dist.
Professor and Chairperson, Department of Geriatrics
Philadelphia College of Osteopathic Medicine
Attending Physician, Family Medicine
Tenet Roxborough Memorial Hospital
Philadelphia, Pennsylvania

CCM/UMA Lead Nurse Planner
Margaret Governo, EdD, APRN BC
Associate Professor
Wagner College
Staten Island, New York

DISCLOSURE POLICY STATEMENT
In accordance with the Accreditation Council for Continuing Medical Education (ACCME) Standards for Commercial Support, educational programs sponsored by Med Learning Group must demonstrate balance, independence, objectivity, and scientific rigor. All faculty, authors, editors, staff, and planning committee members participating in a MLG-sponsored activity are required to disclose any relevant financial interest or other relationship with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services that are discussed in an educational activity.
DISCLOSURE OF CONFLICTS OF INTEREST

Presenter - - Dr. Rafii serves on the speaker’s Bureau for Eli Lilly; is a consultant to AC Immune SA, Janssen Pharmaceuticals, Medical Care Corporation and Stemedica, Inc.; and receives grant support from Accera Inc., Elan, Eli Lilly, Genentech, Hoffman La Roche Inc., Janssen Pharmaceuticals and Merck.

Course Chair - - Dr. Adam Fleisher received consulting and/or speaker fees from Avid Radiopharmaceuticals, Grifols, Eli Lilly and Company, Merck and Co., Inc., and Quintiles and is also a DSMB member for Merck and Co., Inc., NIA and Pfizer Inc. He is on the speakers’ bureaus for Avid Radiopharmaceuticals, Quintiles and Siemens. He received contracted research funding from Avanir Pharmaceuticals, Bristol-Myers Squibb, Genentech/Roche, Merck and Co., Inc., Pfizer Inc, Takeda Pharmaceutical Company Limited, and Wyeth (Pfizer). Dr. Fleisher has received grant funding from Eli Lilly and Company, and NIA.

MLG Course Reviewer - - Dr. Katherine Galluzzi has no relevant financial relationships to disclose.

CCM/UMA Lead Nurse Planner - - Margaret Governo, EdD, APRN BC has disclosed no significant financial relationships.

The staff, planners and managers reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME/CE activity:

Matthew Frese, General Manager of Med Learning Group has nothing to disclose.
Christina Gallo, SVP, Educational Development for Med Learning Group has nothing to disclose.
Kelly Kraines, Director of CME/CE for Med Learning Group has nothing to disclose.
Flavia Piazza, VP, Medical and Scientific Services for Med Learning Group has nothing to disclose.
Sarah Taegder, Director of Accounts for Med Learning Group has nothing to disclose.
DISCLOSURE OF UNLABELED USE
Med Learning Group requires that faculty participating in any CME activity disclose to the audience when discussing any unlabeled or investigational use of any commercial product or device not yet approved for use in the United States.

During the course of this lecture, Dr. Apostolova may mention the use of medications for both FDA-approved and non-approved indications.

Method of Participation
There are no fees for participating and receiving CME credit for this live activity. To receive CME/CE credit participants must:

1. Read the CME/CE information and faculty disclosures.
2. Participate in the live activity.
3. Submit the evaluation form to the Med Learning Group.

You will receive your certificate via email.
DISCLAIMER

Med Learning Group makes every effort to develop CME activities that are scientifically based. This activity is designed for educational purposes. Participants have a responsibility to utilize this information to enhance their professional development in an effort to improve patient outcomes. Conclusions drawn by the participants should be derived from careful consideration of all available scientific information. The participant should use his/her clinical judgment, knowledge, experience, and diagnostic decision-making before applying any information, whether provided here or by others, for any professional use.

AMERICANS WITH DISABILITIES ACT

Event Staff will be glad to assist you with any special needs (i.e. physical, dietary, etc.) Please contact Med Learning Group prior to the live event at info@medlearninggroup.com

Sponsored by Med Learning Group

Supported by an Educational Grant from Lilly USA, LLC.

Participation Statement

This educational activity provides training necessary for licensed attendees to maintain state licensing requirements. The tuition for this educational activity is subsidized in part by unrestricted educational grants, including for those attendees who have successfully completed the state licensing requirements for their respective fields. This subsidy is reflected in the registration fees for this activity.
A Closer Look into the Diagnosis of Alzheimer’s Disease: A Case-based Approach to Utilizing Amyloid-PET Imaging in Clinical Practice

Michael S. Rafii, MD, PhD
Assistant Professor
Neurosciences
UC San Diego School of Medicine
Director
Memory Disorders Clinic
UC San Diego Medical Center
La Jolla, CA

Disclosure

- During the course of this lecture, Dr. Rafii may mention the use of medications for both FDA-approved and non-approved indications
- Dr. Rafii serves on the Speaker’s Bureau for Eli Lilly; is a consultant to AC Immune SA, Janssen Pharmaceuticals, Medical Care Corporation, Novartis AG, Nestle Health Science and StemEdica, Inc.; and receives grant support from Accera Inc., Elan, Eli Lilly, Genentech, Hoffman La Roche Inc., Janssen Pharmaceuticals and Merck.
Learning Objectives

• Discuss the diagnostic criteria for Alzheimer’s Disease (AD) and the current use of biomarkers
• Review data supporting the clinical utility of new radiotracers and Amyloid-PET imaging as tools for improving diagnostic accuracy in MCI and AD
• Analyze the challenges of diagnosis of AD in clinical practice and the appropriate application of Amyloid-PET imaging across the spectrum of AD
• Use of Amyloid imaging in current treatment trials

Alzheimer’s Disease (AD): Amyloid and Beyond
**AD More Likely:**
- Age
- Female sex
- E4 genotype
- Hypertension
- Diabetes
- Homocysteine
- Cholesterol
- Head trauma
- Family history

**AD Less Likely:**
- Education
- Exercise
- Brain fitness
- Antioxidant diet
- Heart health

---

**Amyloid Initiates a Complex Cascade of Events**

- **AB**
- **Monomer**
- **Oligomer**
- **Plaque**
- **Cell death**
- **Neurofibrillary tangles**

**Tangles, oxidation, mitochondrial effects, inflammation, etc**

Spread of AD Pathology


Using Imaging as a Biomarker of Brain Pathophysiology of AD

Challenges in the Diagnosis of AD

Syndromal Definitions
Diagnostic and Statistical Manual - 5

• **Minor Neurocognitive Disorder (MCI)**
  – Cognitive decline 1-2 SD from normal on formal cognitive testing
  – Do not interfere with independence
  – Not due to delirium
  – Not attributed to another mental disorder (eg, major depression, schizophrenia)

• **Major Neurocognitive Disorder (Dementia)**
  – Cognitive decline ≥2 SD from normal on formal cognitive testing
  – Interfere with independence
  – Not due to delirium
  – Not attributed to another mental disorder (eg, major depression, schizophrenia)

MCI = mild cognitive impairment.

Diagnostic Criteria for AD (NIA-AA and IWG)

- **AD at-risk state (preclinical AD)**
  - No cognitive symptoms
  - Biomarker evidence of AD

- **Prodromal AD (MCI of the AD type)**
  - Episodic memory loss or variant presentation
  - No/minor impairment of activities of daily living
  - Biomarker evidence of AD

- **AD dementia**
  - Cognitive impairment
  - Impairment of activities of daily living
  - Biomarker evidence of AD

IWG= International Work Group; NIA-AA=National Institute on Aging–Alzheimer’s Association; MCI = mild cognitive impairment.


Biomarkers for Assessment of AD Pathology in the Clinic

- **Structural**
  - Magnetic resonance imaging (MRI)

- **Functional**
  - Functional MRI (fMRI)
  - Fluorodeoxyglucose positron emission tomography (FDG PET)

- **Molecular and biochemical**
  - CSF
  - Amyloid PET
Use of Volumetrics in the Clinic

Reduction in Cortical Thickness is Associated with Disease Stage and Predicts Decline in Normal Controls

Functional MRI in AD

- Indirect measure of neuronal activity
- fMRI can be acquired during cognitive tasks comparing one condition to a control or to a resting state
- Increased prefrontal cortical activity in MCI may be compensatory mechanism for hippocampal failure

FDG-PET in Normal Aging, MCI, AD and FTD

- AD-Dementia
- Cog NL APOE4 carriers
Cerebrospinal Fluid Tau/Aβ42 in the Prediction of Clinical Decline

From Normal to Very Mild AD

From MCI to AD

27% vs 1% annual conversion rate

AD Progression

Abnormal

Normal

Pre-Symptomatic

eMCI

LMI

Dementia

FDG-PET

MRI hipp

CSF Aβ42

Amyloid imaging

CSF tau

Cog

Fxn

CSF abeta42

FDG-PET

Function (ADL)

MRI Hippocampal volume

Cognitive performance

**Biomarker Changes in Relation to the Estimated Age at Clinical Onset: ADAD Studies**

ADAD= autosomal dominant Alzheimer’s disease


Fleisher AS. AAC. 2013

**The Australian Imaging Biomarker and Lifestyle Study**
Biomarker Changes in Relation to Age of Dementia Diagnosis

NL, MCI, AD = 200
3-5 year f/u

Amyloid Deposition 17 years prior

Hippocampal Atrophy 4 years prior

Case Study- History and Clinical Presentation

70-year-old man with a strong family history of AD. Masters degree in education.
  - 6 years insidious onset and progressive word-finding difficulties and misplacing items
  - Needs reminders for appointments
  - No behavioral problems or depression
  - ADLs:
    - Although he manages finances without difficulty, he has asked his wife to be more involved
    - More difficulty with navigation, but not getting lost, prefers his wife drive

Case Study- History and Clinical Presentation

- **PMHx**: Bladder CA in remission (2006), HTN
- **Meds**: For HTN
- **FamHx**: LOAD: father, 2 paternal aunts, 1 paternal uncle, 1 maternal aunt.
- **PE**: Significant only for a positive snout reflex
Bedside Cognitive Testing

- MMSE 26/30
  - 3 points for memory
  - 1 for date
- Category retrieval 11 animals/1 minute
- MOCA: 25/30
  - 4 point for memory
  - 1 point for date

MOCA Test
Case Study - Question 1

Which clinical syndrome is most compatible with this case's history and clinical presentation?
A. Mild Cognitive Impairment (MCI)
B. Dementia
C. Other

Case Study - Question 2

What further tests would be considered part of a standard dementia workup? (select all that apply)
A. Detailed Neurocognitive testing
B. Structural MRI
C. Labs: CBC, CMP, B12, TSH
D. FDG PET
E. Amyloid PET
F. CSF Abeta and Tau
MCI Categories

- Biomarkers assess likelihood of AD
  - Not all MCI progresses to AD

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Biomarker probability of AD etiology</th>
<th>Aβ (PET or CSF)</th>
<th>Neuronal injury (e.g., FDG, MRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCI-core clinical criteria</td>
<td>Uninformative</td>
<td>Conflicting/indeterminate/untested</td>
<td>Conflicting/indeterminate/untested</td>
</tr>
<tr>
<td>MCI due to AD—intermediate likelihood</td>
<td>Intermediate</td>
<td>Positive</td>
<td>Uninformative or intermediate</td>
</tr>
<tr>
<td>MCI due to AD—high likelihood</td>
<td>Highest</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>MCI—unlikely due to AD</td>
<td>Lowest</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Abbreviations: Aβ, amyloid beta peptide; PET, positron emission tomography; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; MRI, structural magnetic resonance imaging.

Challenges in the Clinical Diagnosis of AD

10-30% of AD-dementia is misdiagnosed using clinical assessment alone

<table>
<thead>
<tr>
<th>AD Dementia Criteria, Incorporating Biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biomarker Probability of AD etiology</td>
</tr>
<tr>
<td>Probable AD dementia based on clinical criteria</td>
</tr>
<tr>
<td>With three levels of evidence of AD pathophysiological process</td>
</tr>
<tr>
<td>Possible AD dementia (atypical clinical presentation) based on clinical criteria</td>
</tr>
<tr>
<td>With evidence of AD pathophysiological etiology</td>
</tr>
<tr>
<td>Dementia unlikely due to AD</td>
</tr>
</tbody>
</table>
Test Results

• Labs (done subsequently): TSH/B12 normal
• MRI (done subsequently):
  • Per radiologist report: “consistent with Normal Pressure hydrocephalus”

Test Results

• Detailed neurocognitive:
  • Difficulty with *learning and immediate recall* of verbal material, with a generally intact ability to retain what he had learned
  • Weakness in his word finding abilities
  • Intact executive functioning, and visuospatial skills
  • Most consistent with a “subcortical process”
Case Study - Question 3

What is the clinical diagnosis for this patient?
A. MCI, due to AD
B. Dementia, due to AD
C. MCI, most likely not due to AD
D. MCI, undetermined

Case Study - Question 4

What additional biomarkers may be useful for improving diagnostic certainty? (select all that apply)
A. FDG PET
B. Amyloid PET
C. CSF amyloid and tau
D. All
Importance of Early Diagnosis of AD

- Earlier and more effective control of symptoms
- Recognition and management of cognitive and behavioral symptoms, so as to reduce stress for all concerned
- Earlier recognition and medical treatment of behavioral symptoms (anxiety, irritability, paranoia, sleeplessness, and depression)
- Allows patient and family to make time-sensitive decisions (advanced directives, financial management, wills, continuing to work and to drive, treatment decisions and use of services (support groups, adult day center programs)
- Allows earlier participation in clinical trials
- Lower cost of long term care and management

Amyloid Imaging in AD Progression and Risk
18F-labeled Amyloid Imaging Compounds

Imaging protocols vary between compounds
Injection, 50-90 minutes uptake time, 10-20 min scans

F18 Amyloid Imaging Tracers

Flutemetamol¹
Florbetapir²
Florbetaben³
Navidea NAV4694⁴

Preclinical AD Amyloid Imaging in The AIBL Study

Prevalence of plaques in HC

(Davies, 1988, n=110)
(Braak, 1996, n=551)
(Sugihara, 1995, n=123)

Prevalence of AD
(Tobois, 2008)

Age (years)

Prevalence (%)  
50 40 30 20 10 0

Prevalence of PiB+ve PET in HC

~15 yrs

~15 yrs

AIBL= The Australian Imaging, Biomarkers and Lifestyle


Amyloid PET Measurements of Fibrillar Aβ Burden: AD Spectrum

Percent positive  
85.3% 46.7% 28.1%

APOE4, Age and Amyloid PET

Percent flutemetapir positivity for mean cortical SUVR cutoff >1.06 for diagnostic groups, split by APOE carriers (E4+) and Non-Carriers (E4-)

Cortical Amyloid Predicts 36 Month Cognitive Decline, MCI, and Dementia Due to AD in Normal Older Controls

ADAS-cog

CDR-SOB

MMSE

NL 69, MCI 51, dAD 31

Doraiswamy PM. In press 2013.

Aβ Related Cognitive Decline - Retrospective
ADNI Normal Subjects (N=72)

Longitudinal ADAS-Cog Scores

Florbetapir + N=23

Florbetapir – N=49

Aβ+ 0.5 pt/year greater decline compared to Aβ- normals (p<0.001)

Australian ADNI (AIBL) - Three-year Risk of Progression: Positive vs Negative Amyloid PET Scan

HC
(n=183)

MCI
(n=87)

Neg
(n=130)
Pos
(n=53)

Neg
(n=27)
Pos
(n=60)

Odds Ratio 4.8

25% to MCI/AD

77% (47/60) to AD dementia

Odds Ratio 14

Hazard Risks for 18-month Progression from MCI to Probable AD

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Overall accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDG PET</td>
<td>90.48%</td>
<td>56.58%</td>
<td>63.92%</td>
</tr>
<tr>
<td>Hipp volume</td>
<td>85.71%</td>
<td>57.89%</td>
<td>63.92%</td>
</tr>
<tr>
<td>Use both</td>
<td>85.71%</td>
<td>80.26%</td>
<td>81.44%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Overall accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloid PET</td>
</tr>
<tr>
<td>Hipp volume</td>
</tr>
<tr>
<td>Use both</td>
</tr>
</tbody>
</table>

What we know

Amyloid on PET is:
• Associated with fibrillar amyloid on pathology
• It distinguishes clinical stages of AD
• Influenced by age and APOE gene
• Associated with increased rate of memory decline in “cognitively intact” elderly
• Associated with degree of lifetime cognitive activity
• Associated with increased rate of brain atrophy
• Associated with reduced glucose metabolism
• It is associated with progression to MCI and dementia

• BUT: not all individuals with positive amyloid PET will develop significant clinical symptoms

Amyloid Imaging for Clinical Treatment Development
Amyloid Imaging in Clinical Trials

- All phase 3 and most phase 2b anti-amyloid therapy trials now incorporate amyloid imaging as study endpoints and/or for enrollment stratification.

- Prevention trials are now incorporating amyloid imaging as trial endpoints, or for enrollment stratification.
  - Amyloid imaging may be particularly important in pre-clinical trials to identify target cohorts for anti-amyloid therapies.
**Amyloid Imaging in Clinical Trials**

- **Gantenerumab (Roche) phase 2 study** – dose dependent decrease in amyloid 8-28 weeks of treatment

  Raw amyloid change

  Percent amyloid change


**Bapineuzumab Clears Plaques in AD**

Trial failed to show clinical benefit. About 17% of cohort found not to have amyloid in the brain. Too little or too late?

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Bapineuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Placebo" /></td>
<td><img src="image2.png" alt="Bapineuzumab" /></td>
</tr>
</tbody>
</table>

* Difference between patients in the placebo group and those in the bapineuzumab group at Week 78 = -0.24 (P = 0.003).

Other Phase 3 Anti-amyloid Clinical Trials

**IGIV (ADCS/Baxter):** N=390 mild to moderate dementia trial
- Did not screen for amyloid at baseline
- Non significant reductions in cortical amyloid by PET

Relkin, AAIC, 2013

**Solanezumab (Eli Lilly):** N=1322 mild to mod dementia trial
- About 25% did not have amyloid in the brain at baseline
- 34% reduction in clinical decline in Mild dementia,
  - But no effect in Moderate dementia

Carlson, AAIC, 2013

Implications of Failed Anti-amyloid Studies

- Amyloid is not the inciting cause of AD?
- Treatment did not remove enough amyloid to have a clinical effect?
- Mild to Moderate dementia (perhaps a misnomer) is too late to have effective amyloid removal impact on clinical disease?
Amyloid Imaging in Anti-amyloid Prevention Trials (2013)

- A4 (ADCS) – Treatment trial in asymptomatic cognitively normal older adults. Biomarker evidence of disease used to enroll high risk individuals and follow treatment effects

- DIAN treatment trial – Pre-symptomatic autosomal dominant AD. Multi-site, multi-mutation family, three different drugs. Biomarkers as primary endpoints. Leading to phase 3 clinical outcome trials

- API-ADAD – Crenezumab trial – Autosomal dominant pre-symptomatic treatment in a single mutation family (90%), plus mixed mutation safety cohort (10%). Five year clinical outcomes

- API-APOE – In 650 cognitively normal APOE homozygotes 60-75 years old. Followed for 5 years


Amyloid Imaging Use in the Clinic
**Amyloid PET Use Impacts Clinician Decision Making**

**Objective:** To determine whether Amyloid imaging could influence the diagnosis and management of patients undergoing evaluation for cognitive decline

**Methods:**
- 229 patients with progressive cognitive decline and an uncertain diagnosis
- Provisional diagnosis given, diagnostic confidence estimated, and a plan for diagnostic evaluation and management both before and immediately following receipt of the florbetapir F18 PET results

**Results:**
- After Amyloid PET physicians changed their diagnosis in 54.6% (125/229) of cases
- Diagnostic confidence increased by an average of 21.6%
  - 86.9% of cases had at least one change in their management plan
- Cholinesterase inhibitor or memantine use increased by 17.7% among Amyloid positive cases and decreased by 23.3% among those with negative scans

**Conclusions:** florbetapir F18 PET altered physician diagnostic thinking and intended testing and management plans in patients undergoing evaluation for cognitive decline.

**Amyloid PET Indication**

- To estimate beta-amyloid neuritic plaque density
- In adult patients with cognitive impairment who are being evaluated for AD and other causes of cognitive decline
- A negative Amyloid scan indicates sparse to no neuritic plaques and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition
- A negative scan result reduces the likelihood that a patient’s cognitive impairment is due to AD
- A positive Amyloid scan indicates moderate to frequent amyloid neuritic plaques
  - Neuropathological examination has shown this amount of amyloid neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition.
- Amyloid is an adjunct to other diagnostic evaluations

Suggested Use of Amyloid Imaging
Amyloid Imaging Taskforce: Appropriate USE Criteria

Amyloid imaging is appropriate in the following situations:
1. A cognitive complaint with objectively confirmed impairment
2. Performed only after full standard w/u is completed:
   • Structured clinical evaluation with objective neurocognitive testing
   • Structural brain imaging
   • Relevant laboratory tests
3. AD as a possible diagnosis, but uncertain
4. Knowledge of Aβ pathology would increase diagnostic certainty and alter management
5. Should only be ordered by dementia experts:
   • Specialty training, ≥25% dementia care practice
   • Geriatric/behavioral Psychiatry and Neurology


Interpreting Amyloid Scans

Case Study - Question 6

Current clinical diagnosis: possible MCI due to AD, based on clinical criteria
Is Amyloid Imaging appropriate for this patient?
   A. Yes
   B. No

Case Study - Question 7

Would FDG PET or CSF Aβ and Tau be recommended prior to amyloid PET?
   A. Yes
   B. No
Case Study - Test Results:

- Biomarker-based diagnostic assessment
  - Amyloid PET (negative for Aβ)

Case Study - Question 8

Does an Amyloid PET negative result make AD unlikely?

A. Yes  
B. No
Case Study - Question 9

Would you still recommend ACHEI at this time?
A. Yes
B. No

Current Diagnosis and Plan

MCI – non-AD, etiology unknown

- Consider further NPH CSF drain and MRI CINE testing, with referral to specialist
- Considering Sleep study and other exploratory testing
- Closer focus on psychiatric evaluation, depression, anxiety, etc
- Follow clinically
- Not recommending ACHEI at this time
Value of Amyloid Imaging in the Clinic

• Earlier diagnosis
  • Care planning
  • Reduced hospitalization
  • Reduced cost of lifetime care

• Improved accuracy of diagnosis
  • Near 50% of patients with clinically diagnosed MCI, and 20% of Dementia are misdiagnosed with AD
    • Leads to excess diagnostic testing
    • Inappropriate treatments given
    • Inappropriate long term planning and use of resources
    • Missing true diagnosis
      • Untreated underlying disease – leading to future complications and cost of care
      • INCREASED COST

Challenges for Amyloid PET Use in the Clinic

• How will clinicians use Amyloid PET now that it is available?

• Cost and access?

• Prediction of clinical dementia – not recommended
  – Not well understood who will become demented with asymptomatic cerebral amyloidosis

• For following over time?
  – Limited evidence of utility
  – Weakly associated with cognitive change in dementia
  – No anti-amyloid therapies available

• Significant risk of misuse and misinterpretation
Conclusions

• There is a need for diagnostic biomarkers in AD, for both clinical and research applications
  • Amyloid PET as an important tool for better understanding AD stages
  • Important tool in symptomatic & pre-symptomatic therapy development

• Amyloid imaging can be a valuable tool to supplement clinical diagnosis and prognosis decisions
  • It can identify cortical amyloid, and rule out AD
  • It can not definitively rule in AD in isolation

• Amyloid Imaging is now available in the clinic
  • Indications and guidelines for use have been defined
  • MEDCAC has determined that Medicare will not cover amyloid PET at this time
    • Some VA systems have covered it
    • Most 3rd party payers do not cover
    • Average cost - $3500, therefore, it currently is only available to patients who can afford it
  • Who will have access and how broadly this tool will be used is yet to be seen