## THE CHANGING PARADIGM FOR THE EVALUATION OF COGNITIVE COMPLAINTS: PRACTICAL AND ETHICAL CONSIDERATIONS

*Emerging Challenges in Primary Care: Update 2013*

### Faculty

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
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<tbody>
<tr>
<td>Norman L. Foster, MD</td>
<td>Director, Center for Alzheimer’s Care, Imaging and Research</td>
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<td>Chief, Division of Cognitive Neurology</td>
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<td></td>
<td>Professor, Department of Neurology</td>
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<td>Senior Investigator, The Brain Institute</td>
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<td>Professor, Department of Neurology</td>
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<td>Salt Lake City, UT</td>
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Conflict of Interest Disclosure

Norman L. Foster, MD
Consultant: Bristol-Myers Squibb
Bioethics Advisory Board: Lilly USA, LLC
Research Support: GE Healthcare, Center for Health Improvement, Janssen Alzheimer Immunotherapy, Baxter Bioscience
Speaker Honoraria: World Molecular Imaging Society, WebMD
Stock: >5% ownership of Proactive Memory Services, Inc., a tech start-up which has received STTR funds from NIH

Edward Zamrini, MD
Research Support: Center for Health Improvement, Janssen, Baxter Bioscience, Allon Therapeutics
Major Shareholder: ProActive Memory Services

Rate Your Confidence

On a scale of 1 to 5, please rate how confident you would be in understanding the role of biomarkers in the evaluation of a patient with cognitive impairment:

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident
Pre-Test Question 2

Case 1: Role of Amyloid Pet Scan

- An 80-year-old former executive began to notice memory problems over the past 3 years and requests an amyloid PET scan without any other testing to determine whether he has Alzheimer's disease. What are the appropriate next steps?
  1. Order the scan if he can pay for it observing the ethical principle of autonomy
  2. Refuse to order the scan until other testing has been completed
  3. Begin treatment with a cholinesterase inhibitor to see if he symptomatically improves before ordering an amyloid PET scan
  4. If his wife confirms that she has noticed memory loss, because of his age he almost certainly has Alzheimer’s disease and an amyloid PET scan isn’t needed

Learning Objectives

- To understand how biomarkers evolve in the course of Alzheimer’s disease and have changed clinical diagnostic criteria
- To recognize the appropriate use of amyloid PET imaging and how to avoid pitfalls
- To know how ethical principles apply when informing patients and families about amyloid PET results
Let’s Start With Some Definitions

Cognitive Complaint ≠ Deficit

- Memory and cognitive complaints are common; normal memory is not computer-like
- Attention problems often interpreted as memory or cognitive problem
  - Sleep disturbance
  - Psychiatric illness, especially depression
  - Medication side effects
  - Serious medical illnesses
- Examine mental status and evaluate functional ability
- If cognition normal - reassure, but reassess in 6 mo.
Dementia ≠ Alzheimer’s!

Dementia is a Syndrome:
- A decline in intellectual function from a previous level of performance sufficient to impair daily activities in someone who is alert and cooperative

Alzheimer’s the Most Common Cause

Mild Cognitive Impairment

- **Objective** evidence of an acquired deficit in one or more cognitive domains insufficient to impair everyday activities
- Prognosis variable
- Mild cognitive impairment involving memory (amnestic MCI) is a risk factor for Alzheimer’s disease; approximately 15%/yr
Alzheimer’s Disease (Dementia)

- Insidious onset of gradual, progressive dementia
- Memory loss usually initial and most prominent symptom
- No focal weakness or sensory loss
- Gait normal and continent until late in the illness
- Familial in about 10%, several genetic defects
- Validated clinical diagnostic criteria available

In My Clinical Practice…

When I see a patient who has the chief complaint of memory loss:

1. My major goal is to decide whether or not the patient is demented without seeking the cause
   OR
2. My major goal is to determine the specific cause of the patient’s cognitive deficits
### In My Clinical Practice…

<table>
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<tr>
<th>Audience Response</th>
<th>RESULTS</th>
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**When I see a patient who has the chief complaint of memory loss:**

1. My major goal is to decide whether or not the patient is demented without seeking the cause
   
   OR

2. My major goal is to determine the specific cause of the patient’s cognitive deficits

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**In My Clinical Practice…**

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1. I treat all patients with neurodegenerative dementia the same way, irrespective of the cause of dementia

   OR

2. I treat patients with neurodegenerative dementia differently, depending upon the cause
In My Clinical Practice…

**RESULTS**

1. I treat all patients with neurodegenerative dementia the same way, irrespective of the cause of dementia

   OR

2. I treat patients with neurodegenerative dementia differently, depending upon the cause

**In My Clinical Practice…**

When I see a patient who has the chief complaint of memory loss:

1. I evaluate and manage the patient without ever involving a specialist

   OR

2. If I am uncertain of the cause, I refer to a specialist
In My Clinical Practice…

When I see a patient who has the chief complaint of memory loss:

1. I evaluate and manage the patient without ever involving a specialist

   OR

2. If I am uncertain of the cause, I refer to a specialist

Current Approach to Cognitive Evaluation

- Perform history, examination and cognitive screen
- Address depression, significant medical conditions, medication side effects and sensory loss
- Laboratory testing
- Structural brain imaging
- Refer to specialist early when cause uncertain
How Biomarkers are Changing the Paradigm of Dementia Care

Pathology of Alzheimer’s Disease

Neuritic plaques (beta amyloid protein)

Neurofibrillary tangles (tau protein)
The Changing Paradigm for The Evaluation of Cognitive Complaints: Practical and Ethical Considerations

Biomarker Data From ADNI

New Clinical Criteria for Alzheimer’s Disease Incorporates Biomarkers
### NIA-AA Alzheimer’s Disease Criteria: Biomarkers

<table>
<thead>
<tr>
<th>Biomarker Class</th>
<th>Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topographic (location of neuronal injury)</td>
<td>AD pattern on FDG-PET</td>
</tr>
<tr>
<td></td>
<td>AD pattern cortical thinning and gray matter loss (hippocampal volume) on MRI</td>
</tr>
<tr>
<td></td>
<td>Encourages quantitative imaging</td>
</tr>
<tr>
<td>Molecular neuropathology (abeta and tau protein)</td>
<td>Elevated binding on amyloid PET</td>
</tr>
<tr>
<td></td>
<td>Low CSF abeta 1-42</td>
</tr>
<tr>
<td></td>
<td>Elevated CSF tau or phosphotau</td>
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</tbody>
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### NIA-AA Diagnostic Criteria for Alzheimer’s Disease

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Characteristics</th>
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</thead>
<tbody>
<tr>
<td>Preclinical AD</td>
<td>Asymptomatic, biological evidence of AD pathology</td>
</tr>
<tr>
<td>Mild Cognitive Impairment Due to AD</td>
<td>Cognitive deficits with normal daily function, biological evidence of AD pathology</td>
</tr>
<tr>
<td>AD Dementia</td>
<td>Typical history and symptoms with functional decline</td>
</tr>
</tbody>
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### NIA-AA Criteria for AD Dementia

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<th>Characteristics</th>
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</thead>
<tbody>
<tr>
<td>Definite AD Dementia</td>
<td>Pathologically Proven with Typical Clinical Course</td>
</tr>
<tr>
<td>Probable AD Dementia</td>
<td>- May be Biomarker Enhanced</td>
</tr>
<tr>
<td>Possible AD Dementia</td>
<td>- Atypical Presentation</td>
</tr>
<tr>
<td></td>
<td>- Comorbidities</td>
</tr>
<tr>
<td></td>
<td>- May be Biomarker Enhanced</td>
</tr>
<tr>
<td>Not AD</td>
<td>Negative Biomarkers</td>
</tr>
</tbody>
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### NIA-AA Alzheimer’s Disease Dementia

<table>
<thead>
<tr>
<th>Biomarker Probability</th>
<th>Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indeterminate</td>
<td>Biomarkers not done OR</td>
</tr>
<tr>
<td></td>
<td>Biomarker results inconsistent results</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Neuronal injury biomarker positive OR</td>
</tr>
<tr>
<td></td>
<td>Molecular biomarker positive</td>
</tr>
<tr>
<td>High</td>
<td>Neuronal injury biomarker positive AND</td>
</tr>
<tr>
<td></td>
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</table>
Why Amyloid PET?

In-vivo evidence of AD molecular neuropathology

Newly FDA approved, widely available

Currently under review for reimbursement by Medicare

Correlation of Florbetapir and AD pathology

Clark JAMA 2011;305:275-283
Florbetapir Amyloid PET

Low Amyloid uptake in cortical grey matter (good grey-matter white matter contrast)

High Amyloid uptake in cortical grey matter (loss of grey-white matter contrast)

Courtesy of Eli Lilly and Company and Avid Radiopharmaceuticals

Florbetapir Results

- Autopsy results in 29 individuals scanned a mean of 99 days before death
- 52% had AD pathology
- Postmortem and scans agreed 96% of time
- Visual reads
  - Specificity for AD pathology – 100% (no false positives)
  - Sensitivity for AD pathology – 93% (rare false negative)
Florbetapir Labeling

“to estimate β-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer’s disease (AD) and other causes of cognitive decline.”

“A negative scan indicates sparse to no neuritic plaques and is inconsistent with a neuropathological diagnosis of AD”

“A positive scan indicates moderate to frequent amyloid neuritic plaques…but may be present in ... older people with normal cognition”

Case 2: Patient with Amyloid PET Scan

A 60-year-old woman brings in a report of a “positive” amyloid PET scan she has received. She has no symptoms and continues to work. On examination she has no objective cognitive deficits. Which of the following is true:

1. The amyloid PET scan probably hasn’t been interpreted correctly
2. The patient should receive an EEG and brain MRI scan
3. The patient has preclinical Alzheimer’s disease
4. The scan should be repeated every 2 years until she develops dementia
When Should We Use Amyloid PET?

Appropriate and Inappropriate Use Criteria, AA-SNMMI Amyloid Imaging Task Force

When Should We Use Amyloid PET?

Amyloid PET imaging is appropriate for individuals with all of the following:

PREAMBLE

- A cognitive complaint with objectively confirmed impairment
- Alzheimer’s disease is a possible diagnosis, but when the diagnosis is uncertain after a comprehensive evaluation by a dementia expert
- When knowledge of the presence or absence of amyloid beta pathology is expected to increase diagnostic certainty AND alter management

Johnson et al., Alzheimer Dement 2013;9:e1-16
The Changing Paradigm for The Evaluation of Cognitive Complaints: Practical and Ethical Considerations

Appropriate in…

1. Patients with persistent or progressive unexplained mild cognitive impairment
2. Patients satisfying core clinical criteria for possible AD because of unclear clinical presentation, atypical clinical course or etiologically mixed presentation
3. Patients with progressive dementia and atypically early age of onset (usually defined as 65 or less)

Inappropriate in…

1. Patients with core clinical criteria for probable AD with typical age of onset
   • Should be little uncertainty about diagnosis
2. To determine dementia severity
   • Amyloid uptake doesn’t correlate with severity
3. Solely based upon a positive family history of dementia or presence of ApoE4 genotype
   • Amyloid PET doesn’t determine whether cognitive problems or dementia are present
Inappropriate in…

4. Patients with a cognitive complaint that is unconfirmed on clinical examination or asymptomatic individuals
   - Don't meet preamble requirements

5. In lieu of genotyping for suspected autosomal mutation carriers
   - Less specific and doesn't assess cognitive status

6. Non-medical usage (legal, insurance, employment screening)
   - Doesn't meet preamble requirements

Let’s Apply the Appropriate Use Criteria
A Case of Life Decision-Making

- 89-year-old former executive, began to notice gradual memory and thinking problems over the past 3 years, confirmed by wife
- Excellent health, hearing problems despite stapedectomy, very active skier
- Daughter has emotional disability living in another city and depends upon family
- He wishes to know whether he should plan for his personal future disability
- PCP finds memory deficits and makes a diagnosis of Alzheimer’s disease (no other tests done)

A Case of Life Decision-Making

Amyloid PET imaging

Vote

1. Appropriate
2. Inappropriate
A Case of Life Decision-Making

Amyloid PET imaging

- Appropriate

- Inappropriate

Inappropriate, Evaluation Incomplete

A Case of Life Decision-Making, Cont’d

- Executive wishing to know whether he should plan for his disability referred to a neurologist by his physician who has made a diagnosis of Alzheimer’s disease
- Exam shows difficulty with word recall, but no functional deficits or difficulty with clock drawing; has hearing problems
- Brain imaging, blood tests normal
- Neurologist diagnosis – Amnestic MCI
A Case of Life Decision-Making, Cont’d

Amyloid PET imaging

Vote

1. Appropriate

2. Inappropriate

Inappropriate, Not a Dementia Specialist, Evaluation Incomplete

UU03576
A Case of Life Decision-Making, Cont’d again

- Executive with hearing loss referred to dementia specialist, difficulty with understanding in social situations “can’t keep up with what people are saying”, admits some irritability and mood problems lately
- On exam, some language deficits during conversation and with verbal recall, dementia specialist recommends neuropsychology and audiology
- Patient angrily says he wants to know whether he has Alzheimer’s disease or not and that he knows that the definitive test is CSF abeta or amyloid PET
- He demands one of these tests and no further wasting of his time

Amyloid PET imaging

Vote

1. Appropriate
2. Inappropriate
A Case of Life Decision-Making, Cont’d again

**Amyloid PET imaging**

- Appropriate

- Inappropriate

**Inappropriate; Deficits Not Objectively Defined**

A Case of Life Decision-Making – Follow Up

- Audiogram and audiology – severe hearing loss worse over past 2 years
- Neuropsychological testing – superior performance, including memory, borderline mood disturbance
- Diagnosis – no cognitive deficits, recommend auditory rehabilitation
- Amyloid imaging would have misrepresented prognosis and treatment, even if positive (which is likely); amyloid imaging should only be done in the context of a multi-disciplinary evaluation by a dementia specialist
Case 3. How to Discuss Scan

A 58-year-old woman developed progressive language difficulty over the past 2 years. She is independent in personal care, but no longer can cook. The appropriate approach to report amyloid PET results is:

1. Require the patient to bring a friend or family member and meet with you in person
2. Have a staff member call the patient’s family with the results and a prescription based upon the scan result
3. Because of HIPAA guidelines, tell only the patient the scan results, unless there is a signed release
4. Before providing results, send the patient to a social worker or psychiatrist to make sure the patient will not become depressed or suicidal when told about a positive scan

Ethical Considerations with Amyloid PET Imaging

- Adopt a pre-test / post-test model of education and disclosure
  
  **PRE-SCAN**
  
  - Disclose limits of test clinical value
  - Assess motivation
  - Discuss potential discrimination in life and long-term care insurance
  - Discuss implications for driving, employability and insurability (long-term care, life insurance)
Ethical Considerations with Amyloid PET Imaging

POST-SCAN

- Disclose results in person with trusted other present
  - Consider problem of automatic release of results to patient portals
- Provide advice for family support
- Discuss prognosis and plan for continuing care
- Develop treatment plan, including community resources

52 Post-Test Questions
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The Changing Paradigm for The Evaluation of Cognitive Complaints: Practical and Ethical Considerations

Post-Test Question 5

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<th>Audience Response</th>
<th>Which of the statements below describes your approach to the evaluation of a patient with cognitive complaints?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>I do not evaluate patients with cognitive impairment, nor do I plan to this year.</td>
</tr>
<tr>
<td>2.</td>
<td>I did not evaluate patients with cognitive impairment before this course, but as a result of attending this course I’m thinking of evaluating them now.</td>
</tr>
<tr>
<td>3.</td>
<td>I do evaluate patients with cognitive impairment and this course helped me change my evaluation strategies.</td>
</tr>
<tr>
<td>4.</td>
<td>I do evaluate patients with cognitive impairment and this course confirmed that I don’t need to change my evaluation strategies.</td>
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Questions?