Dana Mathews Ph.D., M.D.
Professor of Radiology
Division of Nuclear Medicine and Molecular Imaging

Jon A. Anderson, Ph.D., FAAPM
Professor and Chief of Diagnostic Medical Physics
Department of Radiology

Diana Kerwin, M.D.
Assistant Professor
Department Neurology & Neurotherapeutics | Center for Alzheimer's and Neurodegenerative Diseases | Internal Medicine
Presentation Objectives:

• What are Beta-Amyloids, and how to they relate to CI?
• Why should we image Amyloid depositions?
• How are they imaged?
• What are the challenges?
• What does the future hold?

Technologist perspective:
What are Beta-Amyloids?

- Beta-Amyloids are “sticky” and clump together to cause plaques.
- “Plaques” -or- “Deposits”
- Form in between nerve cells and cause a disruption \(^1\).

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Where do Beta-Amyloids come from?

- Derived from larger proteins (Amyloid Precursor Proteins) found in the fatty membrane of surrounding nerve cells (1)
What is TAU?

Protein tangles that disintegrate microtubules within neurons.

Image courtesy of National Institute on Aging/National Institutes of Health
Other Related Neural Cells

B-Amyloid clearing cells:
- Astrocytes
- Microglia

Images courtesy of the National Institute on Aging/National Institutes of Health
Hallmarks of Alzheimer's Disease

1. Neurofibrillary tangles inside the neurons = Tau
2. Amyloid Plaques = Beta-Amyloid
3. Loss of connection between cells
4. Cell death

Post Mortem Diagnosis

TAU Plaque

B-Amyloid Plaque (Congo red stain)

TAU NF Tangles
ALZHEIMER’S DISEASE IS THE 6TH leading cause of death in the United States

16.1 MILLION AMERICANS provide unpaid care for people with Alzheimer’s or other dementias

These caregivers provided an estimated 18.4 BILLION HOURS of care valued at over $232 BILLION

Between 2000 and 2015 deaths from heart disease have decreased 11% while deaths from Alzheimer’s disease have increased 123%

1 IN 3 seniors dies with Alzheimer’s or another dementia

5.7 MILLION Americans are living with Alzheimer’s

By 2050, this number is projected to rise to nearly 14 MILLION

EVERY 65 SECONDS someone in the United States develops the disease

Early and accurate diagnosis could save up to $7.9 TRILLION in medical and care costs

In 2018, Alzheimer’s and other dementias will cost the nation $277 BILLION

By 2050, these costs could rise as high as $1.1 TRILLION

It kills more than breast cancer and prostate cancer combined

Alzheimer’s Association: The brains behind saving yours!
Appropriate Use Criteria

Amyloid imaging is appropriate when the presence or absence of Beta-Amyloid will have a significant impact on a patient’s diagnosis and/or treatment:

1. Patients with persistent or progressive unexplained MCI

2. Patients satisfying core clinical criteria for possible AD because of unclear clinical presentation, either an atypical clinical course or an etiologically mixed presentation

3. Patients with progressive dementia and atypically early age of onset (usually defined as 65 years or less in age)

(In)Appropriate Use Criteria Cont’d

• Amyloid imaging is inappropriate in the following situations: Patients with persistent or progressive unexplained MCI.

4. Patients with core clinical criteria\(^{(2)}\) for probable AD with typical age of onset
5. To determine dementia severity
6. Based solely on a positive family history of dementia or presence of apolipoprotein E (APOE)\(\varepsilon4\)
7. Patients with a cognitive complaint that is unconfirmed on clinical examination
8. In lieu of genotyping for suspected autosomal mutation carriers
9. In asymptomatic individuals
10. Nonmedical use (e.g., legal, insurance coverage, or employment screening)

Why should we image Beta Amyloid?

- Accurate Diagnosis
- Early Detection
- Targeted Treatment
- Better Patient Outcomes
- Cost Savings
Beta-Amyloid Imaging Agents

- **C-11 Pittsburgh compound B**
  - Not FDA approved
  - Requires proximity to cyclotron

- FDA approved Beta-Amyloid PET Radiopharmaceuticals:
  - **Florbetapir F-18 Injection = Amyvid™**
    - Eli Lilly and Company²
  - **Flutemetamol F-18 Injection = Vizamyl™**
    - GE Healthcare²
  - **Florbetaben F-18 Injection = Neuraceq™**
    - Piramal Imaging⁴

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2. Eli Lilly (2012). Amyvid (Florbetapir F-18 Injection): Prescribing Information. Indianapolis, IN
White vs. Grey matter

1. “Structural MRI Imaging.” 3T How To: Structural MRI Imaging, UC San Diego Center for Functional MRI, fmri.ucsd.edu/Howto/3T/structure.html.
C-11 Pittsburgh Compound B²

- 1st Radiotracer developed to image amyloid plaques in the brains of living subjects.
- Previously to PIB, post mortem pathology was only way to confirm amyloid deposits.
- Limited by short half life of C-11

2. PIB is not FDA approved
Development of F-18 Tracers

Amyvid Package Insert

**Indications and use:**

- Amyvid is indicated for Positron Emission Tomography (PET) imaging of the brain 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 Amyvid 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 Amyvid 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. Amyvid is an adjunct to other diagnostic evaluations.

**Limitations of Use:**

- A positive Amyvid scan does not establish a diagnosis of AD or other cognitive disorder
- Safety and effectiveness of Amyvid have not been established for:
  - Predicting development of dementia or other neurologic condition;
  - Monitoring responses to therapies

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1. Eli Lilly (2012). Amyvid (Florbetapir F 18 Injection): Prescribing Information. Indianapolis, IN
Mechanism of Action & Distribution

- Following intravenous injection, florbetapir F 18 diffuses across the human blood-brain barrier and produces a radioactivity signal detectable throughout the brain. Subsequently, cerebral perfusion decreases the brain florbetapir F 18 content, with differential retention of the drug in areas that contain β-amyloid aggregates compared to areas that lack the aggregates. The time-activity curves for florbetapir F 18 in the brain of subjects with positive scans show continual signal increases from time zero through 30 minutes post-administration, with stable values thereafter up to at least 90 minutes post-injection (2).

1. READER TRAINING, amyvid.myregistrationp.com/amyvid/training.do.
2. Eli Lilly (2012). Amyvid (Florbetapir F 18 Injection): Prescribing Information. Indianapolis, IN
Radiation Dosemetry


Display & Interpretation

- Images should be displayed in the trans-axial orientation with access as needed to the sagittal and coronal planes.
- All slices of the brain should be used for interpretation.
Negative scan

- Negative scans show more radioactivity in white matter than in gray matter, creating clear gray-white contrast.
Positive Scan

- Positive scans show cortical areas with reduction or loss of the normally distinct gray-white contrast. These scans have one or more areas with increased cortical gray matter signal which results in reduced (or absent) gray-white contrast. Specifically, a positive scan will have either:
  - Two or more brain areas (each larger than a single cortical gyrus) in which there is reduced or absent gray-white contrast. This is the most common appearance of a positive scan.
    - Or-
  - One or more areas in which gray matter radioactivity is intense and clearly exceeds radioactivity in adjacent white matter.
Acquisition & Reconstruction Parameters

- Check with radiopharmaceutical manufacturer before scanning!!
- Achieve 2-3mm pixel size
- Attenuation correction mandatory
- Varies by camera make and model
Dosage and Administration

- 10mCi Florbetapir² bolus administered intravenously.
- NO PREP!
- 10 minute PET image at starting at 30-50 minutes post injection
- FOV should be centered on, and include the entire brain.
- Acquisition parameters variation

2. Eli Lilly (2012). Amyvid (Florbetapir F 18 Injection): Prescribing Information, Indianapolis, IN
Patient Positioning

- Patient positioning plays a key role in allowing the interpreter to follow the standardized method of interpretation and in producing images similar to those in the manufacturer-developed interpreter training program.
Technologic Pitfalls vs. Normal Variants

- Dosing administration
- Patient Conditions
- Uptake time
- Patient Positioning
- Image reconstruction
- Attenuation correction
Uptake Time (Amyvid)

- Imaged at 30-40 mins post injection

1. READER TRAINING, amyvid.myregistrationp.com/amyvid/modulesAll.do?moduleNumber=1.
Uptake Time (Amyvid)

Imaged at 50-90mins

1. READER TRAINING, amyvid.myregistrationp.com/amyvid/modulesAll.do?moduleNumber=1.
Uptake Time (Amyvid) • Imaged at 15-20mins post injection!

1. READER TRAINING, amyvid.myregistrationp.com/amyvid/modulesAll.do?moduleNumber=1.
Suboptimal Patient Positioning

Low Image Quality

18F-florbetapir images with poor resolution due to dose infiltration (A), imaging beyond recommended time window (B), inadequate smoothing (2 mm FWHM) (C), and scanner issue during acquisition (D). (Courtesy of Avid Radiopharmaceuticals.)
Recon Variations
Normal Variants

- Salivary Glands
- Bony & Scalp uptake
- Atrophy
Normal Variants - Atrophy
Normal Variants


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<table>
<thead>
<tr>
<th>Radiopharmaceutical</th>
<th>Dose amount</th>
<th>Uptake time</th>
<th>Acquisition time</th>
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</thead>
<tbody>
<tr>
<td>Florbetapir</td>
<td>10 mCi</td>
<td>30-90 mins</td>
<td>10 mins</td>
</tr>
<tr>
<td>Florbetaben</td>
<td>8.1 mCi</td>
<td>45-130 mins</td>
<td>15-20 mins</td>
</tr>
<tr>
<td>Flutemetamol</td>
<td>5 mCi</td>
<td>60-120 mins</td>
<td>10-20 mins</td>
</tr>
</tbody>
</table>

**COMPARISON OF 18-F TRACERS**
The Future of Amyloid Imaging in MCI
Clinical Trials

1. https://trialmatch.alz.org/find-clinical-trials#createaccount
alzheimer's association
THE BRAINS BEHIND SAVING YOURS!

ACR
AMERICAN COLLEGE OF RADIOLoGY

IDEAS
Imaging Dementia—Evidence For Amyloid Scanning

CMS
CENTERS FOR MEDICARE & MEDICARE SERVICES
QUESTIONS?
THANK YOU FOR LISTENING!
References/Bibliography:


References/Bibliography Cont'd:

3. “Structural MRI Imaging.” 3T How To: Structural MRI Imaging, UC San Diego Center for Functional MRI, fmri.ucsd.edu/Howto/3T/structure.html.
11. https://trialmatch.alz.org/find-clinical-trials#createaccount