DETAIL

DEMONSTRATING EXCELLENCE THROUGH ADVANCED IMAGING LEARNING

MITA®
MEDICAL IMAGING & TECHNOLOGY ALLIANCE
A DIVISION OF NEMA®

Amyloid PET Imaging Basics:

Background Information for Outreach Activities with Neurologists and Dementia Specialists

Legal Disclaimer

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Purpose

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- The purpose of this self-study tutorial is to provide background information about Amyloid PET Imaging in aid of diagnosis of Alzheimer's Disease (AD)
- The intended audience for this tutorial are non-medical personnel who engage in marketing activities on behalf of an imaging center or department
- Upon completion of this self-study program, a person engaged in marketing activities will be better equipped to speak with referring physicians (neurologists/dementia specialists) about amyloid PET imaging

Agenda

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- Background information about AD
  - Description of disease
  - Demographics and scope of the problem
- Key messages for referring physicians
  - Diagnosis of AD is difficult, but desirable
  - Amyloid imaging provides *in vivo* amyloid status and the ability to rule out AD
  - Amyloid imaging can assist with, and even change, medical management
  - Amyloid imaging is accessible for Medicare patients via the IDEAS ResearchStudy
- Summary

Key Messages for Referring Physicians

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1. Diagnosis of AD is difficult, but desirable.
2. Amyloid imaging provides *in vivo* amyloid status and the ability to rule out AD.
3. Amyloid imaging can assist with and even change medical management.
4. Amyloid imaging is accessible for Medicare patients via the IDEAS Research Study.

What is Alzheimer's Disease ?

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- Alzheimer's disease (AD) is a type of dementia that causes problems with memory, thinking and behavior
- Alzheimer's is the most common form of dementia, accounting for 50 to 60% of all cases
- Dementia is a general term for memory loss and other intellectual abilities serious enough to interfere with daily life
- Dementia is not normal aging

http://www.alz.org/What is Alzheimers

AD Statistics

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2015 ALZHEIMER'S DISEASE FACTS AND FIGURES

1 IN 3

SENIORS
dies with Alzheimer's or another dementia.

It's the only cause of death in the top 10 in America that **CANNOT BE PREVENTED, CURED OR SLOWED.**

6

Alzheimer's disease is the **6TH LEADING CAUSE OF DEATH IN THE UNITED STATES.**

ALMOST TWO THIRDS
of Americans with Alzheimer's disease are women.

EVERY 67 **SECONDS** someone in the United States develops the disease.

http://www.alz.org/facts

Disclosure of AD Diagnosis

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Only

45%

of people with **ALZHEIMER'S** disease or their caregivers report **BEING TOLD OF THEIR DIAGNOSIS.**

More than

90%

of people with the four most common types of **CANCER** have been **TOLD OF THEIR DIAGNOSIS.**

www.alz.org/AD Facts

Cost Implications of AD

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http://www.alz.org/AD Facts

AD Gender and Racial Disparities

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- In 2015, an estimated 700,000 people in the United States age 65 and older will die with AD
- Almost two-thirds of Americans with AD are women
- There are 5.1 million people age 65 and older with AD in the United States
  - 3.2 million: women
  - 1.9 million: men
- Older African-Americans and Hispanics are more likely than older whites to have AD and other dementias

http://www.alz.org/AD Facts

AD Crisis: Baby Boomer Generation

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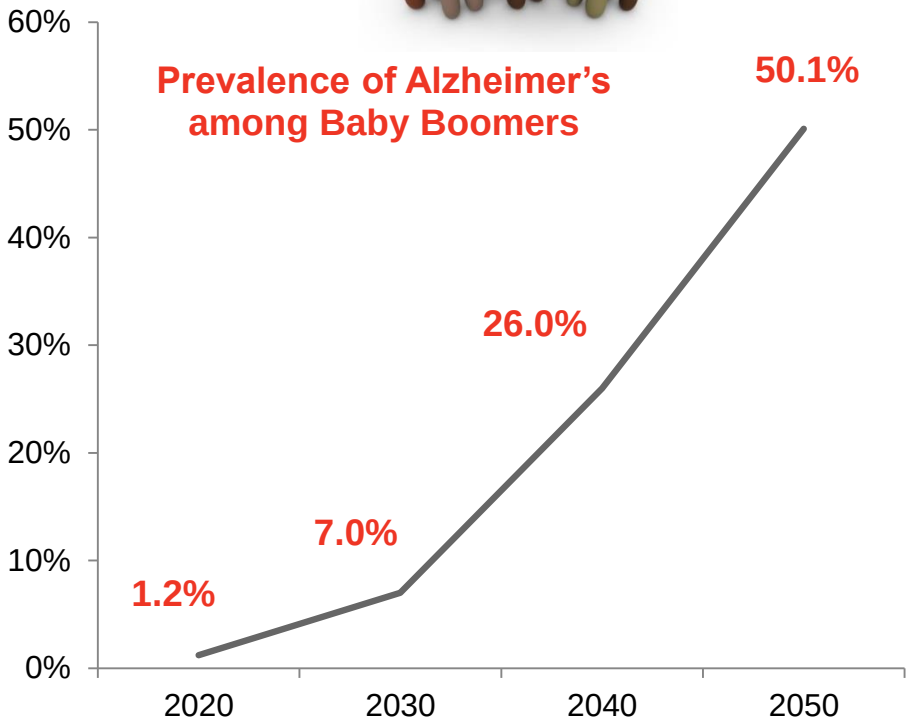
If progression of the disease is not halted or slowed ….

- More than 28 million individuals will develop AD by 2050
- AD will account for nearly 25% of Medicare spending by 2050



www.alz.org/AAIC 2015 AD Statistics

AD Increasing as a Cause of Death

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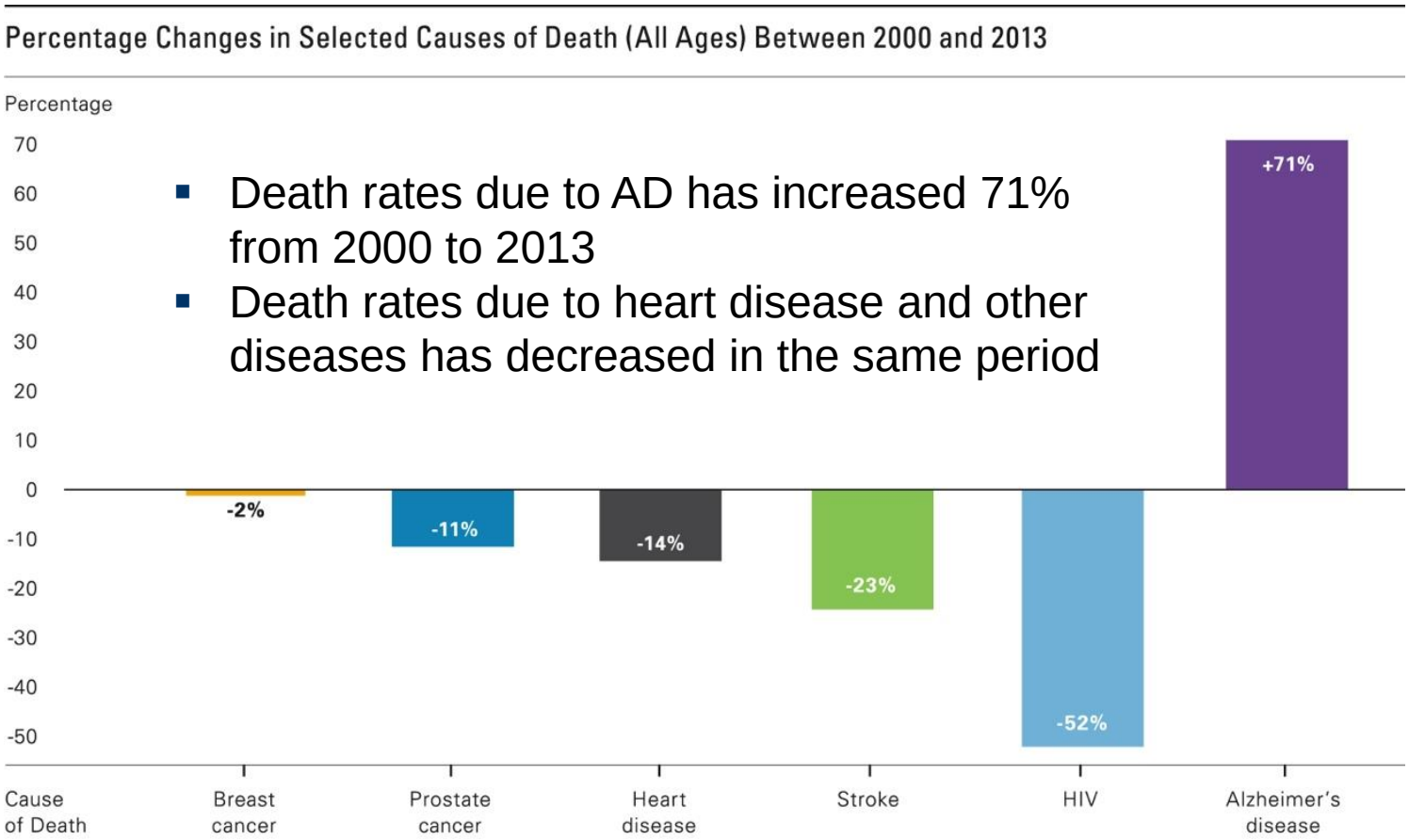

- Death rates due to AD has increased 71% from 2000 to 2013
- Death rates due to heart disease and other diseases has decreased in the same period

Created from the National Center for Health Statistics data.

http://www.alz.org/AD Facts

Progression of AD

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Even while patients are still cognitively normal, beta amyloid neuritic plaque can be identified (more than a decade before symptoms occur)

↑ **Amyloid (CSF Aβ and amyloid PET)**

↑ **Tau (CSF)**

↑ **Brain degeneration (MRI)**

↓ **Cognition (especially memory)**

↓ **Clinical function**

Structural changes such as hippocampal atrophy seen with MR, or neuro-degeneration as seen by hypometabolism on FDG PET, are not visible until much later in the development of amyloid plaque deposition

Cognitively Normal — **MCI** — **Dementia**

~12 years — **~19 years**

By the time patient progresses to full blown dementia, amyloid plaque has been present for almost two decades

- Jack CR Jr, Knopman DS, Jagust WJ, et al. Lancet Neurol 2010; 9:119-28
- Villemagne VL, Burnham S, Bourgeat P, et al. Lancet Neurol 2013; 12:357-6

Treating and Managing AD Today

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- Current drug therapies temporarily treat ***symptoms*** of AD but may not be appropriate in other types of dementia such as frontotemporal dementia (FTD)[1-4]
- Treatment of neuropsychiatric and behavioral symptoms such as apathy, restlessness, anxiety, depression and aggression is often necessary[5]
- Nonpharmacologic management includes[5]
  - Cognitive training, behavioral interventions, sleep hygiene and exercise; caregiver and family support[1]; life planning

1. Alzheimer's Association. 2013 Alzheimer's Disease Facts and Figures
2. Boise L et al. J Gerontol A Biol Sci Med Sci 2004; 59:M621-6
3. Mendez MF et al. Am J Geriatr Psychiatry 2007; 15:84-7
4. National Institute on Aging. Alzheimer's Disease Medications Fact Sheet
5. Zec RF and Burkett NR. NeuroRehabilitation 2008; 23:425-38

Key Message for Referring Physicians

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Diagnosis of AD is difficult, but desirable

Diagnosing AD

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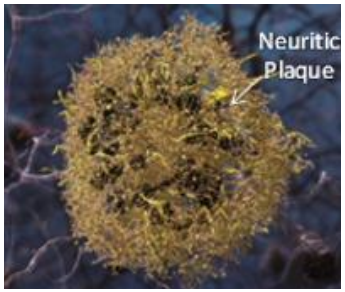
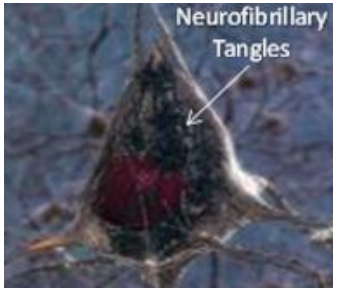
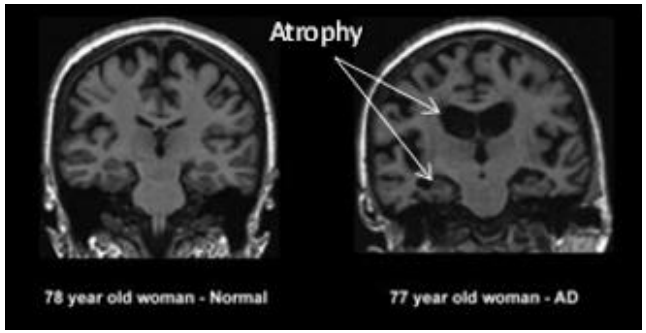
- Normal aging is different from neurodegeneration
- **Definitive** diagnosis of AD requires both clinical features and histopathological confirmation by brain biopsy or autopsy[1,2]
- Three characteristic histopathological findings[3]
  - Beta-amyloid neuritic plaques
  - Neurofibrillary tangles
  - Degeneration with loss of neurons and synapses



β-Amyloid Neuritic Plaque



Neruofibrillary Tangles



Healthy Brain vs. AD Brain

1. Matthews BR and Miller BL, Editors. In: The Behavioral Neurology of Dementia 2009
2. McKhann GM et al. Alzheimers Dement 2011; 7:263-9
3. NIA Primer for Alzheimers Disease

Clinical Diagnosis of AD

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Clinical diagnosis of "probable" or "possible" AD can be made based on the 2011 NIA/AA core criteria[2]

- Based on patient history
- Physical examination
- Cognitive assessment
- Laboratory tests
- Neuroimaging (such as amyloid PET, FDG PET, MR) to rule out reversible or other causes of cognitive impairment[1]

1. Matthews BR and Miller BL. In: The Behavioral Neurology of Dementia 2009
2. McKhann GM et al. Alzheimers Dement 2011; 7:263-9

Use of Biomarkers

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- Biomarkers offer the potential to aid in the diagnosis of AD and other progressive cognitive disorders[2,7]
- Biomarkers that identify patients with amyloid pathology may
  - Enhance confidence in clinical diagnosis[1-5]
  - Lead to earlier diagnosis by identifying individuals with MCI due to AD[6] or prodromal AD[7] who are risk for progression to dementia
- Absence of biomarker signal could promote considering alternative, treatable causes for impairment[1]

1. Grundman M et al. Alzheimer Dis Assoc Disord 2013; 27:4-15
2. McKhann GM et al. Alzheimers Dement 2011; 7:263-9
3. Ossenkoppele R et al. Alzheimers Dement 2013; 9:414-21
4. Frederiksen KS et al. Dement Geriatr Cogn Dis Extra 2012; 2:610-21
5. Schipke CG et al. Dement Geriatr Cogn Disord 2012; 33:416-22 (updated 34:262)
6. Albert MS et al. Alzheimers Dement 2011; 7:270-9
7. Dubois B et al. Lancet Neurol 2010; 9:1118-27

Amyloid PET Impact on Diagnosis

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- Amyloid imaging provides *in vivo* amyloid status and the ability to rule out AD
- Presence of amyloid burden consistent with pathological diagnosis of AD
  - May be present in patients with other neurodegenerative diseases and in cognitively normal elderly patients
- Lack of amyloid burden is inconsistent with AD
- Researchers have demonstrated that Amyloid PET can
  - Increase diagnostic confidence[1-5,7,8] and change clinical diagnosis[1-8]

1. Fredricksen KS et al. Dement Geriatr Cogn Disord Extra 2012; 2:610-21
2. Grundman M et al. Alzheimer Dis Assoc Disord 2012; 00:1-12
3. Schipke GE et al. Dement Geriatr Cogn Disord 2012; 33:416-422
4. Ossenkoppele R et al. Alzheimer's and Dementia 2013; 9:414-421
5. Ghosh PM et al. AAIC 2014;10(4):Supplement P249
6. Sanchez-Juan P et al. Neurology 2014; 82:230-238
7. Zwan MD et al. AAIC 2014; 10(4):Supplement P248
8. Pontecorvo et al. AAIC 2015; 11(7):Supplement P334

Diagnosis: Too Little, Too Late

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- Diagnosis is uncertain with clinical assessment alone, despite standardized clinical diagnostic criteria or level of dementia expertise
  - Up to 22% of dementia patients ≥71 years were undiagnosed[1]
  - PCP failed to diagnose 56% of dementias in poor older adults with functional impairment[2]
  - Compared to autopsy, clinical diagnosis yielded sensitivity for AD from 70.9% to 82.7% and specificity from 54.5% to 70.8%[3]
  - 17% of patients with clinically probable AD did not have AD pathology at autopsy[3]

SENSITIVITY AND SPECIFICITY OF CLINICAL DIAGNOSIS[3]

Clinical Diagnosis	Sensitivity	Specificity
Clinically Probable AD	70.9	70.8%
Clinically Probable or Possible AD	82.7%	54.5%

1. Savva et al. Age and Ageing 2015
2. Wilkins et al. J Am Geriatr Soc 2007
3. Beach et al. JNEN 2012

Frequency of False Positive Clinical Diagnosis

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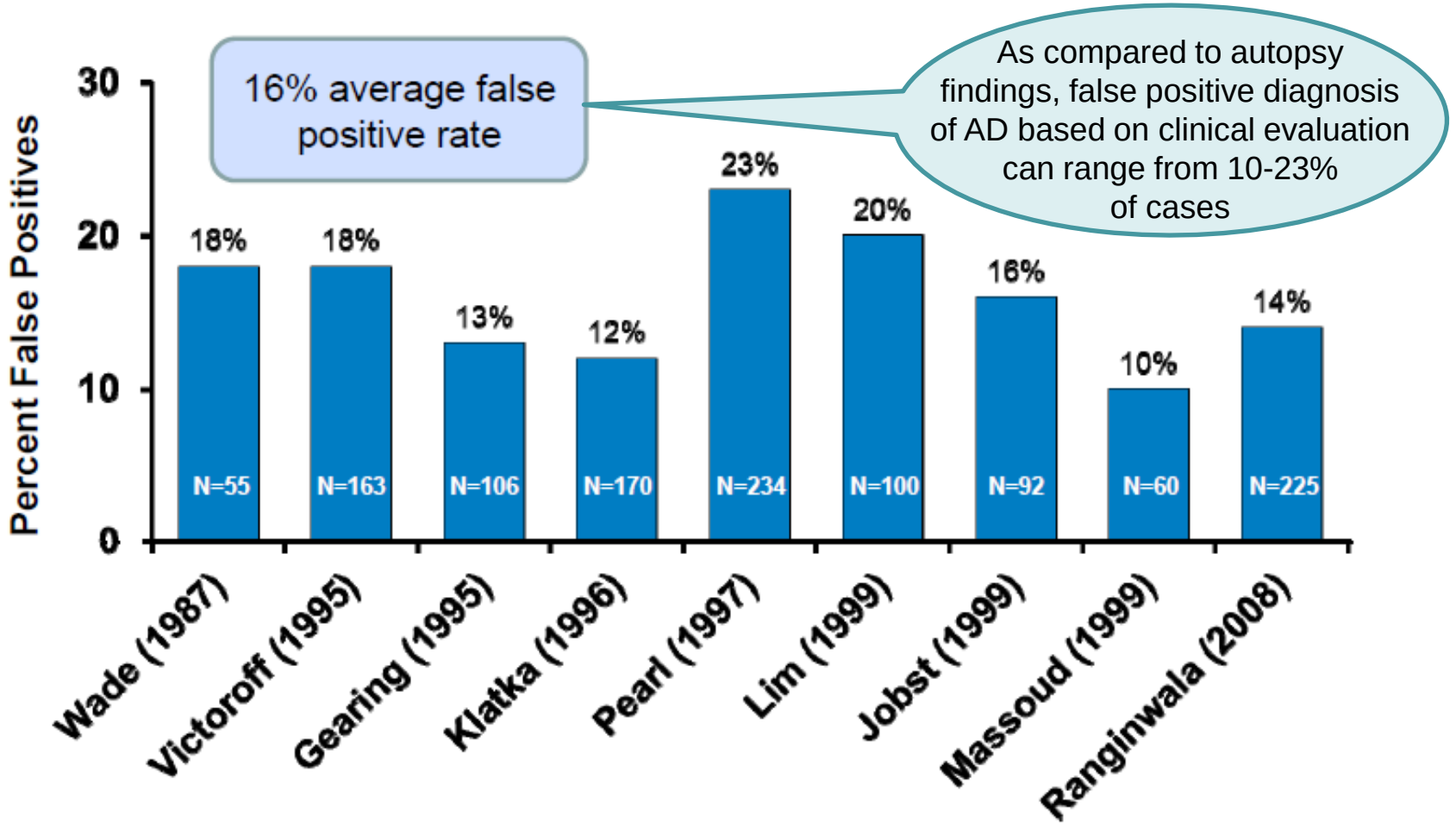

Clinical Diagnosis vs. Autopsy Results

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Beach et al. J Neuropath Exp Neurol 2012

- Neuropathology studies reveal inaccuracies, especially in possible AD
- Comorbid pathology is often missed
- 919 patients clinically diagnosed with dementia had autopsy confirmation of their disease
- In 648 patients who were diagnosed in life as possible or probable AD
  - Clinical diagnosis was sensitive (able to diagnose when disease was truly present) 70.9% to 82.7% of the time
  - Clinical diagnosis was specific (able to rule out disease when it was not truly present) 54.5% to 70.8% of the time

Clinical Diagnosis vs. Autopsy Results

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Beach et al. J Neuropath Exp Neurol 2012, cont.

- 107 out of 271 patients (39%) who were not clinically diagnosed as possible/probable AD had positive neuropathology for AD
- *"In most studies, sensitivity is relatively high while specificity is low and many studies have reported only sensitivity or positive predictive value, which has led to a false impression that the clinical diagnosis of AD is extremely accurate."*

Why Do We Sometimes Fail to Diagnose AD?

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- Uncertainty – symptoms vary widely in life and there are multiple types of dementia (Beach et al. 2012)
  - heightened by a lack of testing methods and tools
- Attitudes about dementia (e.g., fear of causing distress, lack of disease modifying treatment, etc.)
- Delayed diagnosis – “watch and see” effect
- Challenging to deliver the diagnosis, especially if unaware of support resources
- Lack of awareness of management options and benefits of a diagnosis

- Beach et al. JNEN 2012
- Aminzadeh et al. Can Geriatr J 2012
- Koch et al. BMC Family Practice 2010

Patients Value More Control Over the Decision-Making Process

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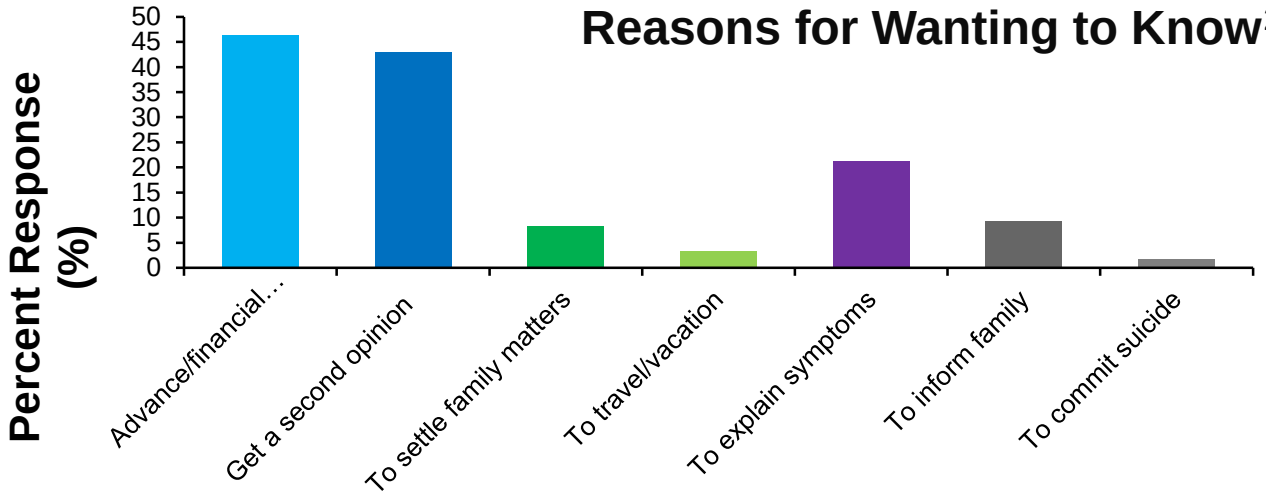
- In a five-country value of knowing project, >85% of respondents would want to see a doctor to determine if Alzheimer's disease (AD)[1] was the cause of their symptoms
- In another study of 200 patients assessing attitudes regarding disclosure of AD diagnosis, 92% would want to be told if they have AD[2]



1. Harvard School of Public Health and Alzheimer Europe. Five-country Alzheimer's disease survey. AAIC July 20, 2011
2. Turnbull Q et al. J Geriatr Psychiatry Neurol. 2003;16(2):90-93

The Potential Impact of Timely Diagnosis is Significant

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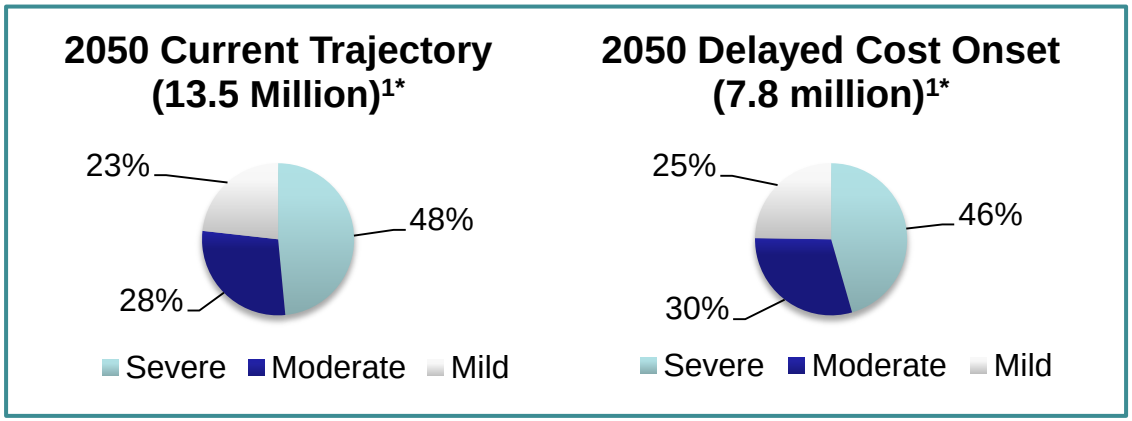
- When diagnosed early, in active patients, any treatment delaying progression has the potential to prolong productive life, reduce the high cost to society and delay progression to dementia[1]
- Improved diagnostic certainty in patients diagnosed early may provide stronger motivation to start prevention treatment, change unhealthy lifestyle habits, reduce societal costs incurred by caregiver support and loss of earnings[2,3]



Impact of a Treatment that Delays Onset on the Proportion of Americans Age 65 and Older Living with Alzheimer's by Disease Stage, 2050

*Totals may not add up due to rounding.

[1] www.alz.org/documents_custom/trajectory.pdf
[2] www.alz.co.uk/research/WorldAlzheimerReport2011.pdf
[3] www.alz.co.uk/research/WorldAlzheimerReport2014.pdf

Benefits of an Early and Accurate Diagnosis

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- May reduce the impact of misdiagnosis
- Provides access to a pathway of care – including enrolling in clinical trials
- Allows patients and their families to seek support and plan for the future; a proper diagnosis offers hope
- Targeted medication, lifestyle management and treatment of comorbid conditions can improve quality of life
- Addresses safety considerations in the setting of cognitive impairment, including ability to continue driving

www.alz.org/2016 Facts and Figures

Key Message for Referring Physicians

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Amyloid imaging provides *in vivo* amyloid status and the ability to rule out AD

Benefits of Amyloid PET Imaging

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Amyloid PET imaging

- Is non-invasive
- Provides a direct measure of amyloid status *in vivo*
- Links to a specific molecular mechanism
  - Accumulation of neuritic amyloid plaque
- May lead to early detection or exclusion of AD
- May be useful in selecting patients for clinical trials
  - Amyloid PET imaging as a biomarker for therapeutic efficacy

Benefits of Amyloid PET Imaging

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- Reports show that adjunctive amyloid PET can increase diagnostic certainty and physician confidence[1-5,7,8]
- Reports show that amyloid PET results can impact clinical decision-making and patient management[1-8]

1. Fredricksen KS et al. Dement Geriatr Cogn Disord Extra 2012; 2:610-21
2. Grundman M et al. Alzheimer Dis Assoc Disord 2012; Volume 00:1-12
3. Schipke GE et al. Dement Geriatr Cogn Disord 2012; 33:416-422
4. Ossenkoppele R et al. Alzheimer's and Dementia 2013, 9:414-421
5. Ghosh PM et al. AAIC 2014; 10(4):Supplement P249
6. Sanchez-Juan P et al. Neurology 2014; 82:230-238
7. Zwan MD et al. AAIC 2014; 10(4):Supplement P248
8. Pontecorvo et al. AAIC 2015; 11(7):Supplement P334

What is PET Amyloid Imaging?

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- **P**ositron **E**mission **T**omography (PET) Scan for purposes of detecting **beta amyloid plaque**
- The patient is injected intravenously with an amyloid PET radiopharmaceutical (small amount of radioactivity)
- Amyloid radiopharmaceutical binds to β-amyloid neuritic plaques in the brain
- The F-18 isotope produces a positron signal that is detected by a PET scanner

What is PET Amyloid Imaging?

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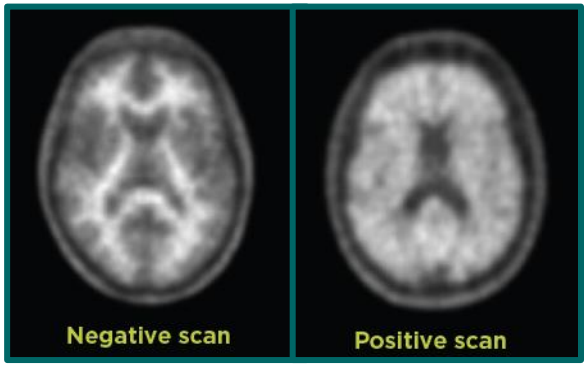
- Image are acquired 30-130 minutes post-injection depending upon the radiopharmaceutical
- Scanning typically takes 10-20 minutes depending on the radiopharmaceutical used and the camera requirements
- Images are interpreted for presence of beta amyloid plaque

http://www.jrtassociates.com

~30-130 min

http://www3.gehealthcare.com

~10-30 min



Amyloid F-18 Imaging Radiopharmaceuticals

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- **Florbetapir F-18 Injection = Amyvid™**
  - Eli Lilly and Company[1]
- **Flutemetamol F-18 Injection = Vizamyl™**
  - GE Healthcare[2]
- **Florbetaben F-18 Injection = Neuraceq™**
  - Piramal Imaging[3]

1. Eli Lilly (2012). Amyvid (Florbetapir F 18 Injection): Prescribing Information. Indianapolis, IN
2. General Electric Company (2013). Vizamyl (Flutemetamol F 18 Injection): Prescribing Information. Manufactured for GE Healthcare by Medi-Physics, Inc. Arlington Heights, IL
3. Piramal Imaging SA (2014). Neuraceq (Florbetaben F 18 Injection): Prescribing Information. Matran, Switzerland

Amyloid F-18 Imaging Radiopharmaceuticals

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- The difference between a positive and negative amyloid F-18 PET image is the **presence of uptake in the gray matter cortex** vs. existing white matter
- There are product-specific guidelines for dosing, administration, processing, display and interpretation of F-18 labeled amyloid agents
- Amyloid images should be displayed according to the radiopharmaceutical-specific validated method
- Readers should be trained on the radiopharmaceutical-specific training method provided by the manufacturer

Mechanism of Action

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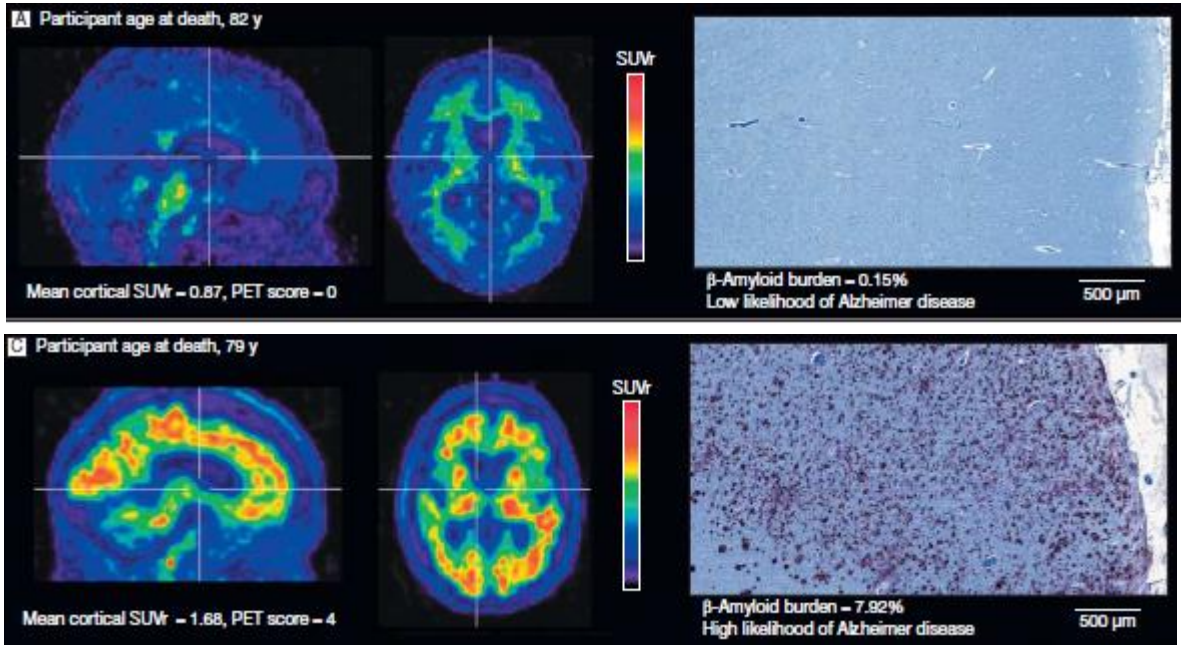
- Amyloid radiopharmaceuticals bind to β-amyloid neuritic plaques in the brain
- The F-18 isotope produces a positron signal detected by a PET scanner[1,2,3]
- Binding is specific to beta amyloid[4] (vs. tau or other proteins)

Florbetapir PET Scans

β-Amyloid Antibody 4G8 Immunohistochemistry



1. Eli Lilly (2012). Amyvid (Florbetapir F 18 Injection): Prescribing Information. Indianapolis, IN
2. General Electric Company (2013). Vizamyl (Flutemetamol F 18 Injection): Prescribing Information. Manufactured for GE Healthcare by Medi-Physics, Inc. Arlington Heights, IL
3. Piramal Imaging SA (2014). Neuraceq (Florbetaben F 18 Injection): Prescribing Information. Matran, Switzerland
4. Choi SR et al. Alzheimer Dis Assoc Disorder 2012; 26:8-16

Negative Scan

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- A negative scan indicates sparse to no neuritic plaques and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition[1-3]
- A negative scan result reduces the likelihood that a patient's cognitive impairment is due to AD[1-3]

1. Eli Lilly (2012). Amyvid (Florbetapir F 18 Injection): Prescribing Information. Indianapolis, IN
2. General Electric Company (2013). Vizamyl (Flutemetamol F 18 Injection): Prescribing Information. Manufactured for GE Healthcare by Medi-Physics, Inc. Arlington Heights, IL
3. Piramal Imaging SA (2014). Neuraceq (Florbetaben F 18 Injection): Prescribing Information. Matran, Switzerland

Negative Scan

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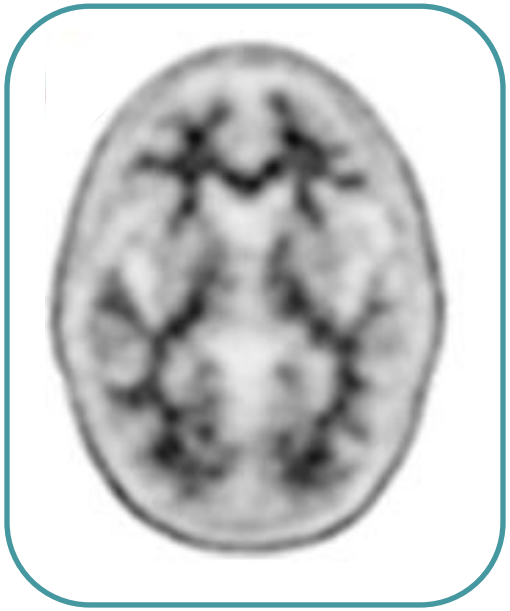
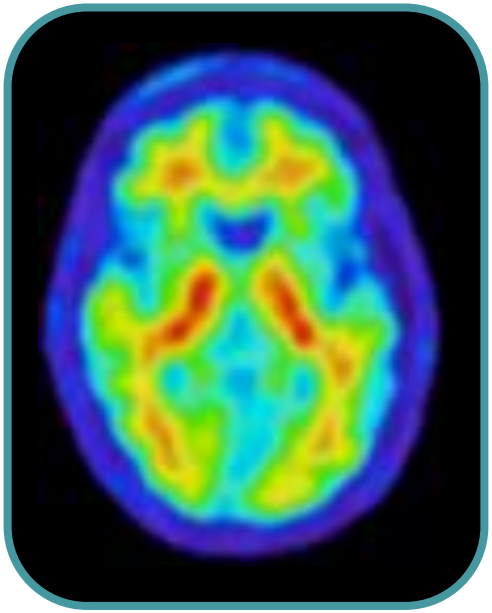
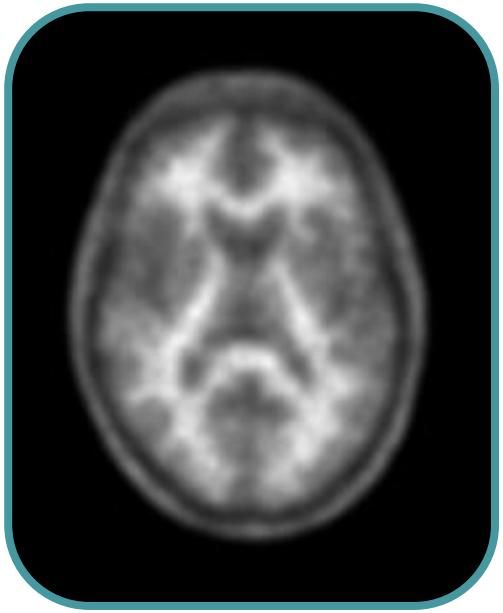


florbetapir F-18



flutemetamol F-18



florbetaben F-18

Positive Scan

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- A positive scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown that this amount of amyloid neuritic plaque is present in patients with AD[1-3]
- May also be present in patients with other types of neurologic conditions as well as older people with normal cognition[1-3]

1. Eli Lilly (2012). Amyvid (Florbetapir F 18 Injection): Prescribing Information. Indianapolis, IN
2. General Electric Company (2013). Vizamyl (Flutemetamol F 18 Injection): Prescribing Information. Manufactured for GE Healthcare by Medi-Physics, Inc. Arlington Heights, IL
3. Piramal Imaging SA (2014). Neuraceq (Florbetaben F 18 Injection): Prescribing Information. Matran, Switzerland

Positive Scan

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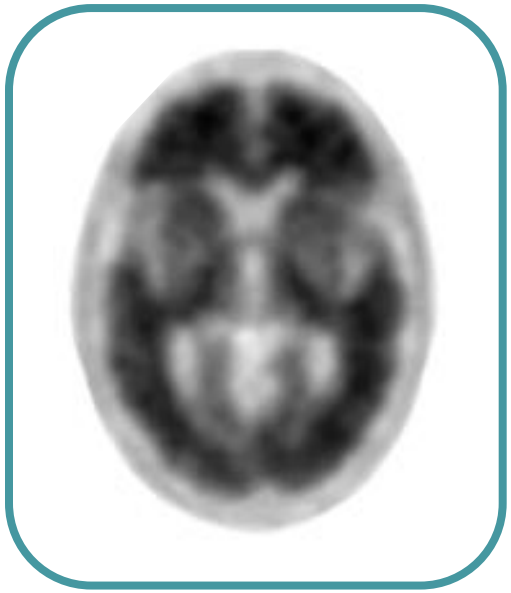
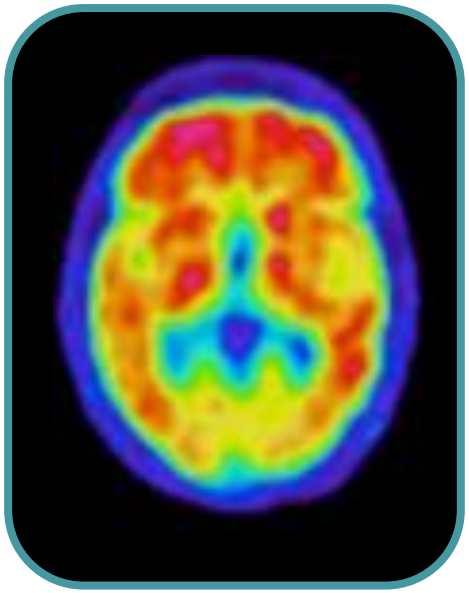
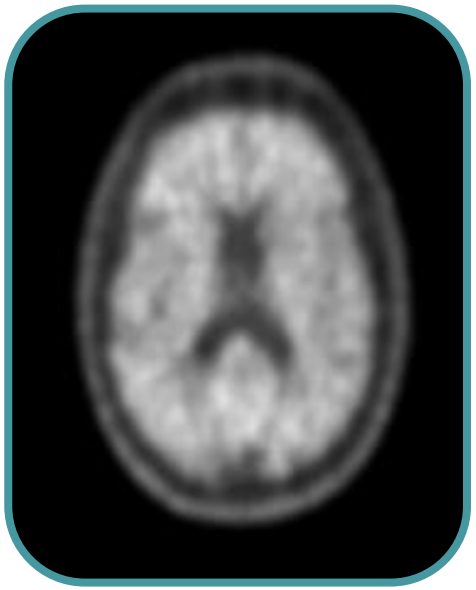


florbetapir F-18



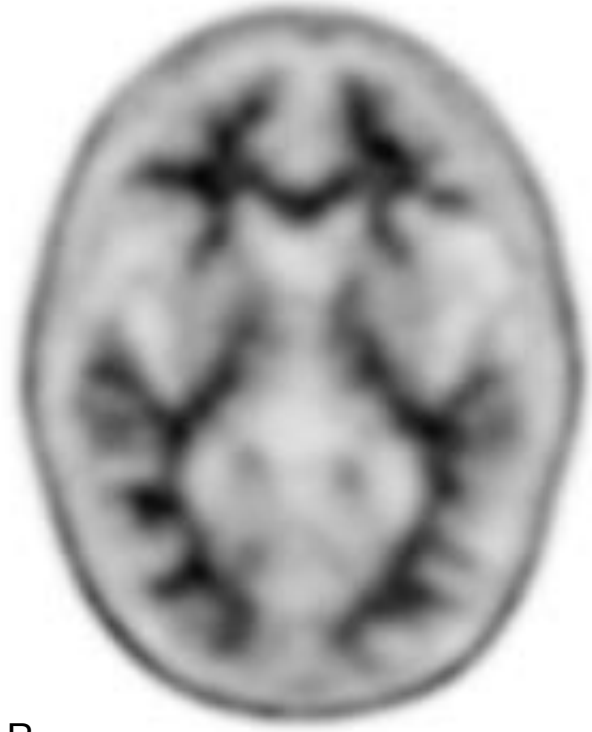
flutemetamol F-18



florbetaben F-18

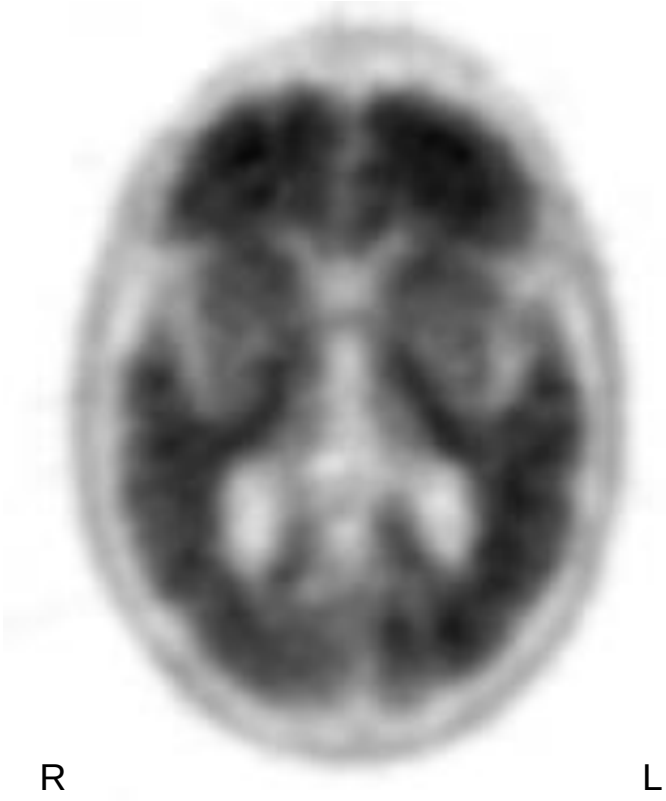
Florbetapir: Negative vs. Positive

DETAIL
DEMONSTRATING EXCELLENCE THROUGH ADVANCED IMAGING LEARNING



R L

Negative



R L

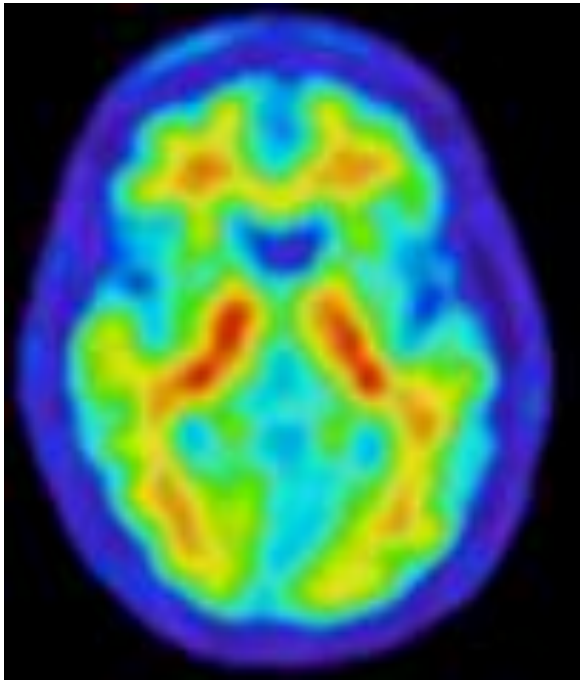
Positive

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

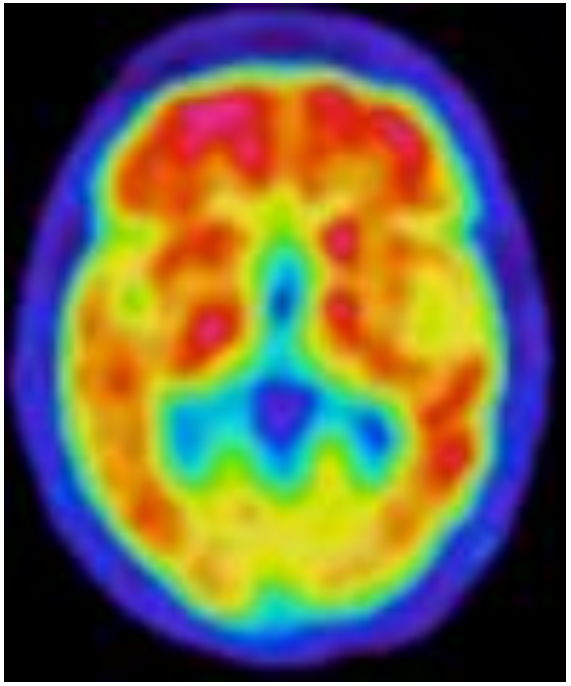
Flutemetamol: Negative vs. Positive

DETAIL

DEMONSTRATING EXCELLENCE THROUGH ADVANCED IMAGING LEARNING



R Negative L

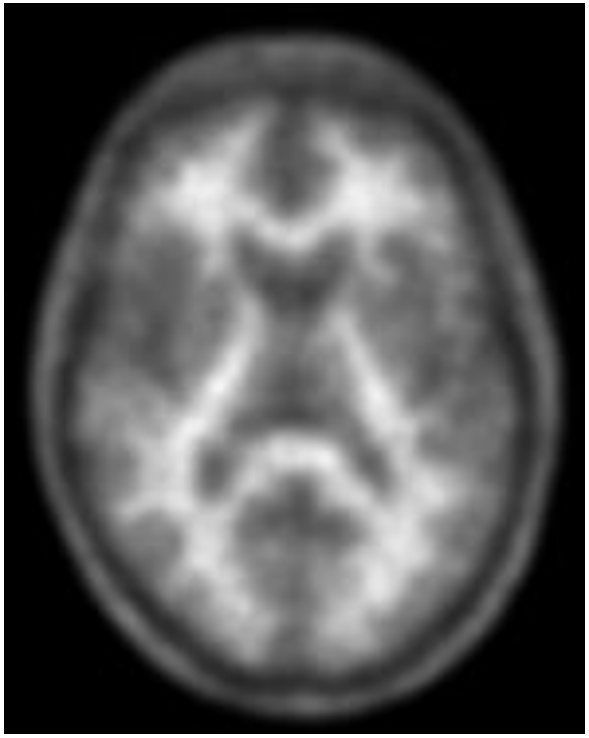


R Positive L

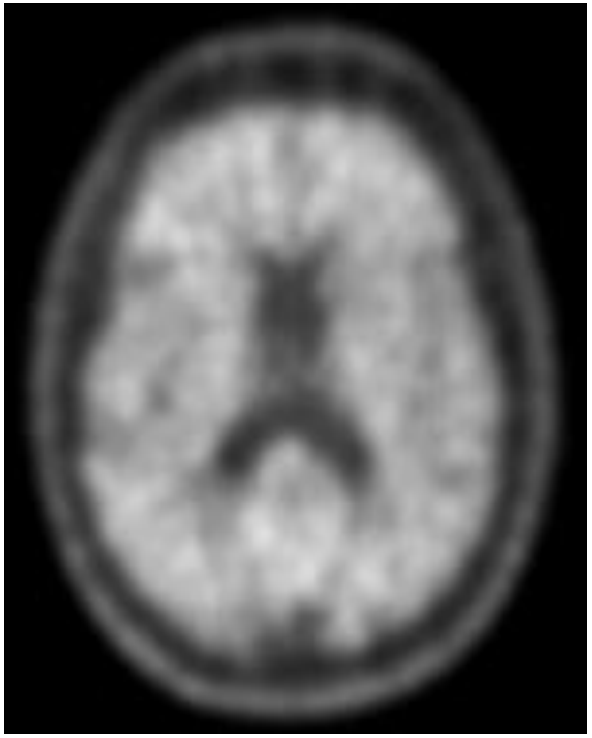
General Electric Company (2013). Vizamyl (Flutemetamol F 18 Injection): Prescribing Information. Manufactured for GE Healthcare by Medi-Physics, Inc. Arlington Heights, IL

Florbetaben: Negative vs. Positive

DETAIL
DEMONSTRATING EXCELLENCE THROUGH ADVANCED IMAGING LEARNING



R Negative L



R Positive L

Piramal Imaging SA (2014). Neuraceq (Florbetaben F 18 Injection): Prescribing Information. Matran, Switzerland

Risk of Interpretation Errors

DETAIL
DEMONSTRATING EXCELLENCE THROUGH ADVANCED IMAGING LEARNING

- Errors may occur in the estimation of brain neuritic plaque density during image interpretation.
- Image interpretation should be performed independently of the patient's clinical information. The use of clinical information in the interpretation of images has not been evaluated and may lead to errors. Other errors may be due to extensive brain atrophy that limits the ability to distinguish gray and white matter on the scan as well as motion artifacts that distort the image.
- Scan results are indicative of the brain neuritic amyloid plaque content only at the time of image acquisition and a negative scan result does not preclude the development of brain amyloid in the future.

1. Eli Lilly (2012). Amyvid (Florbetapir F 18 Injection): Prescribing Information. Indianapolis, IN
2. General Electric Company (2013). Vizamyl (Flutemetamol F 18 Injection): Prescribing Information. Manufactured for GE Healthcare by Medi-Physics, Inc. Arlington Heights, IL
3. Piramal Imaging SA (2014). Neuraceq (Florbetaben F 18 Injection): Prescribing Information. Matran, Switzerland

Key Message for Referring Physicians

DETAIL

DEMONSTRATING EXCELLENCE THROUGH ADVANCED IMAGING LEARNING

Amyloid imaging can assist with
and even change medical management

Impact of Amyloid Imaging on **DIAGNOSIS**

DETAIL
DEMONSTRATING EXCELLENCE THROUGH ADVANCED IMAGING LEARNING

Review of clinical studies/literature

- PET amyloid imaging can result in a change of diagnosis[1-8]
  - In **probable** AD patients[1,3,4]
  - In **uncertain diagnosis** (less than 85-90% certainty)[1,2,4,7,8]
  - Changes occurred in 14-55% of cases[1-5,7,8]
  - Changes occurred even from clinical evaluation by dementia specialists[1-8]
- PET amyloid imaging increases **clinician confidence** in diagnosis by 16-78%[1-5,7,8]

1. Fredricksen KS et al. Dement Geriatr Cogn Disord Extra 2012; 2:610-21
2. Grundman M et al. Alzheimer Dis Assoc Disord 2012; 00:1-12
3. Schipke GE et al. Dement Geriatr Cogn Disord 2012; 33:416-422
4. Ossenkoppele R et al. Alzheimer's and Dementia 2013; 9:414-421
5. Ghosh PM et al. AAIC 2014; 10(4):Supplement P249
6. Sanchez-Juan P et al. Neurology 2014; 82:230-238
7. Zwan MD et al. AAIC 2014; 10(4):Supplement P248
8. Pontecorvo MI et al. AAIC 2015; 11(7):Supplement P334

Impact of Amyloid Imaging on AD **MANAGEMENT**

DETAIL
DEMONSTRATING EXCELLENCE THROUGH ADVANCED IMAGING LEARNING

Review of Clinical Studies/Literature

- Change in AD management occurred in 52-87% of cases[1-3,6,7]
  - ↓ in further diagnostic imaging
  - ↓ in further neuropsychological testing
- Change in AD medications occurred in 11-35% of cases[1,2,4-7]
  - ↓ AD medications in amyloid-negative patients
  - ↑ AD medications in amyloid-positive patients

1. Grundman M et al. Alzheimer Dis Assoc Disord 2012; Volume 00:1-12
2. Schipke GE et al. Dement Geriatr Cogn Disord 2012; 33:416-422
3. Ossenkoppele R et al. Alzheimer's and Dementia 2013, 9:414-421
4. Ghosh PM et al. AAIC 2014; 10(4):Supplement P249
5. Sanchez-Juan P et al. Neurology 2014; 82:230-238
6. Zwan MD et al. AAIC 2014; 10(4):Supplement P248
7. Pontecorvo MI et al. AAIC 2015; 11(7):Supplement P334

Grundman et al. 2013

DETAIL
DEMONSTRATING EXCELLENCE THROUGH ADVANCED IMAGING LEARNING

In the largest study published to date, after receiving the results of the florbetapir scan, diagnosis changed in 125/229 of cases, or 54.6% (95% CI: 48.1% to 60.9%)

CHANGE IN DIAGNOSIS FROM PRE-SCAN TO POST-SCAN FOR EACH DIAGNOSIS CATEGORY

Pre-Scan Diagnosis	Post-Scan Diagnosis			Change
	Indeterminate	Due to AD	Not due to AD	
Negative scan result				
Indeterminate (n=74)	41 (55.4%)	0 (0.0%)	33 (44.6%)	33 (44.6%)
Etiology due to AD (n=33)	22 (66.7%)	1 (3.0%)	10 (30.3%)	32 (97.0%)
Not due to AD (n=9)	1 (11.1%)	0 (0.0%)	8 (88.9%)	1 (11.1%)
Positive scan result				
Indeterminate (n=48)	1 (2.1%)	47(97.9%)	0 (0.0%)	47 (97.9%)
Etiology due to AD (n=53)	0 (0.0%)	53 (100.0%)	0 (0.0%)	0 (0.0%)
Not due to AD (n=12)	0 (0.0%)	12 (100.0%)	0 (0.0%)	12 (100.0%)

Note: Subjects in whom the physician was highly confident in pre-scan diagnosis (i.e., >85% confidence the diagnosis was AD or not AD) were excluded from enrolment

Grundman et al. Alzheimer Dis Assoc Disord 2013; 27:4-15

Grundman et al. 2013

DETAIL
DEMONSTRATING EXCELLENCE THROUGH ADVANCED IMAGING LEARNING

- Percentage of patients for whom physician intended to add or remove AD medication as a result of the amyloid PET finding

Subjects	Amyloid Positive	Amyloid Negative
With dementia (N=83)	25.4	20.8
Without dementia (N=146)	38.9	32.6

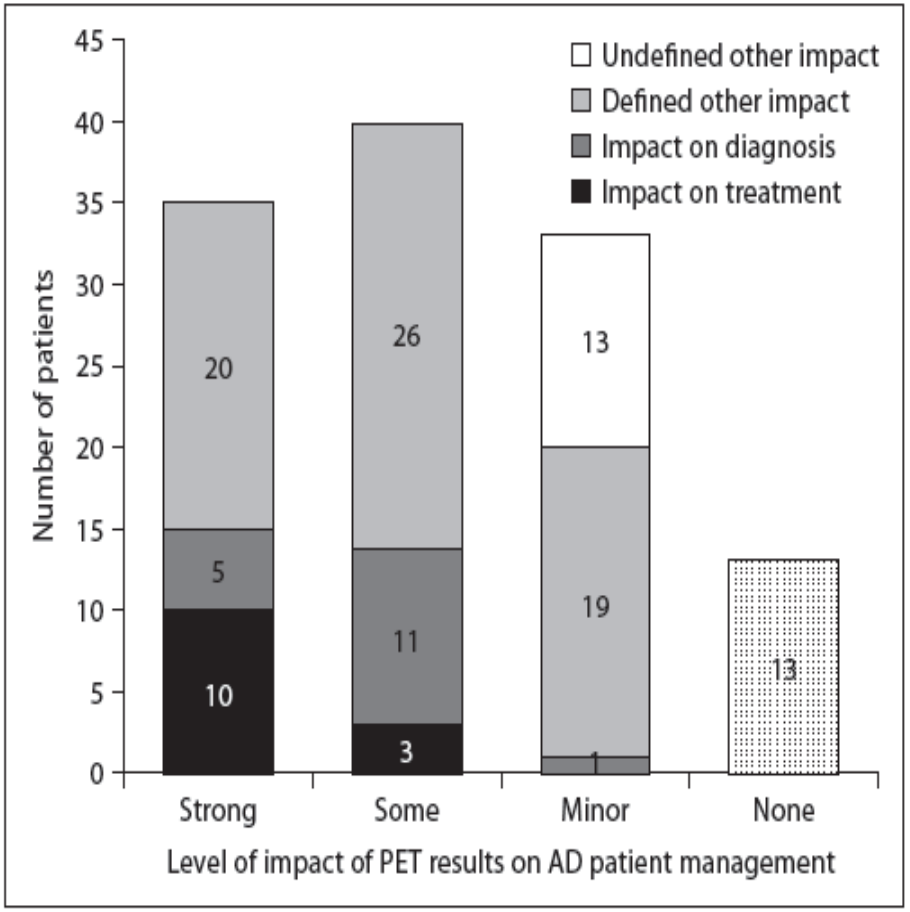
- 10.9% amyloid positive and 5.2% amyloid negative patients were referred to clinical trial

Grundman et al. Alzheimer Dis Assoc Disord 2013; 27:4-15

Schipke et al. 2012

DETAIL
DEMONSTRATING EXCELLENCE THROUGH ADVANCED IMAGING LEARNING

- In 121 patients with a clinical diagnosis of probable AD:
  - A negative florbetaben PET scan resulted in decreased physician confidence in pre-scan diagnosis in 100% of cases
  - A positive scan resulted in an increased diagnostic confidence in 78% of cases

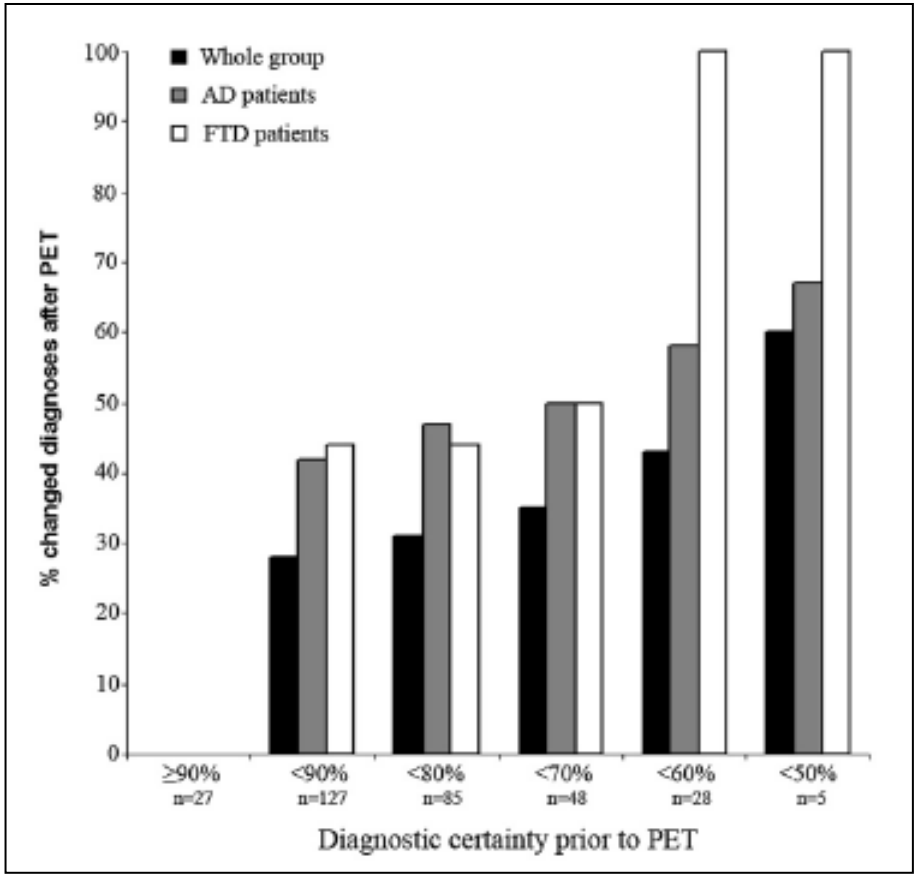


Schipke GE et al. Dement Geriatr Cogn Disord 2012; 33:416-422

Ossenkoppele et al. 2013

DETAIL
DEMONSTRATING EXCELLENCE THROUGH ADVANCED IMAGING LEARNING

- 154 patients in a memory clinic
- Clinical diagnosis changed in 23% of patients as a result of amyloid PET imaging
- Overall diagnostic certainty increased from 71% before amyloid PET to 87% post-PET scan ($p<0.001$)



Ossenkoppele R et al. Alzheimer's and Dementia 2013; 9:414-421

Zwan et al. 2015

DETAIL
DEMONSTRATING EXCELLENCE THROUGH ADVANCED IMAGING LEARNING

VUmc VU University Alzheimer Center Amsterdam
Neuroscience Campus Amsterdam

Dutch Flutemetamol Study

Impact on diagnosis in early-onset dementia patients (n=211)

Pre-PET diagnosis	AD (n=145)		non-AD (n=66)	
PET result	**positive**	**negative**	**positive**	**negative**
n	111 (77%)	34 (23%)	22 (33%)	44 (67%)
Change in diagnosis	0	26 (18%)	15 (23%)	0

- 7 frontotemporal dementia
- 3 dementia with lewy bodies
- 4 other dementia
- 12 other

- 14 Alzheimer's disease
- 1 dementia with lewy bodies

Zwan et al. AAIC 2015; 11(7):Supplement P3–4

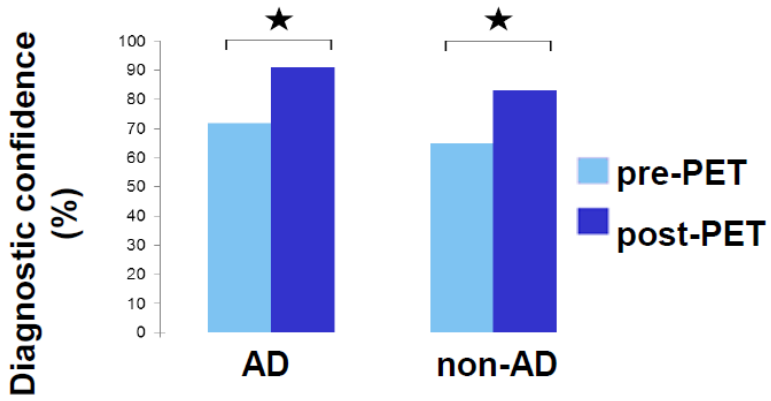
Zwan et al. 2015

DETAIL
DEMONSTRATING EXCELLENCE THROUGH ADVANCED IMAGING LEARNING

VUmc VU University Alzheimer Center Amsterdam
Neuroscience Campus Amsterdam

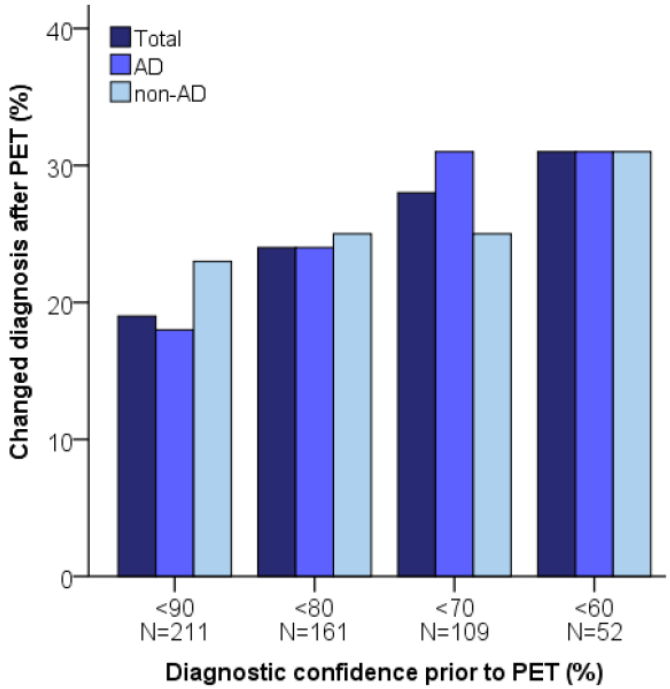
Results: Dutch Flutemetamol Study

1) Diagnostic confidence



In both AD and non-AD, PET increased diagnostic confidence overall

2) Pre-PET confidence & impact on diagnosis



Zwan et al. AAIC 2015; 11(7):Supplement P3–4

Zwan et al. 2015

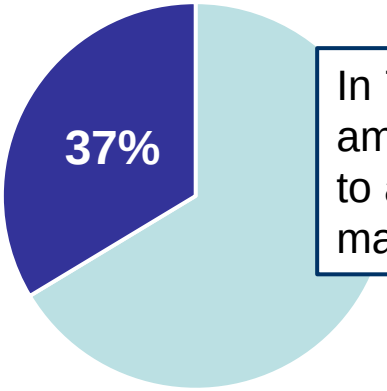
DETAIL
DEMONSTRATING EXCELLENCE THROUGH ADVANCED IMAGING LEARNING

Results: Dutch Flutemetamol Study

VUmc VU University Alzheimer Center Amsterdam
Neuroscience Campus Amsterdam

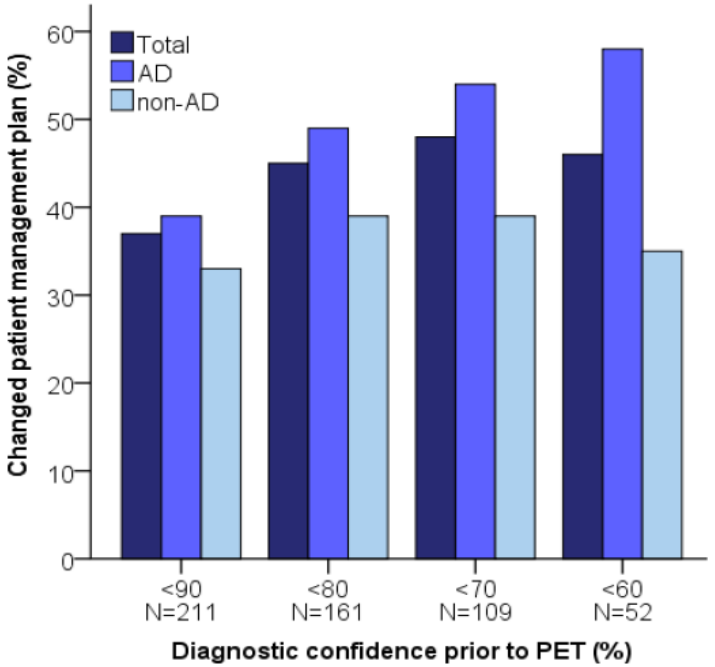
3) Change in patient management plan

- Prescription in medication
- Change in care plan
- Change in request for ancillary investigations



In 79 (37%) of patients, amyloid PET results led to a change in patient management plan overall

4) Pre-PET confidence related to impact on patient management plan



Zwan et al. AAIC 2015; 11(7):Supplement P3–4

Key Message for Referring Physicians

DETAIL
DEMONSTRATING EXCELLENCE THROUGH ADVANCED IMAGING LEARNING

Amyloid imaging is accessible for Medicare patients via the **IDEAS Study**

IDEAS Study

- Imaging Dementia – Evidence for Amyloid Scanning (IDEAS) Study:
  A Coverage with Evidence Development Longitudinal Cohort Study
- Directed by: Alzheimer's Association
- Sponsored & Managed by: American College of Radiology (ACR); American College of Radiology Imaging Network (ACRIN)
- Advised by: Centers for Medicare & Medicaid Services (CMS)
- Tracer Agnostic: All amyloid tracers can be used
  - florbetaben (*Neuraceq*; Pirmal Imaging)
  - florbetapir (*Amyvid*; Eli Lilly and Company)
  - flutemetamol (*Vizamyl*; GE Healthcare)

Study Overview

- An open-label, longitudinal cohort study that will assess the impact of brain amyloid PET imaging on patient outcomes under Coverage with Evidence Development (CED) in patients meeting Appropriate Use Criteria (AUC)[1,2]
- The **primary hypothesis** is that, in diagnostically uncertain cases, knowledge of amyloid status as determined by brain amyloid PET will lead to significant changes in patient management, and this will translate into improved medical outcomes

1. J Nucl Med 2013; 54:476-490
2. Alzheimers Dement 2013; 9:e1-e16

IDEAS Aim 1

- To assess the impact of brain amyloid PET imaging on the management of patients meeting AUC at 90 days
  - Patient management plans are recorded in pre- and post-PET case report forms completed by the Dementia Specialist

Aim 1 Study Primary Objective

- Test whether amyloid PET imaging will lead to a ≥30% change between intended and actual patient management within ~90 days in a composite measure of at least one of the following:
  - AD drug therapy
  - Other drug therapy
  - Counseling about safety and future planning
- The hypothesis will be tested separately for mild cognitive impairment (MCI) and dementia

IDEAS Aim 2

- To assess the impact of brain amyloid PET on hospital admissions and emergency room (ER) visits in study patients (amyloid PET-known) compared to matched patients not in the study (amyloid PET-naïve) over 12 months
  - CMS Claims Data to address Aim 2 will be collected for all study participants and from concurrent controls matched according to a validated algorithm
  - 7,438 additional participants needed for a total of 18,488
  - Metric: 10% relative reduction in hospitalizations / ER visits

Aim 2 Rationale

- Individuals with dementia at increased risk for hospitalizations and ED visits compared to those without dementia[1]
  - Annual hospitalizations: 26.7% vs. 18.7%[1]
  - Annual ED visits: 34.5% vs. 24.5%[1]
  - *Two-thirds deemed preventable* (CHF exacerbation, bacterial pneumonia, UTI)[2]
- Dementia associated with increased mortality and shorter survival after hospitalizations
- Preliminary data from Kaiser shows targeted dementia plan led to 18% reduction in ED visits and 11% reduction in hospitalizations[3]

1. Feng et al. Health Aff 2014; 33(4):683-390
2. Phelan et al. JAMA 2012; 307(2):165-172
3. Whitmer RA. Unpublished data

Overall Rationale (Aims 1 and 2)

Diagnostic clarity helps to

- Prompt physicians, individuals and their families to develop targeted strategies to manage medical comorbidities
- Develop a care plan to better protect personal safety in the setting of cognitive impairment

Increased diagnostic clarity will lead to targeted care plan, which will translate into decreased hospitalizations and ER visits

AA-SNMMI Amyloid Imaging Taskforce

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

Keith A. Johnson[1], Satoshi Minoshima[2], Nicolaas I. Bohnen[3], Kevin J. Donohoe[4], Norman L. Foster[5], Peter Herscovitch[6], Jason H. Karlawish[7], Christopher C. Rowe[8], Maria C. Carrillo[9], Dean M. Hartley[9], Saima Hedrick[10], Virginia Pappas[10], and William H. Thies[9]

- **Patient should meet following criteria:**
  - Cognitive complaint with objectively confirmed impairment
  - Uncertain diagnosis (with AD as a possibility) after comprehensive evaluation by a dementia expert
  - Knowledge of Aβ status expected to increase diagnostic certainty and alter management

Appropriate Use Criteria: Top Clinical Scenarios

- **Persistent/progressive unexplained MCI**
- **Patients with "possible" AD**
  - Atypical clinical course, mixed presentation
  - Significant co-morbidities (e.g. vascular, psychiatric, substance abuse)
- **Patients with atypically early age-of-onset (<65 years)**
  - Note this population is excluded from IDEAS

Inappropriate Uses of Amyloid PET

- **Initial evaluation of cognitive complaints**
  - Scan not a substitute for clinical evaluation
- **Screening of cognitively normal individuals**
  - Pre-clinical AD is a research concept only!
  - Non-medical use (disability, employment)
- **Based on family history or genetic risk**

Johnson et al.
Alzheimer's & Dementia/J Nuc Med 2013

Amyloid PET Not Useful

- **Differentiate AD from other Aβ diseases**
  - Dementia with Lewy bodies; cerebral amyloid angiopathy
- **Determine dementia severity**
- **Unlikely to add value in straightforward clinical phenotypes**

Best Practices: Pre-PET Screening Visit

- **Assess mood (depression, anxiety)**
  - Consider use of standardized scales
    - e.g. State-Trait Anxiety Inventory (STAI), Geriatric Depression Scale (GDS)
- **Educate about amyloid PET**
  - Relationships between amyloid and AD, relevance to patient's symptoms
  - Meaning of positive and negative scan
  - Consider utilizing Alzheimer's Association brochure to anchor discussion

Adopted from Harkins et al. Alzheimers Res Ther 2015

Best Practices: Pre-PET Screening Visit

- **Discuss ramifications of positive and negative scan result**
  - Diagnosis, prognosis and management
  - Psychological impact
- **Assess patient and family understanding**
  - Consider using “teach back” method
  - Why is the scan being ordered? How will results impact care?
  - What will be the psychological impact of positive or negative result?

Adopted from Harkins et al. Alzheimers Res Ther 2015

Best Practices: Pre-PET Screening Visit

- **IDEAS Exclusion criteria 4.2.2**
  - *Knowledge of amyloid status, in the opinion of the referring dementia expert, may cause significant psychological harm or otherwise negatively impact the patient or family*

Best Practices: Amyloid Status Disclosure

- **Disclosure should be made by referring dementia expert, in person whenever possible**
  - Avoid first disclosure by EMR
  - Encourage caregiver/family member/friend attendance to offer support
  - Schedule enough time in the appointment to allow for questions
- **Prior to disclosure**
  - Assess mood, recent clinical developments
  - Assess willingness to receive results
  - Consider revisiting what the scan is measuring and why it was ordered

Adopted from Harkins et al. Alzheimers Res Ther 2015

Best Practices: Following Disclosure

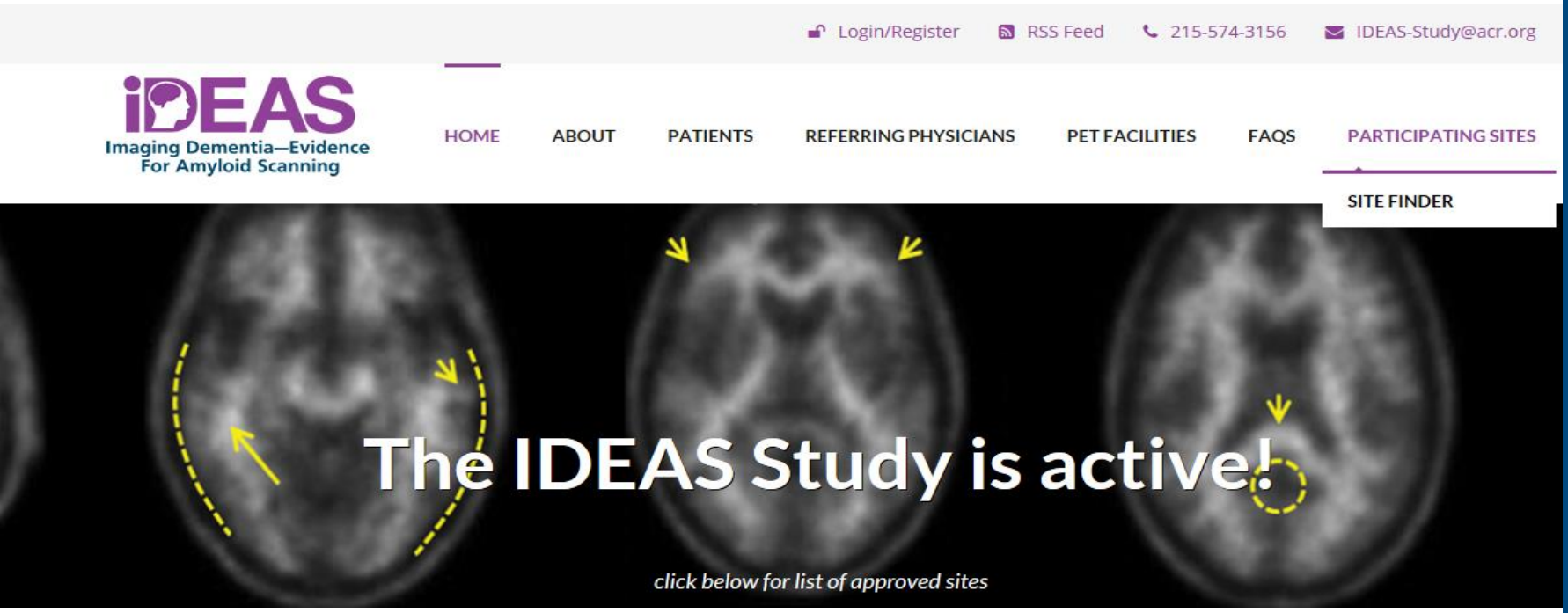
- Revisit clinical implications
- Assess understanding
- Assess immediate psychological impact
- Encourage questions
- Provide a written summary
- Provide contact information for dementia practice and community support resources
- In some instances, follow-up contact a few days after disclosure may be prudent

Adopted from Harkins et al. Alzheimers Res Ther 2015

IDEAS Research Study

For study information (site/HCP applications, logistics, FAQs, etc.) and registration, go to:

www.IDEAS-Study.org



IDEAS-Study.org

IDEAS
Imaging Dementia—Evidence For Amyloid Scanning

Summary

DETAIL
DEMONSTRATING EXCELLENCE THROUGH ADVANCED IMAGING LEARNING

- Amyloid imaging provides *in vivo* amyloid status and the ability to rule out AD
- **Definitive** diagnosis of AD requires both clinical features and histopathological confirmation by brain biopsy or autopsy
- Clinical diagnosis of “probable” or “possible” AD can be made based on the 2011 NIA/AA core criteria
- The three characteristic findings of AD are beta-amyloid neuritic plaques, neurofibrillary tangles and degeneration with loss of neurons and synapses
- Reports show that adjunctive amyloid PET can increase diagnostic certainty and physician confidence and impact clinical decision-making and patient management

Summary

DETAIL
DEMONSTRATING EXCELLENCE THROUGH ADVANCED IMAGING LEARNING

- In amyloid F-18 PET imaging, amyloid radiopharmaceuticals bind to β-amyloid neuritic plaques in the brain and produces a positron signal detected by a PET scanner; this binding is specific to beta amyloid vs. tau or other proteins
- The difference between a positive and negative amyloid F-18 PET image is the **presence of uptake in the gray matter cortex** vs. existing white matter
- The presence of amyloid burden is consistent with a pathological diagnosis of AD
- Amyloid imaging is accessible for Medicare patients via the IDEAS Research Study

References

DETAIL
DEMONSTRATING EXCELLENCE THROUGH ADVANCED IMAGING LEARNING

Recommended websites for further information

- Alzheimer's Association: www.alz.org – fact sheets and statistics
- IDEAS Study: www.ideas-study.org
- NIH National Institute on Aging: www.nia.nih.gov – access the primer on AD and the AD medication fact sheet
- Society of Nuclear Medicine and Molecular Imaging: www.snmmi.org – click "Guidance" to access AUC and Practice Standards
- World Alzheimer Reports: www.alz.co.uk/research/world-report

Full Scientific References

DETAIL
DEMONSTRATING EXCELLENCE THROUGH ADVANCED IMAGING LEARNING

(in alphabetical order)

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DETAIL
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- Ghosh PM, Madison C, Santos M, et al. Amyloid PET has greater clinical impact than FDG PET in the differential diagnosis of AD and FTD. AAIC 2014; 10(4):Supplement P249

Full Scientific References, cont.

DETAIL
DEMONSTRATING EXCELLENCE THROUGH ADVANCED IMAGING LEARNING

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Important Safety Information

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- Errors may occur in the PET amyloid estimation of brain neuritic plaque density during image interpretation. See individual product labels for additional information.
- Image interpretation should be performed independently of the patient's clinical information. The use of clinical information in the interpretation of Amyloid PET images has not been evaluated and may lead to errors.
- Other errors may be due to extensive brain atrophy that limits the ability to distinguish gray and white matter on the Amyloid PET scan as well as motion artifacts that distort the image.
- Amyloid PET scan results are indicative of the brain neuritic amyloid plaque content only at the time of image acquisition and a negative scan result does not preclude the development of brain amyloid in the future.
- Amyloid PET agents, similar to other radiopharmaceuticals, contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk of cancer.

Amyvid USPI

Neuraceq USPI

Vizamyl USPI