DEMENTIA Care Aware
Early detection. Better care.

The First Signs of Alzheimer's – and What You Should Do About Them

Speakers:

Moderator: Anna Chodos, MD, MPH
Executive Director at Dementia Care Aware, Division of Geriatrics, UCSF

Jessica De Leon, MD
Associate Professor of Neurology, UCSF

Today's speakers

Moderator
Anna Chodos, MD, MPH
Executive Director,
Dementia Care Aware
Division of Geriatrics, UCSF

Presenter
Jessica De Leon, MD
Associate Professor,
The Edward and Pearl Fein
Memory and Aging Center, UCSF

Learning Objectives

After this session, learners will be able to:

1. Describe 2 early signs of Alzheimer's disease.
2. List 2 ways to detect Alzheimer's disease in the earliest stages.
3. Demonstrate how to discuss an early diagnosis of Alzheimer's disease with patients and their caregivers.

Types of Cognitive Decline

Type of Cognitive Decline	Magnitude of Decline	Affects Daily Function?
Age-related decline	"Normal" decline in cognitive functions for age	No
Mild Neurocognitive Disorder	**Abnormal** decline in cognitive functions for age	No. May be using compensatory strategies to accomplish activities of daily living
Major Neurocognitive Disorder	**Abnormal** decline in cognitive functions for age	Yes. Unable to use compensatory strategies to accomplish activities of daily living

Dementia: DSM-5 Definition

Acquired cognitive decline in at least 1 domain:

Learning and memory

Executive function

Complex attention

Perceptual-motor skills

Social cognition

Language

+

Acquired functional decline

+

No other causes, e.g., medical or psychiatric, that may explain the decline

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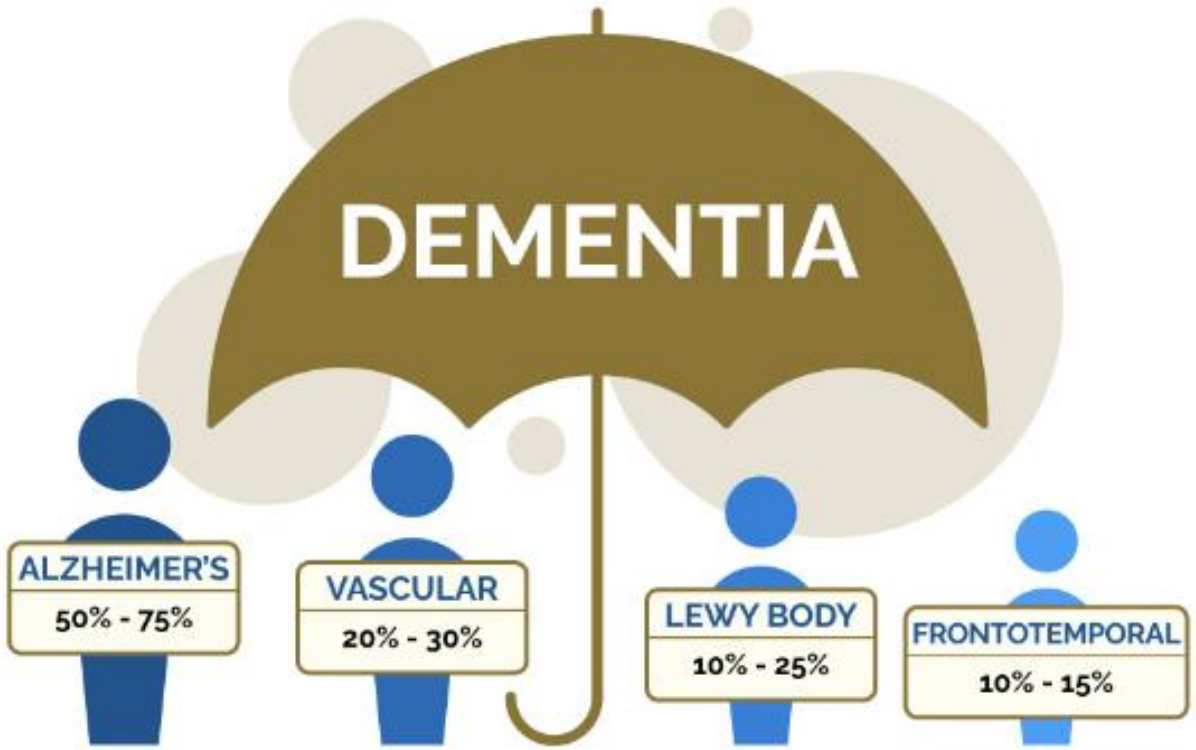
Causes of Dementia



Dementia is a syndrome that is often associated with a neurodegenerative disease.

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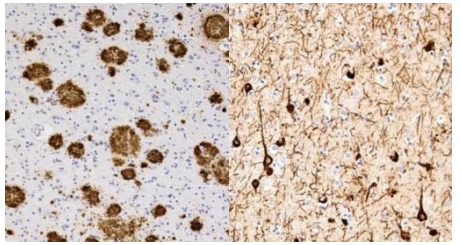
What is the difference between dementia and Alzheimer's disease?

Cognitive Impairment

Dementia is an umbrella term that refers to cognitive impairment that impairs function in everyday life. There are many causes of cognitive impairment, many stages of cognitive impairment (dementia is one), and many syndromes that present with cognitive impairment.

Alzheimer's disease (AD) is a specific brain disease defined by specific brain pathology (amyloid plaques and tau neurofibrillary tangles). AD is the most common cause of cognitive impairment in the elderly, though many patients with AD have other contributing conditions.

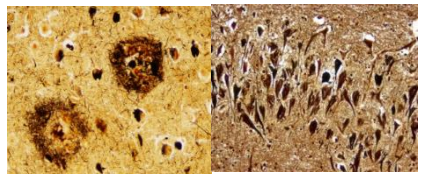


Amyloid Plaques | Tau Tangles

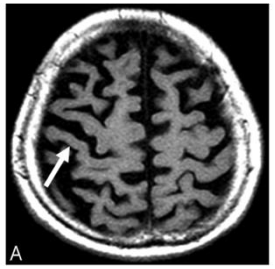
"Alzheimer's Disease"

The Symptom-Biological Relationship is Complex

Simple Model of AD:



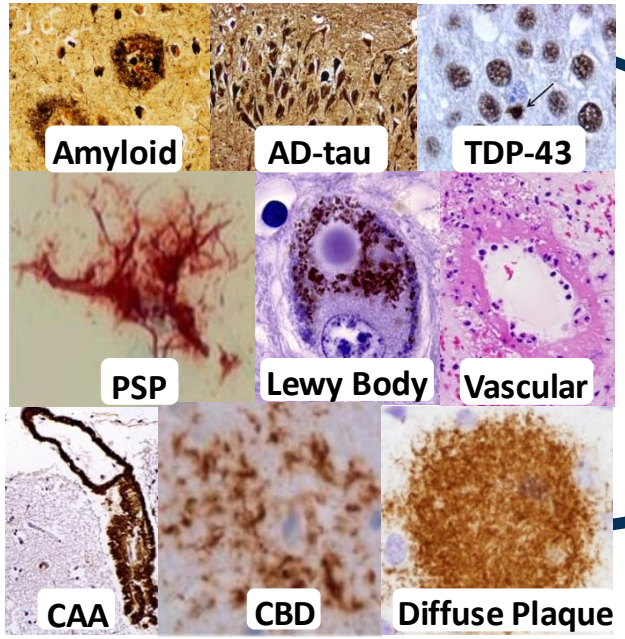
Amyloid/Tau



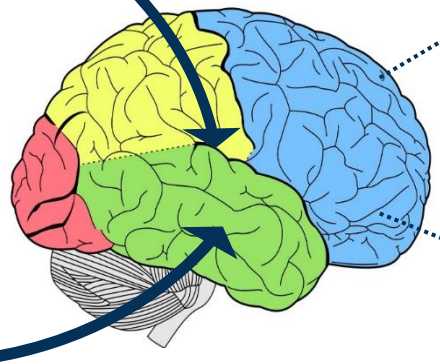
Neurodegeneration

Dementia

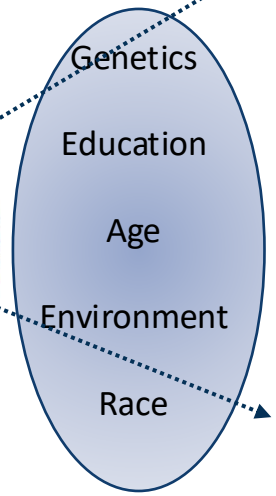
Pathologic Changes
(often multiple)



Location
(often variable)



Individual Factors
(often diverse)



Syndrome
(often atypical)

AD-Related Syndromes
Late-Onset Amnestic
Early-Onset Amnestic
Corticobasal Syndrome
Frontal/Dysexecutive
Logopenic Aphasia
Posterior Cortical Atrophy

Syn-Related Syndromes
Parkinson's Disease
Dementia with Lewy Bodies
Multiple System Atrophy
Pure Autonomic Failure

Tau-Related Syndromes
Corticobasal Syndrome
Richardson's Syndrome
Non-fluent Aphasia Variant
Behavioral Variant of FTD

TDP-Related Syndromes
Behavioral Variant of FTD
Semantic Variant of PPA
Non-fluent Aphasia Variant
LATE

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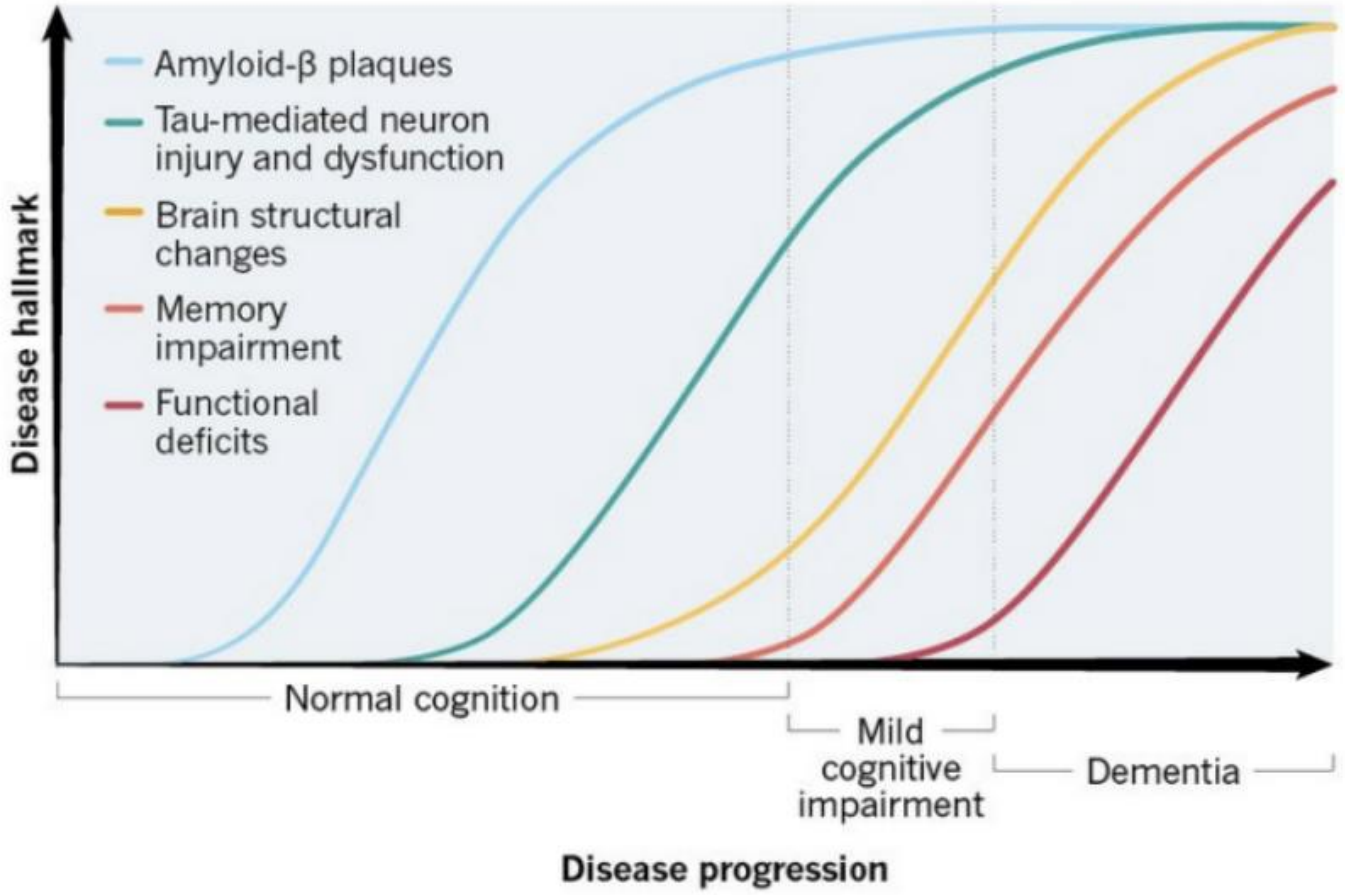
Adapted from slides from Lawren VandeVrede, MD/PhD

Alzheimer's Disease: Timeliness and Disease Progression



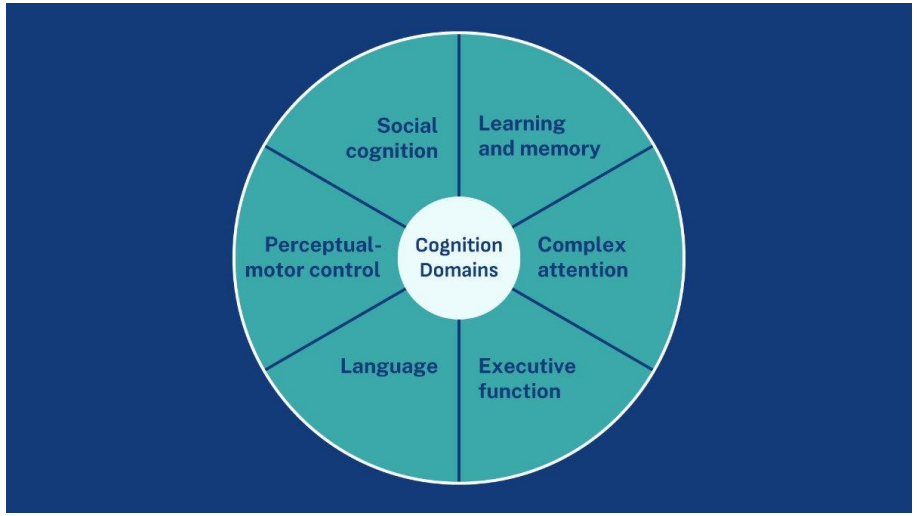
Drew, Nature, 2018

Early Symptoms of Dementia

Many people present with symptoms, and you don't know yet if it's Alzheimer's disease or not.

Many people have mild symptoms that go unrecognized for years.

In general, symptoms of dementia can present in any area of cognition.



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Normal vs. Not normal

In the mildest cases, what is normal versus not can be hard to tell.

Examples:

- Occasional forgetfulness. E.g., briefly forgetting a name but recalling it later, is common and likely normal even if it is new for an older person.
- When a person cannot retain newly learned information, compensatory strategies stop working, or symptoms interfere with independent daily activities, it is more likely to be abnormal.

Increasing **severity** and a worsening **trajectory** for a particular symptom raise the concern that the symptom is not normal.

Note: **subjective cognitive impairment**= symptoms but no objective findings and is higher risk for converting to MCI.

Jessen et al., Lancet Neurol, 2020

Early Symptoms of Dementia Caused by Alzheimer's Disease

However, the earliest symptoms in people with *Alzheimer's disease* specifically are:

- **Episodic memory**: Repeatedly asking the same question, forgetting a recent visit or conversation, or misplacing items and being unable to retrace steps.

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Executive Function

- **Executive function:** New difficulty managing finances, following multistep tasks, planning, organizing, or solving familiar problems.

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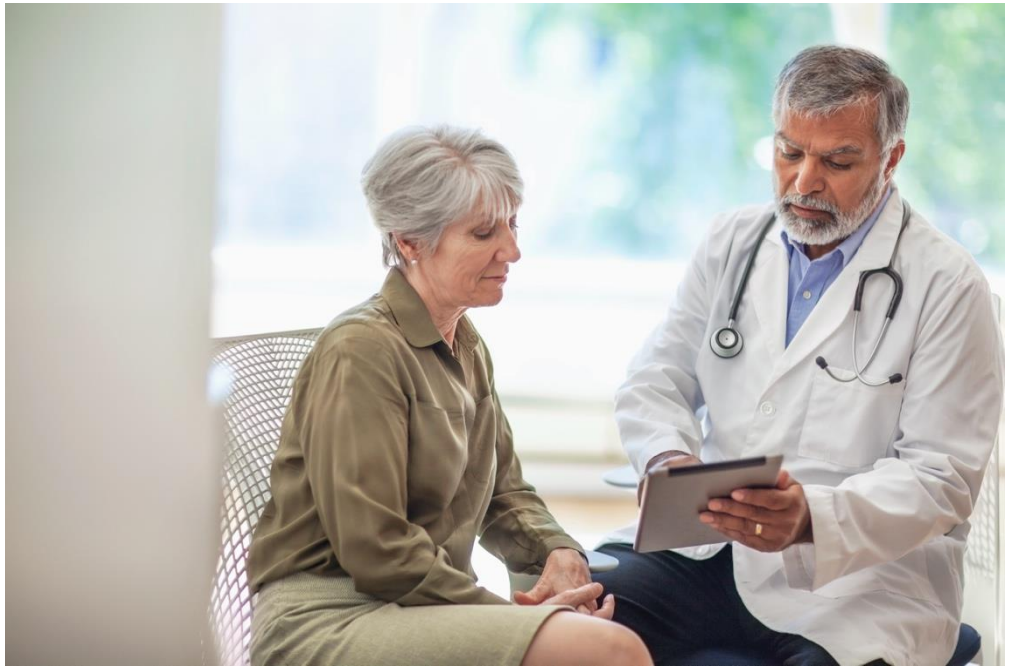
Language

- **Language:** Pauses for ordinary words, substituting vague or incorrect words, or more difficulty following a complex conversation.



Visuospatial Ability

- **Visuospatial ability**: Getting lost on a familiar route, difficulty judging distances, or trouble interpreting visual information.

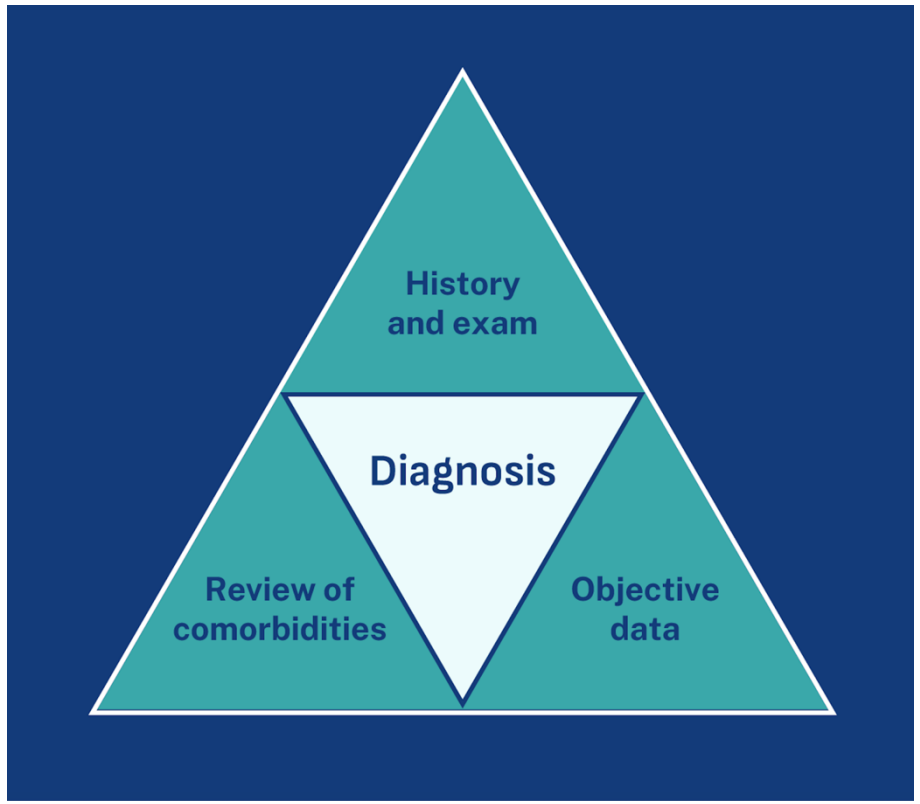
Judgment and Behavior

- **Judgment and behavior:** More vulnerability to scams or poor decisions, apathy/withdrawal, or new anxiety, irritability, or suspiciousness.

Examples of Common Presentations

- Person is losing weight
- Person is missing medications
- Interpersonal dynamics are strained in the family
- Sleep problems
- Depression
- Anxiety
- “Psychotic” symptoms
- New self-presentation, e.g., less put together
- Financial problems
- Worsening substance use

How Can I Get to a Diagnosis?



DSM-5 definition

Acquired cognitive decline in at least 1 domain

+

Acquired functional decline

+

No other causes, e.g., medical or psychiatric

Alzheimer's Disease-Specific Diagnostics

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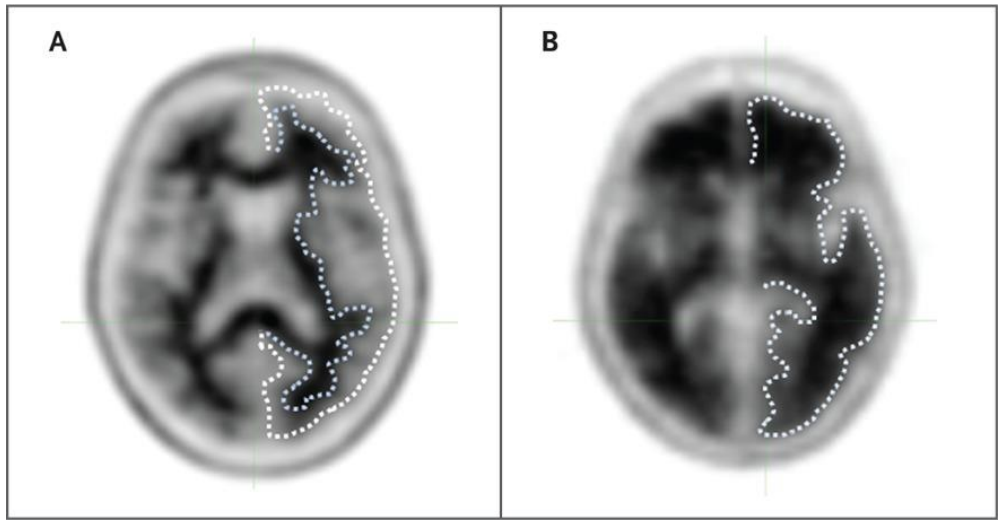
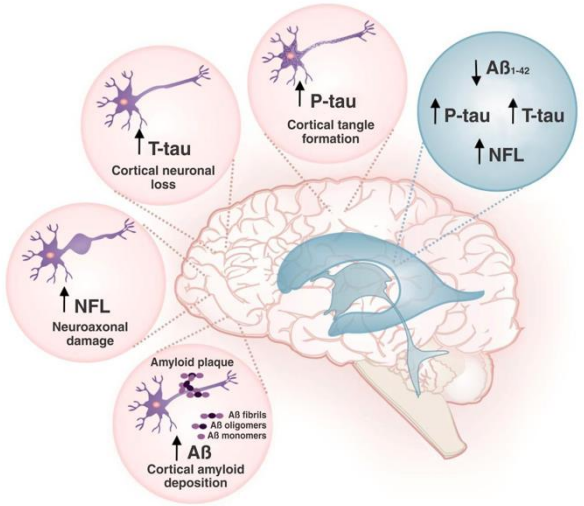
Alzheimer's Disease Biomarker Tests



PET



CSF

Blood

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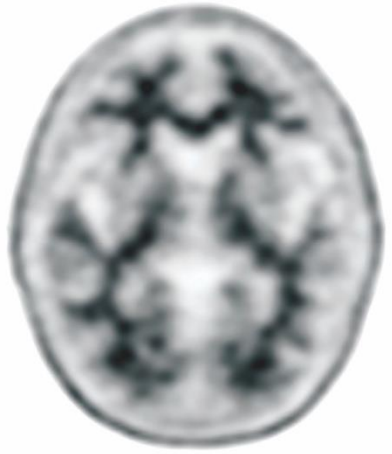
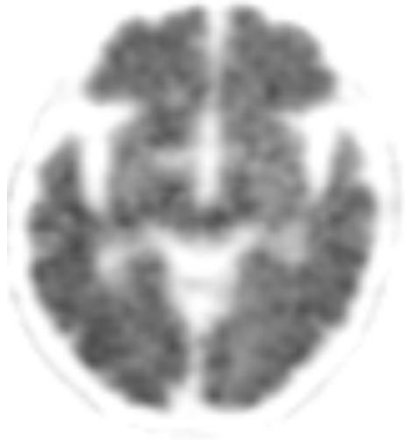
Adapted from slides from Lawren VandeVrede, MD/PhD

Amyloid PET

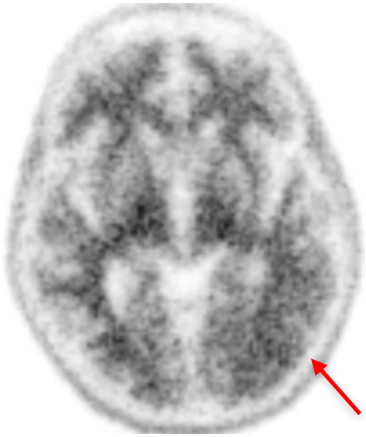
- **Procedure:** Patient is injected with a radiotracer that binds amyloid plaques and a PET scan shows the radiotracer binding
- **Interpretation:** Visually read as "positive" or "negative"; though can be quantified as "centiloids"
- **Advantages:**
  - Visualizes the burden and distribution of amyloid plaques;
  - Can track amyloid plaque removal by anti-amyloid treatments;
  - Insurance coverage is clear for certain indications (CMS)
- **Drawbacks (non-modifiable):**
  - Requires expensive, specialized equipment and highly trained personnel not available at every center;
  - Requires a small amount of radioactivity;
  - Cost is typically ~$5,000/scan



Negative



Diffusely Positive



Focally Positive

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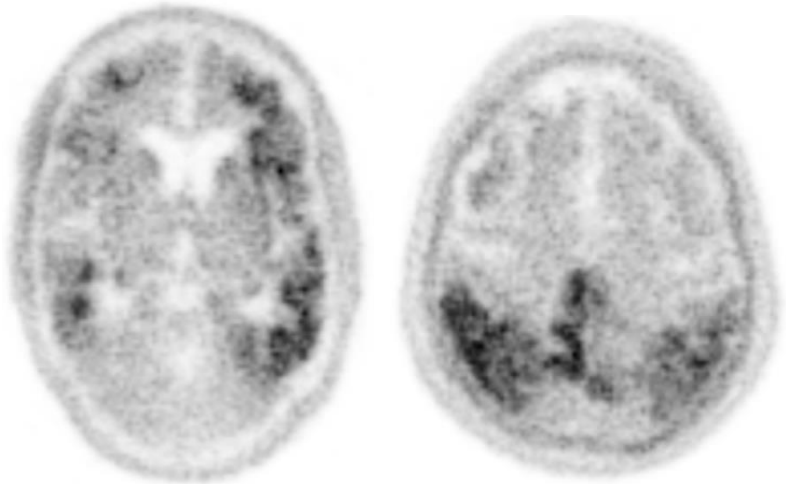
Adapted from slides from Lawren VandeVrede, MD/PhD

Tau PET

- **Procedure:** Patient is injected with a radiotracer that binds tau tangles and a PET scan images the radiotracer binding
- **Interpretation:** Visually read as "positive" or "negative"; though can be quantified (ongoing area of research)
- **Advantages:**
  - Visualizes the burden and distribution of tau tangles;
  - Location and amount of signal correlates with symptoms and disease severity
- **Drawbacks (non-modifiable):**
  - Requires expensive, specialized equipment and highly trained personnel not available at every center;
  - Requires a small amount of radioactivity;
  - Insurance coverage is unclear in most cases and cost is typically ~$10,000/scan



Logopenic Variant | Posterior Cortical Atrophy

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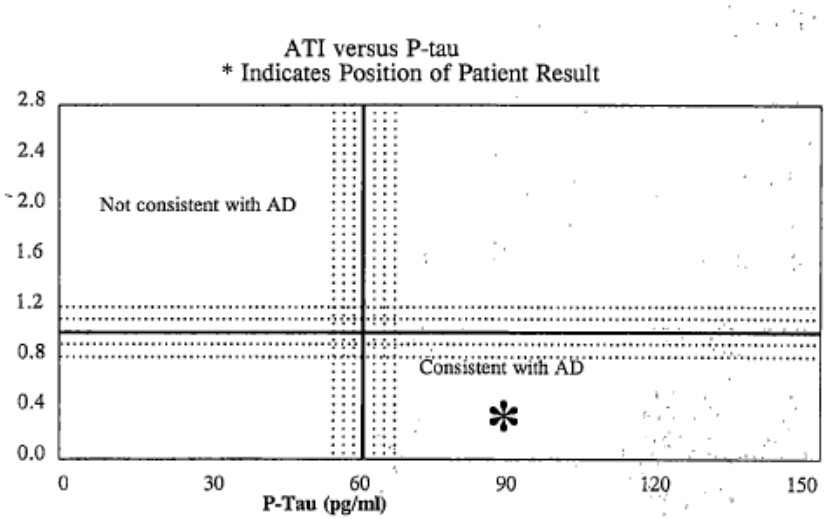
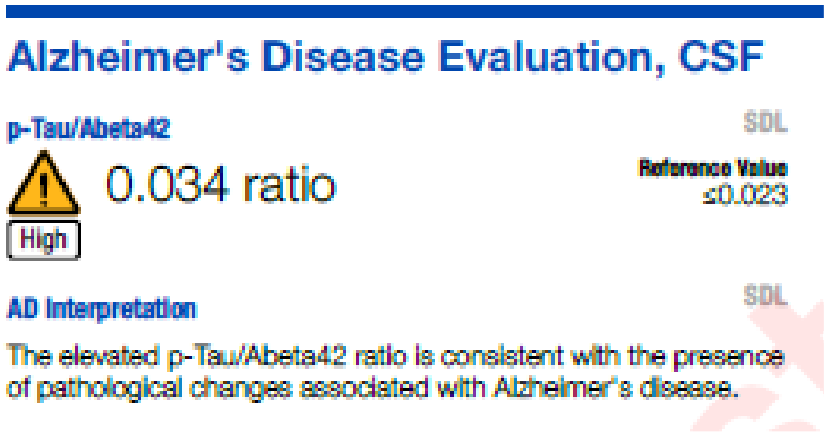
Adapted from slides from Lawren VandeVrede, MD/PhD

CSF Testing

- Procedure:
  - Patient undergoes a lumbar puncture (LP) to collect cerebrospinal fluid (CSF) and certain proteins related to plaques and tangles are measured
- Interpretation: Positive or negative (or intermediate) based on the cut-off value for a ratio; continuous values provided
- Advantages:
  - Tests for non-AD conditions can be performed;
  - Covered by most insurances for AD diagnosis
- Drawbacks (non-modifiable):
  - Barriers due to negative stigma around lumbar puncture and patient contraindications;
  - Time-consuming and expensive to set up clinics, frequently poorly reimbursed;
  - Occasionally unsuccessful, patients may have side effects.





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Adapted from slides from Lawren VandeVrede, MD/PhD

Blood-based Biomarkers

- Procedure:
  - Patient undergoes a blood draw and certain proteins related to plaques and tangles are measured
- Interpretation: Positive or negative (or intermediate) based on the cut-off value; continuous values provided
- Advantages:
  - More acceptable/accessible and less burdensome;
  - Less expensive than other modalities (with similar accuracies);
  - Blood work routine part of current medical paradigm
- Drawbacks (potentially modifiable/addressable):
  - Lack of reimbursement or inconsistent reimbursement;
  - Variability in the accuracy (difficult to parse for non-experts);
  - Certain peripheral factors impact test results (kidney and liver disease, extremes of BMI, motor neuron disease)

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Adapted from slides from Lawren VandeVrede, MD/PhD

P-tau217 is Gold Standard BBM for AD

Plasma phosphorylated tau 217 and phosphorylated tau 181 as biomarkers in Alzheimer's disease and frontotemporal lobar degeneration: a retrospective diagnostic performance study

Elisabeth H Thijssen, Renaud La Joie*, Amelia Strom, Corrina Fonseca, Leonardo Iaccarino, Amy Wolf, Salvatore Spina, Isabel E Allen, Yann Cobigo, Hilary Heuer, Lawren VandeVrede, Nicholas K Proctor, Argentina Lario Lago, Suzanne Baker, Rajeev Sivasankaran, Agnieszka Kieloch, Arvind Kinhikar, Lili Yu, Marie-Anne Valentin, Andreas Jeromin, Henrik Zetterberg, Oskar Hansson, Niklas Mattsson-Carlgren, Danielle Graham, Kaj Blennow, Joel H Kramer, Lea T Grinberg, William W Seeley, Howard Rosen, Bradley F Boeve, Bruce L Miller, Charlotte E Teunissen, Gil D Rabinovici, Julio C Rojas, Jeffrey L Dage, Adam L Boxer, on behalf of the Advancing Research and Treatment for Frontotemporal Lobar Degeneration investigators†*

nature medicine

Article | Open access | Published: 21 February 2024

Highly accurate blood test for Alzheimer's disease is similar or superior to clinical cerebrospinal fluid tests

Nicolas R. Barthélemy, Gemma Salvadó, Suzanne E. Schindler, Yingxin He, Shorena Janelidze, Lyduine E. Collij, Benjamin Saef, Rachel L. Henson, Charles D. Chen, Brian A. Gordon, Yan Li, Renaud La Joie, Tammie L. S. Benzinger, John C. Morris, Niklas Mattsson-Carlgren, Sebastian Palmqvist, Rik Ossenkoppele, Gil D. Rabinovici, Erik Stomrud, Randall J. Bateman ✉ & Oskar Hansson ✉

JAMA Neurology | Original Investigation

Diagnostic Accuracy of a Plasma Phosphorylated Tau 217 Immunoassay for Alzheimer Disease Pathology

Nicholas J. Ashton, PhD; Wagner S. Brum; Guglielmo Di Molfetta, MSc; Andrea L. Benedet, PhD; Burak Arslan, MD; Erin Jonaitis, PhD; Rebecca E. Langhough, PhD; Karly Cody, PhD; Rachael Wilson, PhD; Cynthia M. Carlsson, PhD; Eugeen Vanmechelen, PhD; Laia Montoliu-Gaya, PhD; Juan Lantero-Rodriguez, PhD; Nesrine Rahmouni, MSc; Cecile Tissot, PhD; Jenna Stevenson, PhD; Stijn Servaes, PhD; Joseph Therriault, PhD; Tharick Pascoal, MD, PhD; Alberto Lleó, MD, PhD; Daniel Alcolea, MD, PhD; Juan Fortea, MD, PhD; Pedro Rosa-Neto, MD, PhD; Sterling Johnson, MD, PhD; Andreas Jeromin, PhD; Kaj Blennow, MD, PhD; Henrik Zetterberg, MD, PhD

JAMA Neurology | Original Investigation

Detection of Alzheimer Neuropathology in Alzheimer and Non-Alzheimer Clinical Syndromes With Blood-Based Biomarkers

Lawren VandeVrede, MD, PhD; Hanna Cho, MD, PhD; Mark Sanderson-Cimino, PhD; Fattin Wekselman, BS; Yann Cobigo, PhD; Maria Luisa Gorno-Tempini, MD; Hilary W. Heuer, PhD; Joel H. Kramer, PhD; Argentina Lario Lago, PhD; Dana Leichter, BS; Peter Ljubenkov, MD; Bruce L. Miller, MD; David C. Perry, MD; Gil D. Rabinovici, MD; Julio C. Rojas, MD, PhD; Howard J. Rosen, MD; Rowan Saloner, PhD; Adam Staffaroni, PhD; Gallen Triana-Baltzer, PhD; Salvatore Spina, MD, PhD; William W. Seeley, MD; Lea T. Grinberg, MD, PhD; Hartmuth C. Kolb, PhD; Renaud La Joie, PhD; Adam L. Boxer, MD, PhD

JAMA | Original Investigation

Blood Biomarkers to Detect Alzheimer Disease in Primary Care and Secondary Care

Sebastian Palmqvist, MD, PhD; Pontus Tideman, MSc; Niklas Mattsson-Carlgren, MD, PhD; Suzanne E. Schindler, MD, PhD; Ruben Smith, MD, PhD; Rik Ossenkoppele, PhD; Susanna Calling, MD, PhD; Tim West, PhD; Mark Monane, MD, MBA; Philip B. Verghese, PhD; Joel B. Braunstein, MD, MBA; Kaj Blennow, MD, PhD; Shorena Janelidze, PhD; Erik Stomrud, MD, PhD; Gemma Salvadó, PhD; Oskar Hansson, MD, PhD

Adapted from slides from Lawren VandeVrede, MD/PhD

Appropriate Use for Clinical AD Biomarker Testing

Patients who are undergoing an evaluation who have objective evidence of cognitive impairment (recommend AGAINST testing patients with no symptoms):

1. In whom AD is considered a potential cause of cognitive impairment;
2. AND biomarker testing is expected to affect diagnosis and/or management by:
    a) improving the accuracy of dementia diagnosis;
    b) and/or determining whether patients may be candidates for AD-specific treatments, such as anti-amyloid antibodies.

In general, it may make sense to talk to a Neurologist or other specialist to help your patient decide to get and then how to interpret these results.

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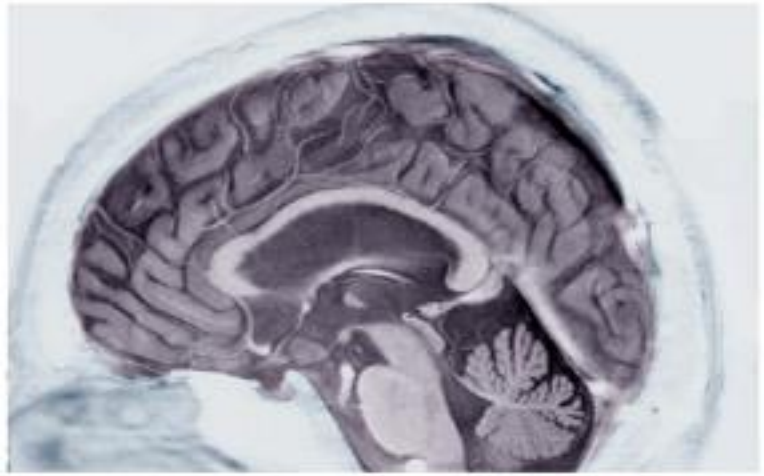
Novel Therapies for Alzheimer's Disease

Alzheimer's Drug May Benefit Some Patients, New Data Shows

The drug, lecanemab, made by Eisai and Biogen, also carried risks of brain swelling and bleeding and should be studied further, a report of the findings said.

Share full article



A brain scan of an Alzheimer's patient. Zephyr/Science Source

By Pam Belluck

Nov. 29, 2022

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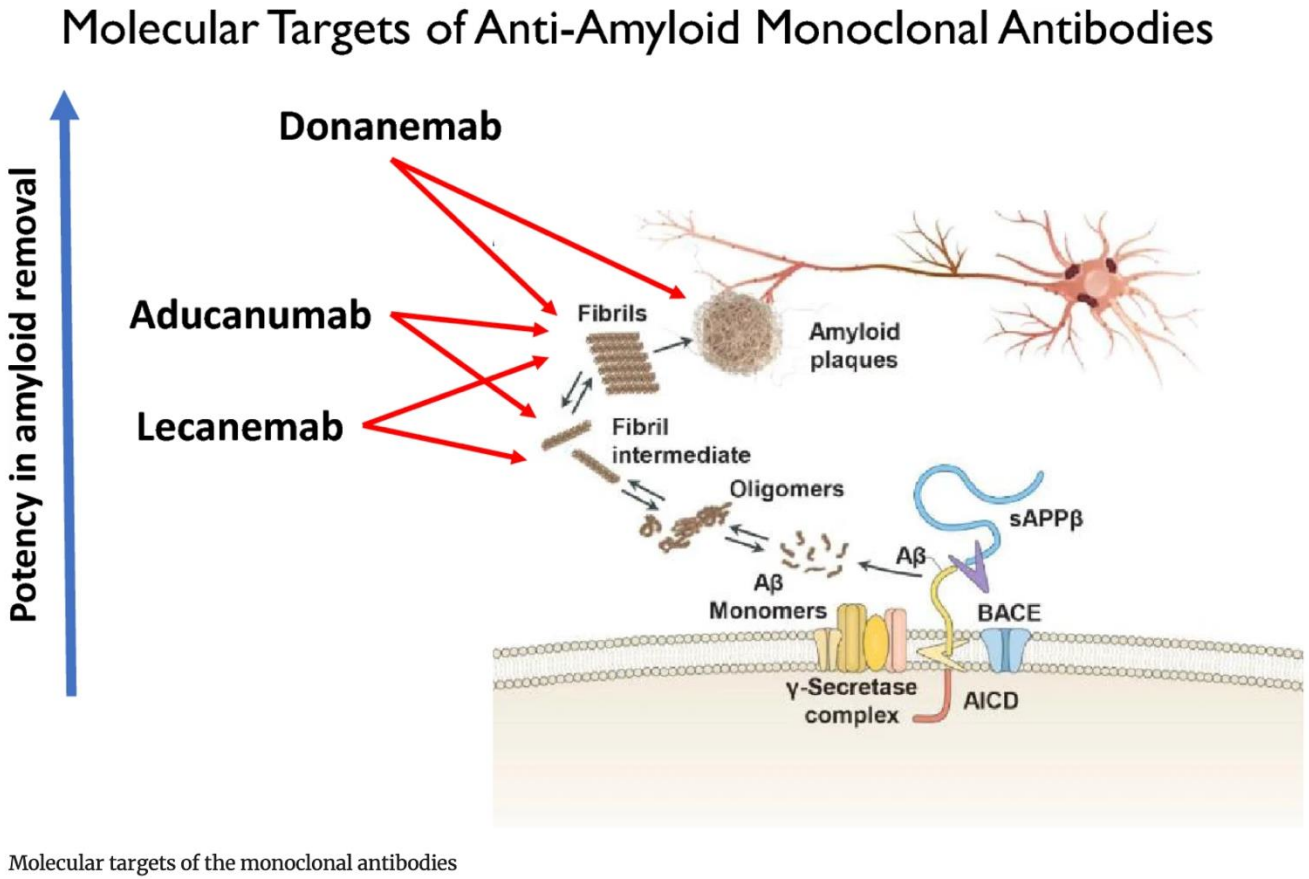
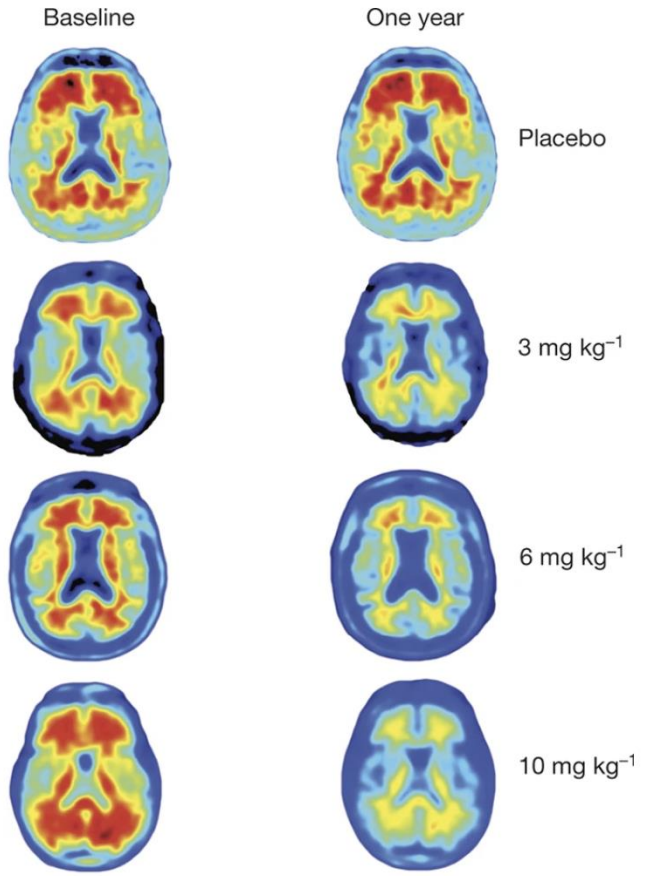
Adapted from slides from Charles Windon, MD

How do Novel Therapies Work?



Molecular targets of the monoclonal antibodies

Leisher, CNS Drugs, 2023



Sevigny, Nature, 2016

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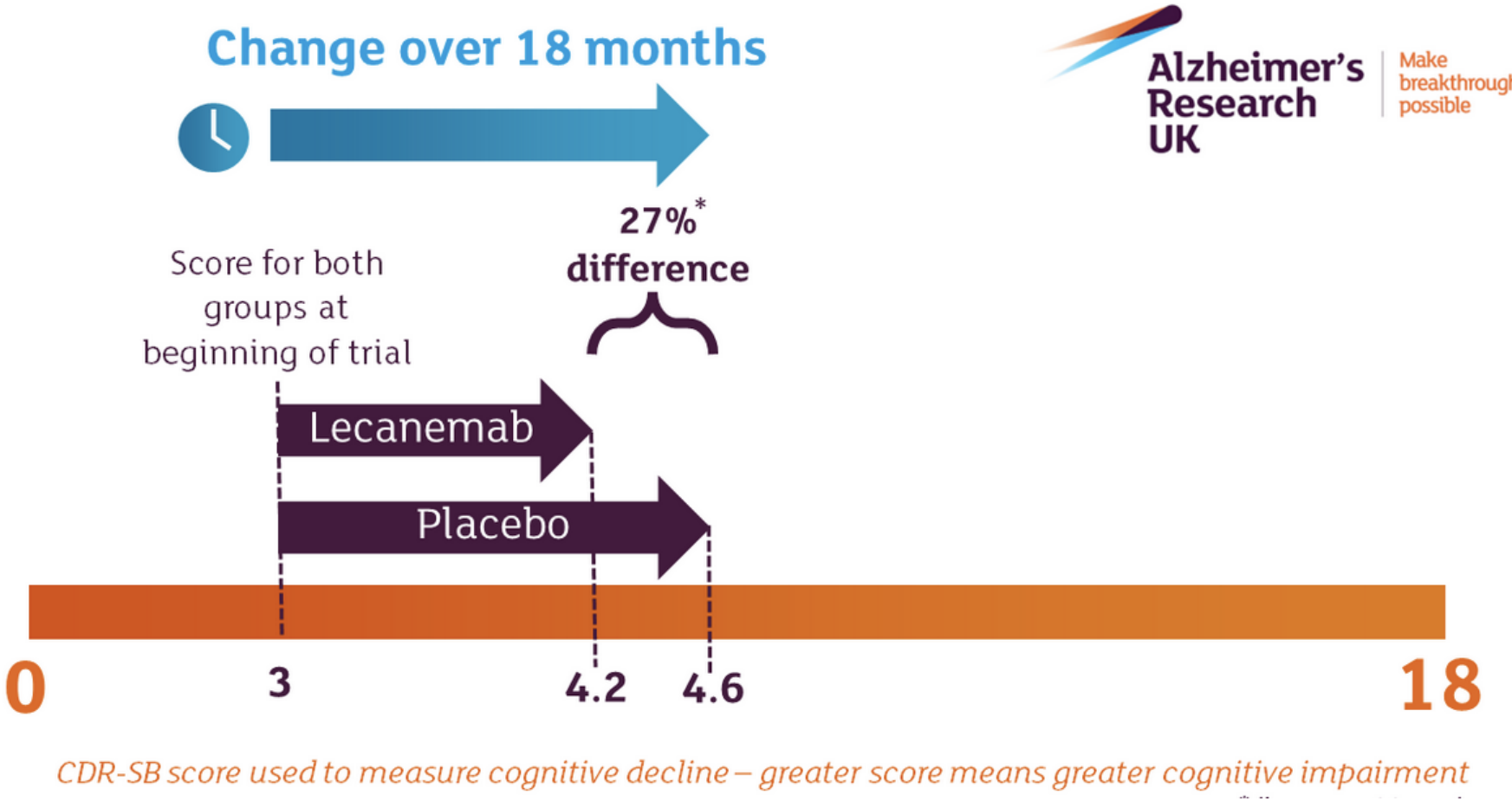
How Effective are Novel Therapies?



Alzheimer's Research UK
Make breakthroughs possible

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Adapted from slides from Charles Windon, MD

Who can Receive Novel Therapies?

Inclusion and Exclusion Criteria Applied in the Clarity AD Trial of Lecanemab	Appropriate Use Recommendations for Patients Considered for Treatment with Lecanemab
Inclusion Criteria	
Diagnosis of Mild Cognitive Impairment (MCI) or mild AD dementia	Clinical diagnosis of MCI or mild AD dementia as defined in Table 1
Objective impairment in episodic memory as indicated by at least 1 standard deviation below age-adjusted mean in the Wechsler Memory Scale IV-Logical Memory (subscale) II (WMS-IV LMII)	Clinical diagnosis of MCI or mild AD dementia as defined in Table 1
Positive biomarker for brain amyloid pathology	Positive amyloid PET or CSF studies indicative of AD
50-90 years of age	Physician judgement used for patients outside the 50-90 year age range
Mini Mental State Examination (MMSE) score > 22 at Screening and Baseline and < 30 at Screening and Baseline	MMSE 22-30 or other cognitive screening instrument with a score compatible with early AD
Body mass index (BMI) greater than (>)17 and less than (<) 35 at Screening	Physician judgement used for patients at the extremes of BMI
If receiving an acetylcholinesterase inhibitor (donepezil, rivastigmine, galantamine) or memantine or both must be on a stable dose for at least 12 weeks prior to Baseline	Patients may be on cognitive enhancing agents (donepezil, rivastigmine, galantamine, or memantine) for AD; patients may not be on aducanumab
Unless otherwise stated, participants must have been on stable doses of all other (that is, non-AD-related) permitted concomitant medications for at least 4 weeks prior to Baseline	Patients may be on standard of care for other medical illnesses (see below for specifics regarding anticoagulation)
Have an identified study partner	Have a care partner or family member(s) who can ensure that the patient has the support needed to be treated with lecanemab
Provide written informed consent	Patients, care partners, and appropriate family members should understand the requirements for lecanemab therapy and the potential benefit and potential harm of treatment

Cummings, JPAD, 2023

Meet Ms. Ramirez

Ms. Elena Ramirez is a 71-year-old retired elementary-school administrator who comes with her daughter, Sofia, after Sofia noticed “little things” over the past 18 months.

Ms. Ramirez says, “I’m getting older. Everybody forgets names.” She cannot state any concrete examples of cognitive changes.

She remains socially active, drives locally, manages her medications, and lives independently.

Her medical history includes hypertension, hyperlipidemia, obstructive sleep apnea with inconsistent CPAP use, and bilateral hearing loss.

Her medications are amlodipine, atorvastatin, and occasional hydroxyzine for sleep.

Talking to Sofia

When you ask permission to speak with Sofia, she describes a gradual change:

- Ms. Ramirez repeats the same question within an hour, especially about upcoming plans.
- She misplaced her debit card twice and recently paid the same utility bill twice.
- She used to organize extended-family events but now becomes overwhelmed by multiple steps and asks Sofia to "check" her work.
- She is still independent in basic ADLs and most instrumental ADLs, but Sofia has begun quietly overseeing finances.
- There have been no episodes of hallucinations, falls, new gait disorder, prominent personality change, or focal neurologic symptoms.

Examine Ms. Ramirez

In addition to the history you obtained on cognition and function, you assess:

- Ms. Ramirez has BP 142/76 mm Hg, normal gait, no parkinsonism, no focal weakness.
- Hearing is reduced when she does not use her hearing aids. PHQ-9 is 4, and there is no evidence of major depression.
- She has a high school education in LA, and you use a MOCA, a validated cognitive tool appropriate to her language and education. **She scores 23/30**
    - Impaired delayed recall that does not improve substantially with cueing, errors on trail making and clock drawing, and relatively preserved naming and orientation.

Labs and Imaging

- Normal: CBC, Chem, TSH, B12, RPR, HIV
- Imaging: normal

Do I offer her a biomarker test for Alzheimer's disease?

How to Discuss Biomarker Testing

"We have done the usual assessment: talked about the changes you and your family have noticed, tested memory and thinking, reviewed medications and health conditions, and looked for other possible contributors. The overall pattern makes Alzheimer's disease one possible cause.

A biomarker test looks for signs of Alzheimer's-related changes in the brain. Depending on the test, it may measure Alzheimer-related proteins in the blood or with a brain scan called an amyloid PET scan.

The test cannot tell us everything. It does not explain every memory problem, and it cannot precisely predict the future. But it can help us answer if Alzheimer-related brain changes are likely contributing to the symptoms we are seeing?

We would consider it if knowing that answer would help us make a decision, for example, whether to pursue an Alzheimer-specific treatment, join a clinical trial, or have more clarity for planning.

You do not have to do this test today. We can discuss the benefits, downsides, costs, and what we would do with each possible result."

Diagnosis and Next Steps:

Diagnosis: mild cognitive impairment

Next steps:

- A brain health plan to address modifiable risk factors for decline
- Support for her and her family
- Regular follow-up

Ms. Ramirez Chooses To Receive Biomarker Testing

"Ms. Ramirez, we have the results from the Alzheimer's disease test. Is this a good time to discuss?

We found there is an elevated level of amyloid. This highly suggests that Alzheimer's disease may be causing part of the memory and thinking changes."

Next steps:

- Discussion regarding role of amyloid PET scan (if not already completed)
- Discussion regarding treatments (e.g. anticholinergics, anti-amyloid therapies) or trials
- Referral to neurologist
- Advance care planning

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