


Detection, diagnosis, and drug treatment:
What is the role of
Alzheimer's disease biomarkers?

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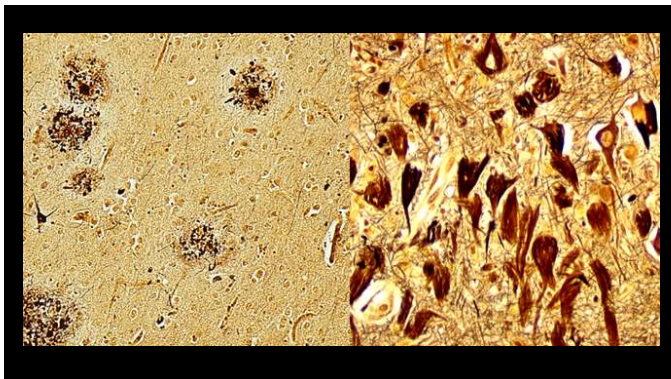


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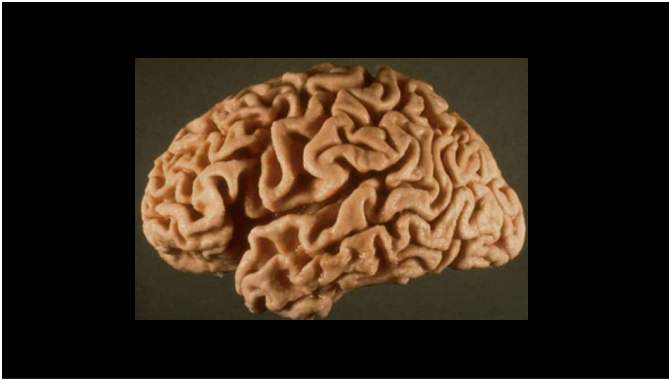
Disclosures

- NIH R01AG037639
- NIH R01AG062285
- NIH R01AG059312
- NIH R01AG070883
- NIH R01AG070973
- Weston Family Foundation
- Research precursors and radiotracers from Avid Radiopharmaceuticals, subsidiary of Eli Lilly

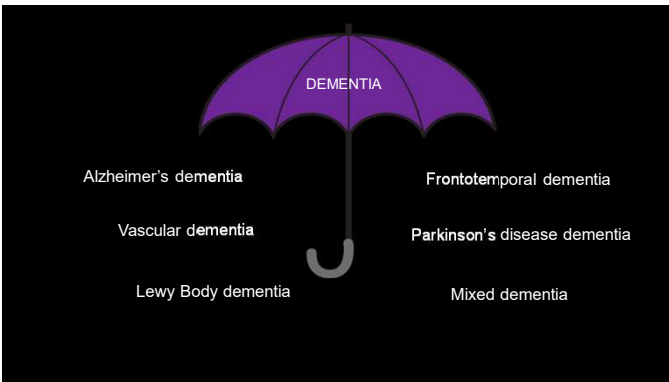
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- Memory and thinking skills
- Loss of function
- Behavioral

- Cause of symptoms

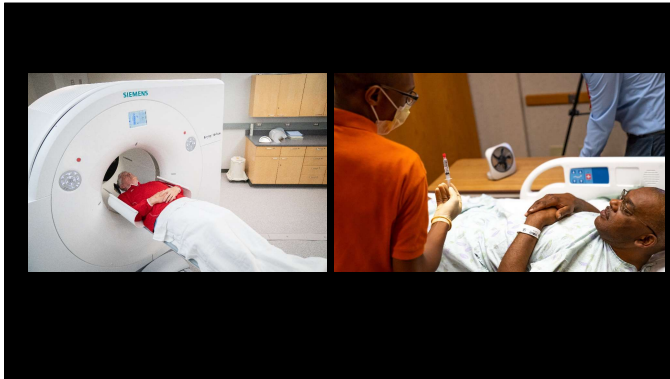
6

So, what is a biomarker and how do we use it?

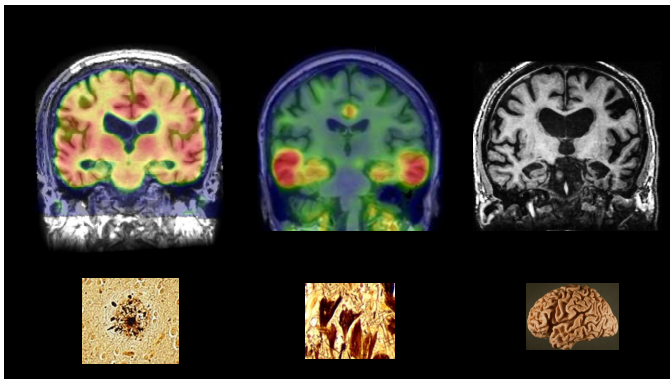
A biomarker (short for biological marker) is a measurable substance or characteristic that indicates the presence or progression of a disease or condition in the body. Biomarkers can include a wide range of substances and characteristics, such as proteins, genes, antibodies, and imaging findings.

Biomarkers can be used to identify risk for disease, measure disease, and measure the efficacy of treatments.

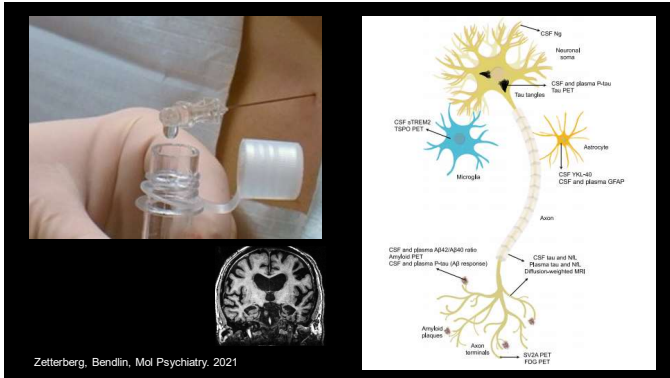
7



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10



11

To participate in an anti-amyloid drug trial, you must have elevated amyloid to qualify.

12

- Aducanumab
- Lecanemab
- Donanemab
- Monoclonal antibody
- Infusion therapy

HOW IT WORKS

- 1 Clumps of amyloid protein clog up brain and poison cells
- 2 Patient given jab packed with antibodies that find and latch on to the clumps
- 3 This alerts the immune system, which sends in cells able to break up the toxic amyloid and flush it out of the brain.

13

Aducanumab impacts amyloid but clinical trials did not show an impact on cognition.

Baseline One year

Placebo
3 mg kg⁻¹
6 mg kg⁻¹
10 mg kg⁻¹

<https://www.nature.com/articles/nature19323>

14

Lecanemab Impacts Amyloid

Adjusted Mean Change from Baseline (BSE) in Amyloid PET using Centiloids

Baseline 75.0, 77.9

Placebo

Lecanemab

**** p < 0.0001

Mean <30 Centiloids for lecanemab at 18 months*

Difference of ~50.1 Centiloids at 18 months

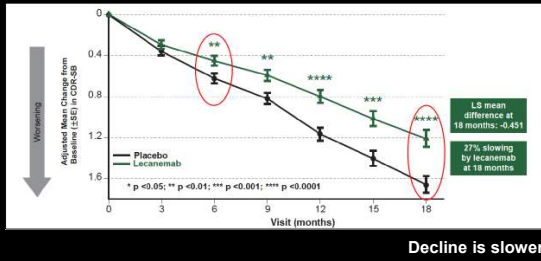
Visit (months): 0, 3, 5, 12, 18

Amyloid is lower

Results from Clarity AD research study

15

Lecanemab Impacts Cognition



Results from Clarity AD research study

Decline is slower

16

Donanemab

May 4, 2023, Lilly announced positive top-line results for Trailblazer-ALZ2.

In this Phase 3 study, treatment significantly slowed decline on the primary outcome of Integrated Alzheimer's Disease Rating Scale by 40 percent, and improved all secondary clinical endpoints.

Aducanumab and Lecanemab received accelerated FDA approval. Donanemab is expected to follow.

17

What are the risks?

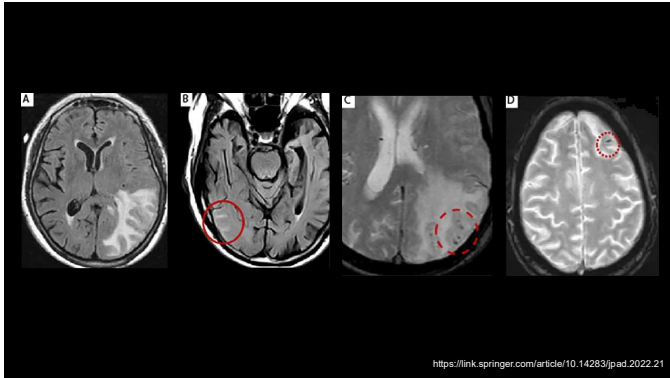
Infusion reaction.

ARIA: Amyloid-Related Imaging Abnormalities.

Potential serious adverse events.



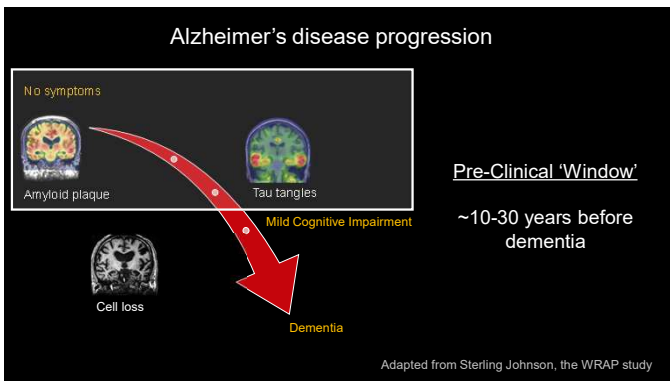
18



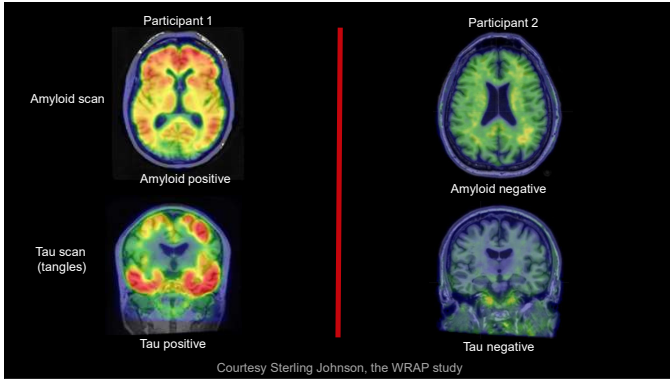
19

Are biomarkers helpful in people who don't have a dementia diagnosis?

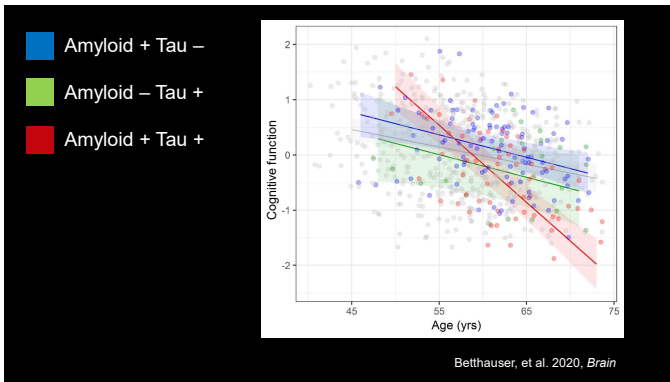
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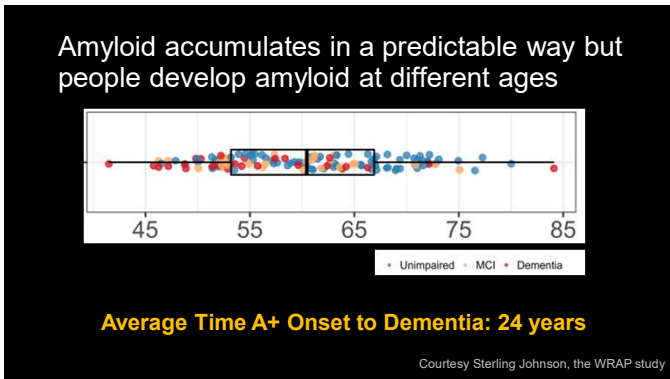
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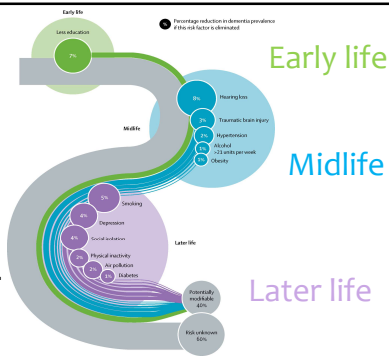
24

What factors contribute to resilience?



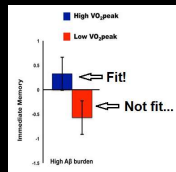
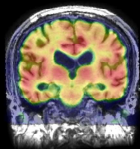
25

Potentially modifiable factors account for 40% of dementia risk.



26

Among those with high amyloid, higher physical fitness = better memory performance.



27

Most pathologies are mixed

Addressing vascular risk factors: clear evidence for dementia risk reduction

Vascular

Alzheimer's disease

α -synuclein

TDP-43

Combination therapy

28

What about blood biomarkers?

29

PET scans and blood tests are closely related

Amyloid PET

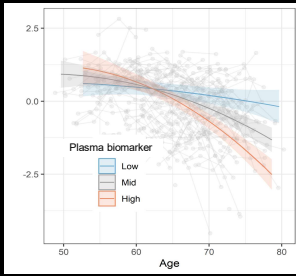
Plasma biomarker

TN

TP

30

Blood tests predict cognitive change



<https://doi.org/10.1093/braincomms/fcad057>

31

Your doctor can order blood tests



32

What are the caveats?

May work less well when:

- Early in the disease process
- Kidney disease
- Obesity
- Heart disease/stroke
- Other co-morbidities



Many are tests still in development.

33

What are the caveats?

Other considerations:

- Inclusion of biomarker results in medical record?
- Long term care insurance?
- Access to treatment?
- Commercial tests recommended for people with symptoms.
- Disclosure in research studies for people without symptoms.



34



- Healthy adults ages 55-80.
- Not diagnosed with Alzheimer's disease or another dementia.
- Have a study partner.
- Have elevated or intermediate amyloid found by imaging as part of the study.

35

Summary

- Biomarkers: brain imaging, CSF, and blood measures.
- Tell us what is happening in the brain.
- Identify people at risk for dementia.
- Tell us about cause of dementia.
- Help enroll people with disease into clinical trials.
- Can be used to monitor effect of therapies.
- Expected to become used more routinely in the future.

36



37
