

Memory, Aging, and Alzheimer's Disease

What We Know Today—and What's Ahead

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Alzheimer's disease is a biological process that can begin before symptoms are obvious

We usually notice the disease when memory or thinking changes.



But the biology may have been changing for years.

Normal aging

Early biology

Mild change

**MCI/early
dementia**

**More advanced
disease**

What changes with normal aging?

Often compatible with normal aging

- ❑ Slower retrieval
- ❑ More “tip-of-the-tongue” moments
- ❑ More difficulty multitasking
- ❑ Greater need for cues

More concerning when persistent or progressive

- ❑ Repeating important questions
- ❑ Getting lost in familiar places
- ❑ Losing the ability to manage finances
- ❑ A clear decline noticed by others

Mild cognitive impairment (MCI)

There is a measurable change in thinking, but independence is largely preserved

Mild Cognitive Impairment

- ❑ Measurable cognitive decline greater than expected for age
- ❑ Memory or thinking changes are noticeable
- ❑ Independence in daily activities is preserved
- ❑ May remain stable, improve, or progress

Dementia

- ❑ Progressive decline in memory and other cognitive abilities
- ❑ Clear change from prior functioning
- ❑ Interferes with daily life and independence
- ❑ Caused by underlying brain diseases (e.g., Alzheimer's)

Clinical stage tells us what a person can do.

Biology helps explain why.

CLINICAL

How is the person functioning?

Symptoms, cognitive testing, independence and change over time.

BIOLOGICAL

What is happening in the brain?

Amyloid, tau, neuronal injury, vascular disease and other processes.

Alzheimer's disease can begin before memory loss

The biology may be detectable before a person or family notices a problem.



**This is why earlier detection matters:
it gives us a chance to understand disease
before substantial functional loss**

What happens in Alzheimer's disease?

1

Amyloid

Protein builds up outside neurons.

A β plaques and related amyloid biology appear early.

2

Tau

Abnormal tau accumulates inside neurons.

Tau pathology tracks more closely with the spread of symptoms.

3

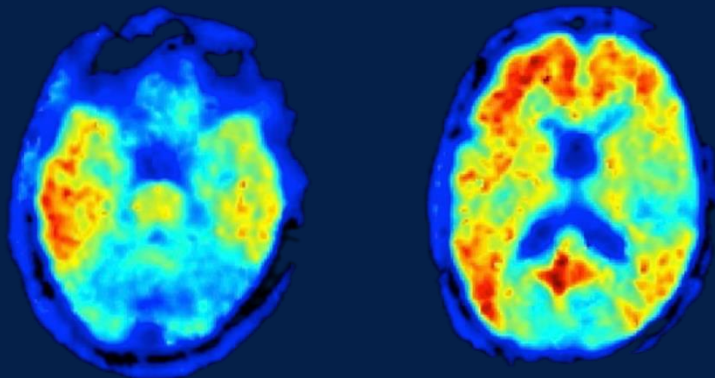
Neurodegeneration

Connections fail; neurons are injured and lost.

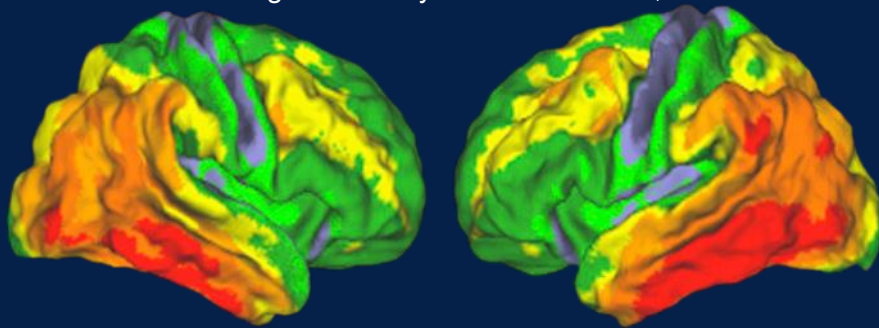
Brain networks become less efficient, then lose tissue.

Amyloid: the first major biological signal

Amyloid is important — but a positive amyloid result is not the same as dementia



Images courtesy of Gil Rabinovici, MD



Ossenkoppele et al, *Alzheimer's & Dementia*, 2020.

Amyloid PET or certain fluid biomarkers can tell us whether Alzheimer's-related amyloid biology is present.

- Often detectable before symptoms
- Important for establishing Alzheimer's biology
- Does not tell the whole story about severity or prognosis

Neurodegeneration: when networks begin to fail

Why can the same disease look so different from one person to another?



Temporal

memory and language

Parietal

visuospatial skills and
networks, navigation

Frontal

planning, judgment,
behavior

**Distributed
Networks**

attention and integration

Clinical phenotype is partly a story of selective vulnerability.

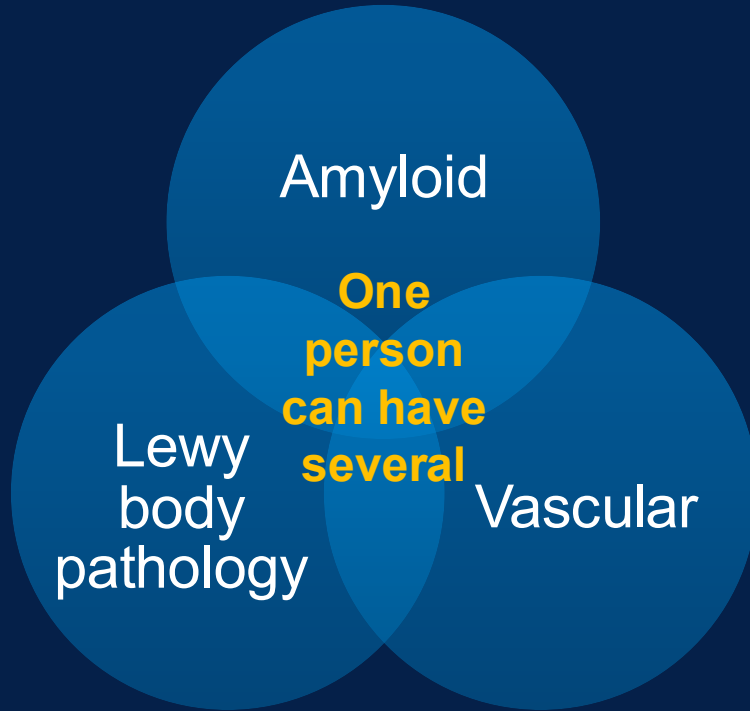
Not all dementia is Alzheimer's disease

The clinical label “dementia” tells us about function — not necessarily the underlying pathology

Alzheimer's disease	Amyloid + tau Memory often prominent
Lewy body dementia	α-synuclein Attention, visuospatial, fluctuations
Frontotemporal dementia	Tau or TDP-43 Behavior or language often prominent
Vascular dementia	Vascular brain injury Executive/processing changes

Mixed pathology is common

Older brains often contain more than one disease process.



- Biomarkers help separate overlapping causes.
- Clinical symptoms are the result of the brain's total burden — not a single protein in isolation.

How do we diagnose Alzheimer's disease today?

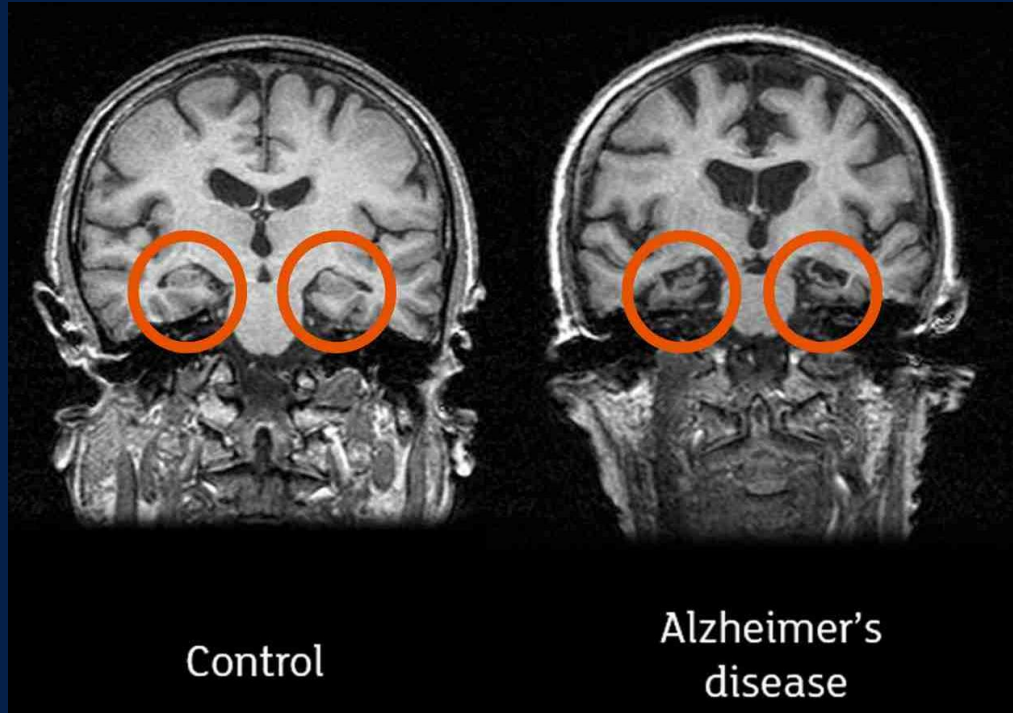
The answer is increasingly multimodal.

Clinical history	Cognitive testing	MRI	Amyloid/tau PET	Blood or CSF biomarkers
What changed? What is the trajectory?	Which abilities are affected?	What structural changes are present?	Where is the protein pathology?	Is the biology detectable in fluid?

No single test replaces clinical judgment.

MRI: what structure can tell us

MRI is especially useful for seeing atrophy, vascular injury and alternative explanations.

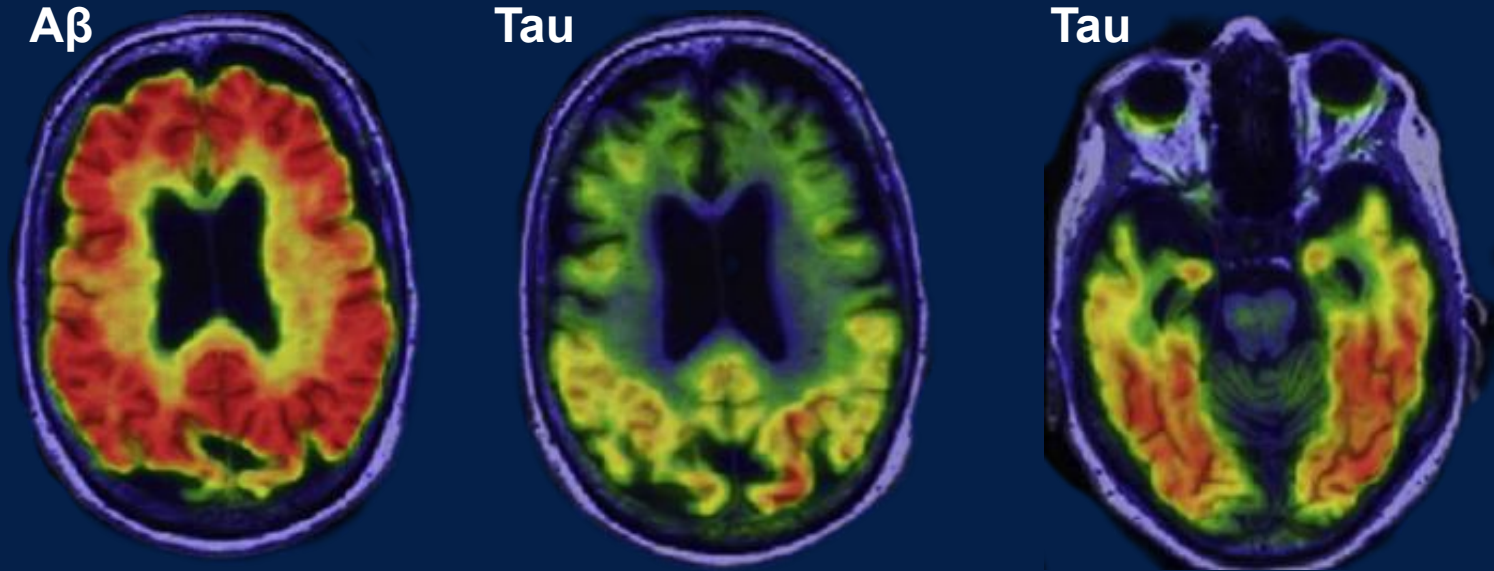


MRI can show regional atrophy

It can also show stroke, white-matter disease, hydrocephalus, tumors and other structural problems.

PET: looking for the disease itself

Amyloid PET asks “is amyloid there?” Tau PET asks “where is tau?”



PET is powerful because it gives spatial information.

Blood biomarkers are changing the field

A blood draw can now provide information about Alzheimer's biology that once required PET or CSF.

	Cognitively unimpaired	MCI	Dementia
A β pathology			
Tau pathology			
AD diagnosis	p-tau231 (or p-tau217) + A β_{42} /A β_{40}	p-tau217 (+MTBR-tau)	p-tau217 (+MTBR-tau)
Predicting AD dementia	p-tau217 + cognitive tests (+MTBR-tau)	p-tau217 + cognitive tests (+MTBR-tau)	NA

- p-tau217, A β ratios, NfL
- Less invasive, scalable, accessible
- Assay quality and clinical context matter

A blood biomarker
is not a crystal ball

The result has to be
interpreted in context.

The diagnostic toolbox is converging

Each tool answers a different question.

Phenotype	Clinical exam: What is happening to the person?
Pattern	Neuropsychology: Which cognitive systems are changing?
Structure	MRI: What structural changes are present?
Biology	Amyloid PET/plasma: is AD biology present
Stage	Tau PET: How far has the biology progressed

Together these tools turn a vague complaint into a biological and clinical model

A hypothetical patient

What changes when we combine the pieces?

- 72-year-old with 18 months of worsening memory
- Repeats questions
- Misses appointments
- Still manages medications and finances
- Family notices a clear change

Cognitive testing	amnesic pattern
MRI	medial temporal change
Blood biomarker	AD biology detected
Clinical synthesis	MCI due to AD?

**The diagnosis becomes more precise
as the biology becomes visible.**

What can current treatments do?

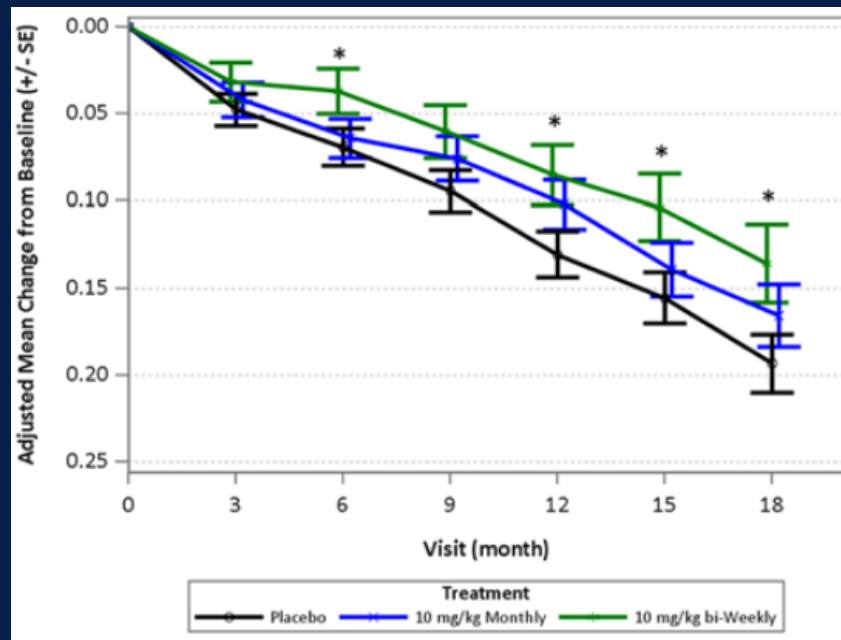
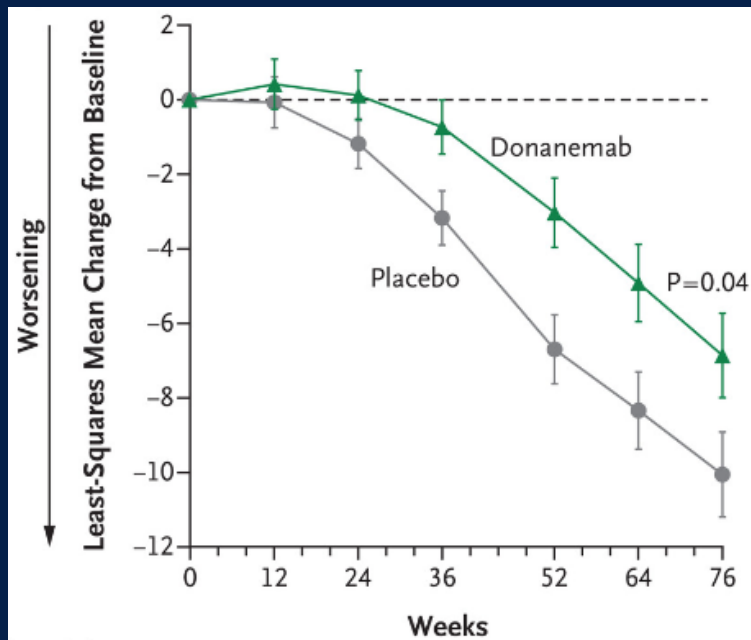
For the first time, we have disease-modifying therapies for Alzheimer's disease.

What they target	Amyloid beta pathology
Who was studied	People in the early symptomatic stages
What the trials show	Slower decline, not reversal
What remains uncertain	Long-term benefit, ideal timing, access

The bigger scientific shift is conceptual: biology can be a treatment target.

Two anti-amyloid antibodies — one principle

Lecanemab and donanemab reduce amyloid, and clinical effects are measured over time.



Clinical goal: slow progression in early symptomatic Alzheimer's disease

Treatment brings a new set of questions

The benefit has to be weighed against risk, monitoring and logistics.

- **ARIA-E:** brain swelling/edema
- **ARIA-H:** microhemorrhages/bleeding
- **MRI monitoring:** safety surveillance is part of treatment
- **APOE genotype:** changes ARIA risk

“Disease-modifying” does not mean “risk-free.”

Why earlier detection matters

The best biological window may be earlier than the point when a family first recognizes dementia.

- Current anti-amyloid therapy is aimed at the early symptomatic window
- Alzheimer's biology begins earlier than symptoms
- Future therapies may move earlier — or target other steps in the disease process

Beyond amyloid: the next generation

The brain contains multiple interacting systems that may become therapeutic targets.

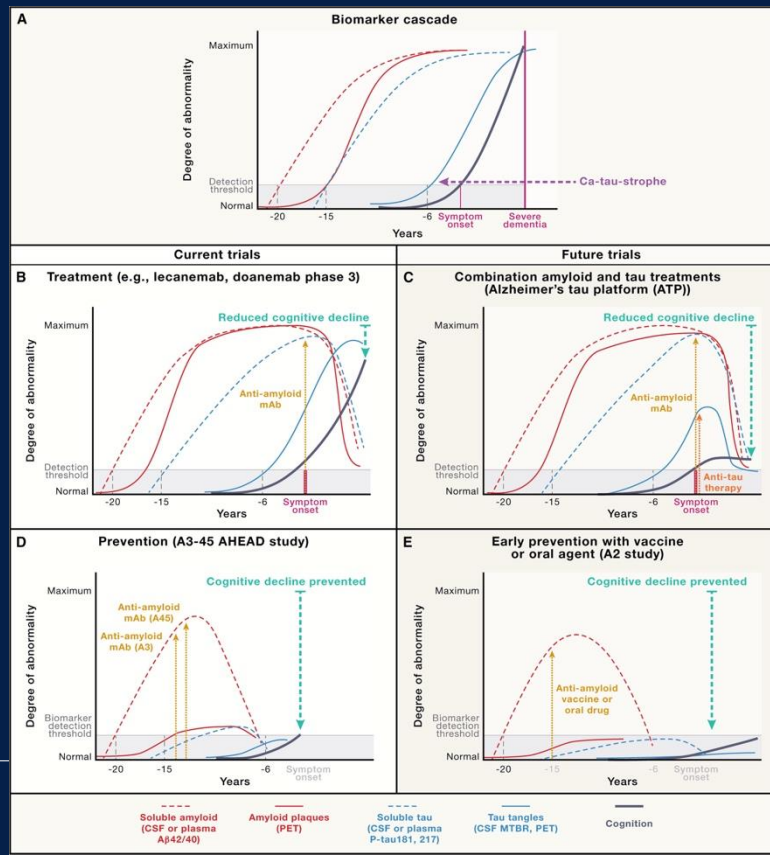
- **Alzheimer's Tau Platform (ATP):** UCSF-led trial to evaluate two anti-tau therapies and an anti-amyloid therapy
- 900 participants with early Alzheimer's at UCSF and nationwide
- Allows combination trials and requires substantially fewer participants
- Other drugs may be added to the "rolling platform" format
 - Medications that target metabolic dysfunction, inflammation, etc.



Adam Boxer, MD, PhD



Keith Johnson, MD



Risk and resilience change the trajectory

Biology matters, but biology is not the whole story.

Education &
cognitive
stimulation

Hearing loss

Depression

Head
protection

Exercise

Smoking

Hypertension

High LDL
cholesterol

Healthy
weight &
obesity

Alcohol
consumption

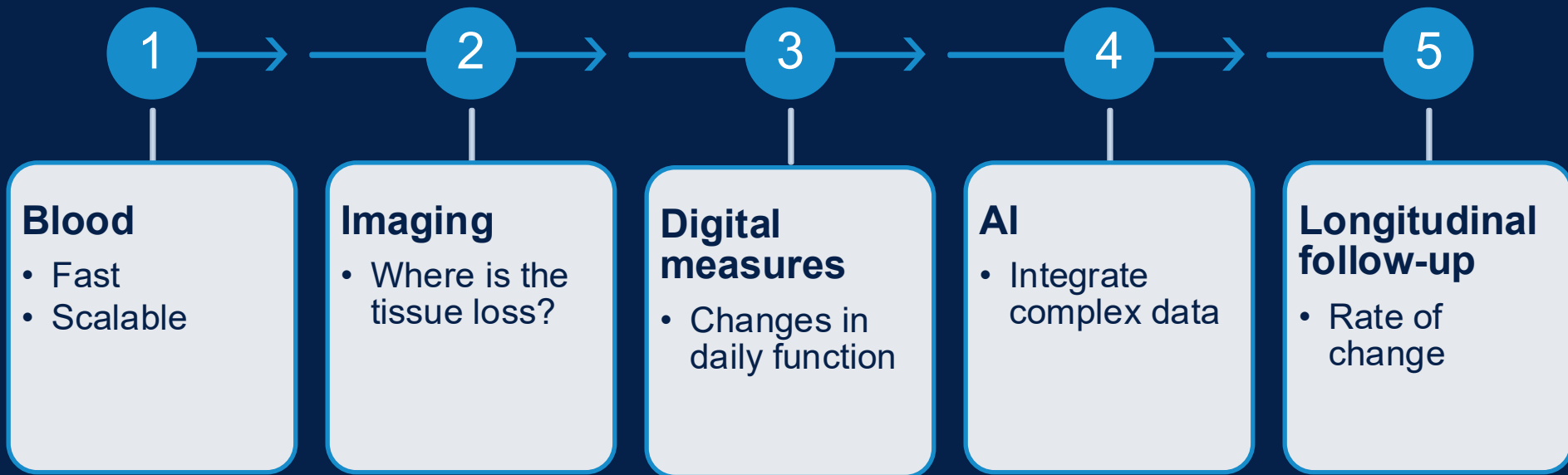
Social
isolation

Vision loss

Air pollution

The future toolbox will be multimodal

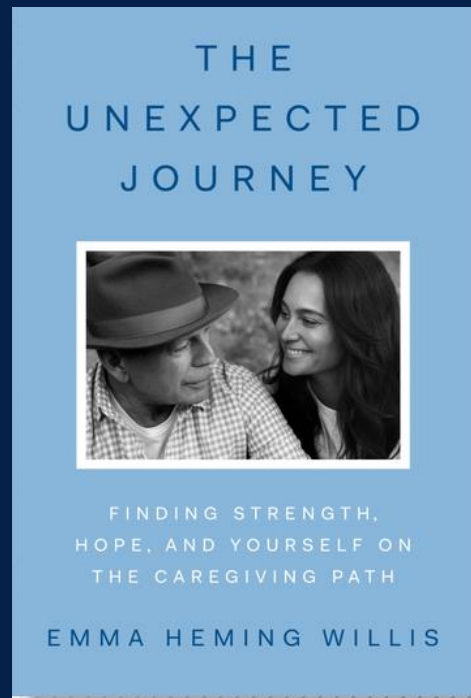
The goal is not simply to detect disease — it is to measure the right biology at the right time.



A better disease map could make diagnosis earlier, trials faster and treatment more individualized.

The Caregiver Roadmap

“Caregiving is hard,
and there are many
people doing it with
little to no support ...
The only way I can
get through this is
to help someone
else feel less alone.”
—*Emma Heming Willis*



Take-Aways

The field is moving from naming syndromes to measuring disease biology

1. Memory change is not the same as Alzheimer's disease.
2. Alzheimer's begins biologically before dementia.
3. Biomarkers are making the diagnosis more precise.
4. Treatment is moving earlier — and the science is moving beyond amyloid.

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