Alzheimer Disease: State of the Science and Research Update

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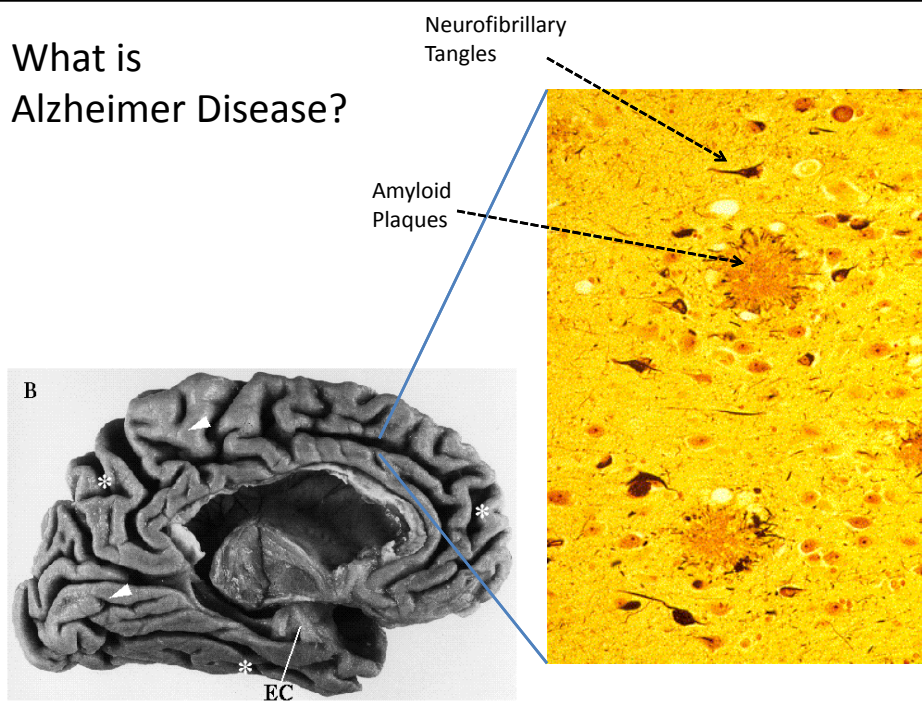MEMORY & BRAIN
WELLNESS CENTER

- 5 million Americans have Alzheimer dementia
- 9% of Americans over age 65 have AD
- The most treatment-resistant top disease
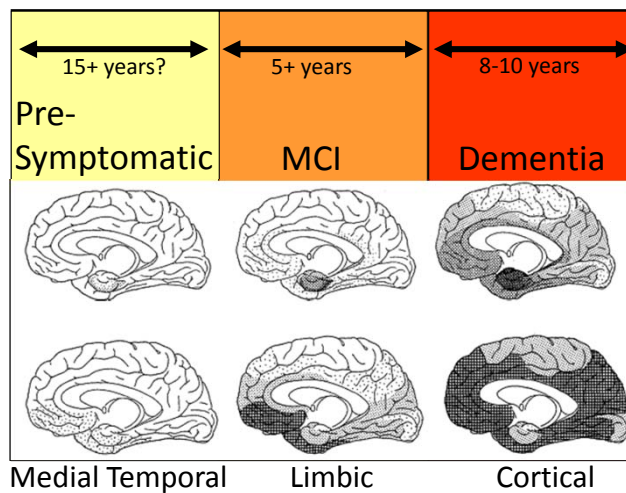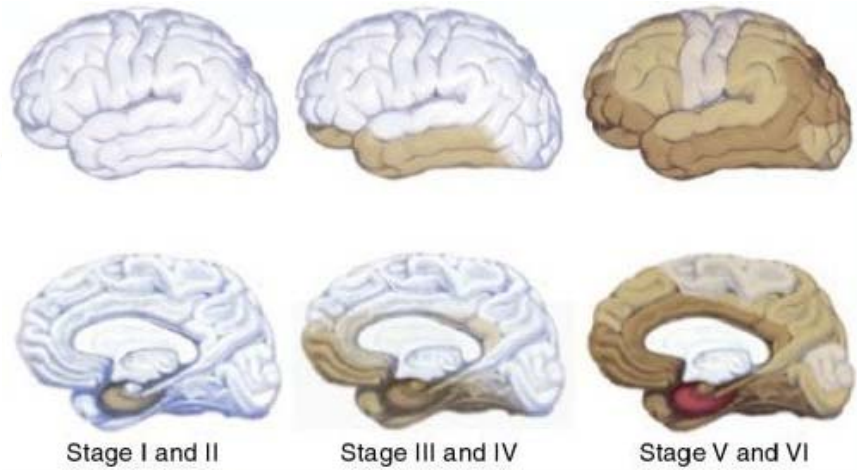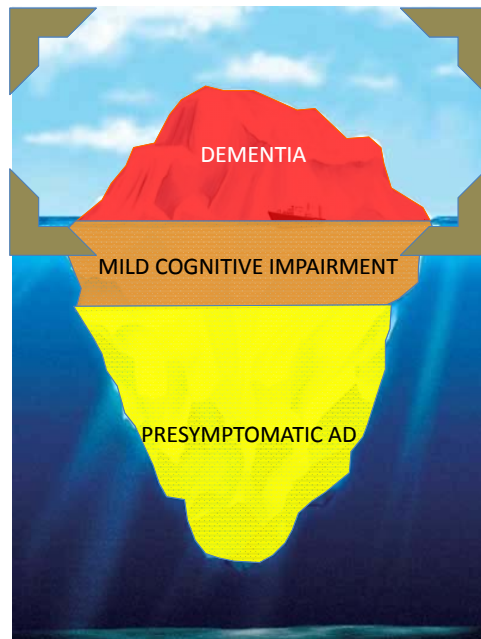- Numbers will double or triple in the next decades

Outline

- Appreciating <u>preclinical</u> Alzheimer disease
- Delivering <u>biomarkers</u> to detect early disease
- Toward <u>precision medicine</u> for Alzheimer disease

What is Alzheimer Disease?

Neurofibrillary Tangles

Amyloid Plaques

Six stages of AD tau tangles

Stage I and II   Stage III and IV   Stage V and VI

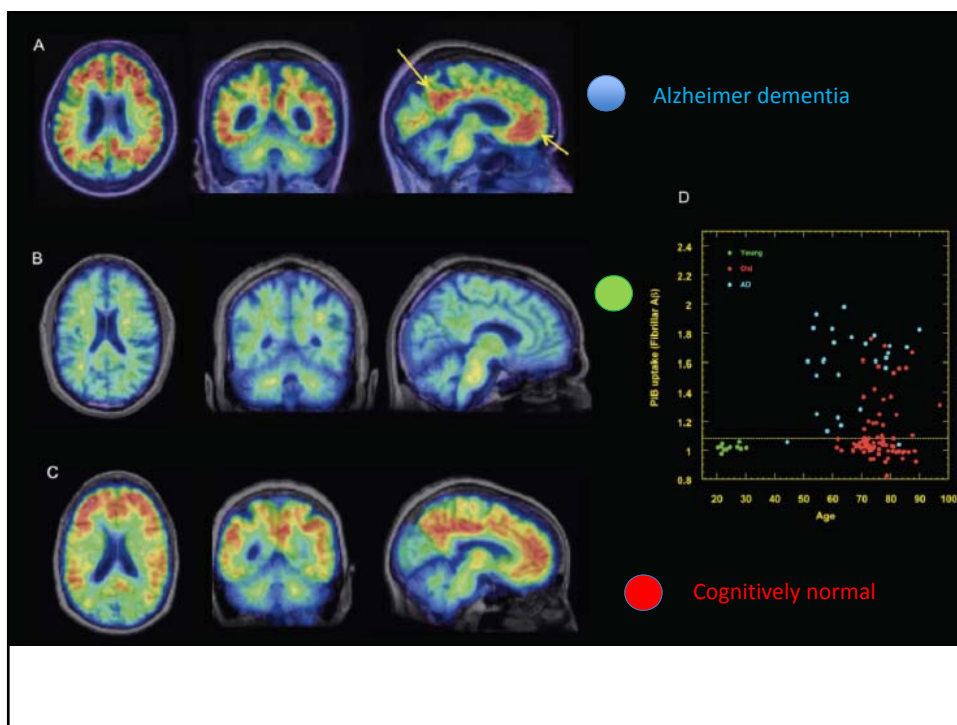| 15+ years?	5+ years	8-10 years
Pre-Symptomatic	MCI	Dementia

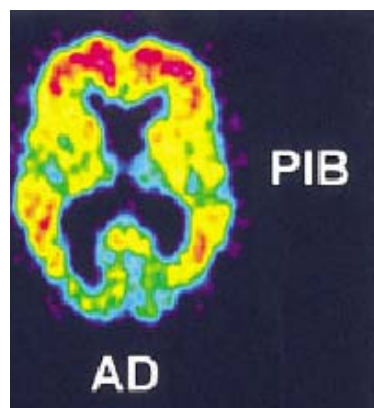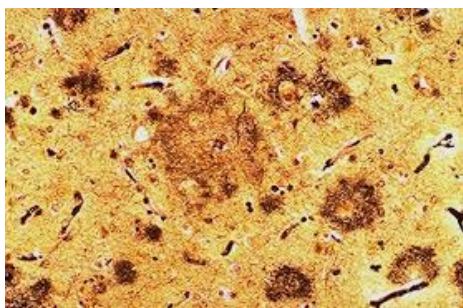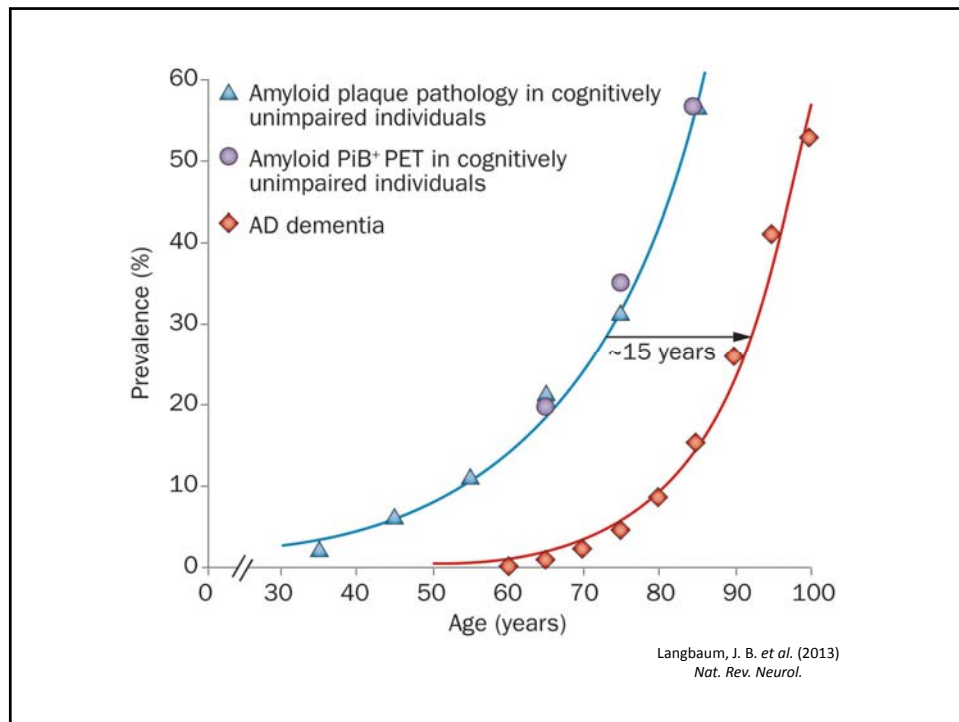Medial Temporal   Limbic   Cortical

Appreciating preclinical AD

- 1% of adults aged 65 have AD dementia
  BUT 25-30% aged 65 have amyloid on a scan

- Latent presymptomatic AD is <u>common</u>

- Alzheimer disease not the same as dementia

- The window for prevention of dementia is wide

Biomarkers: Amyloid PET

Alzheimer dementia

Cognitively normal

Langbaum, J. B. *et al.* (2013)
Nat. Rev. Neurol.

iDEAS
Imaging Dementia—Evidence
For Amyloid Scanning

- The way Medicare will pay for amyloid PET
- Clinical Evidence Development
  - Does it affect clinical decision making and care?
  - Does it affect clinical outcomes?
- 18,000 subjects beginning Jan 2016, 200+ centers
- Appropriate Use Criteria

Appropriate Use

- Persistent unexplained MCI
- Atypical symptoms
- Young age of onset
- Memory loss in setting of other conditions
  - Depression
  - Past head injury
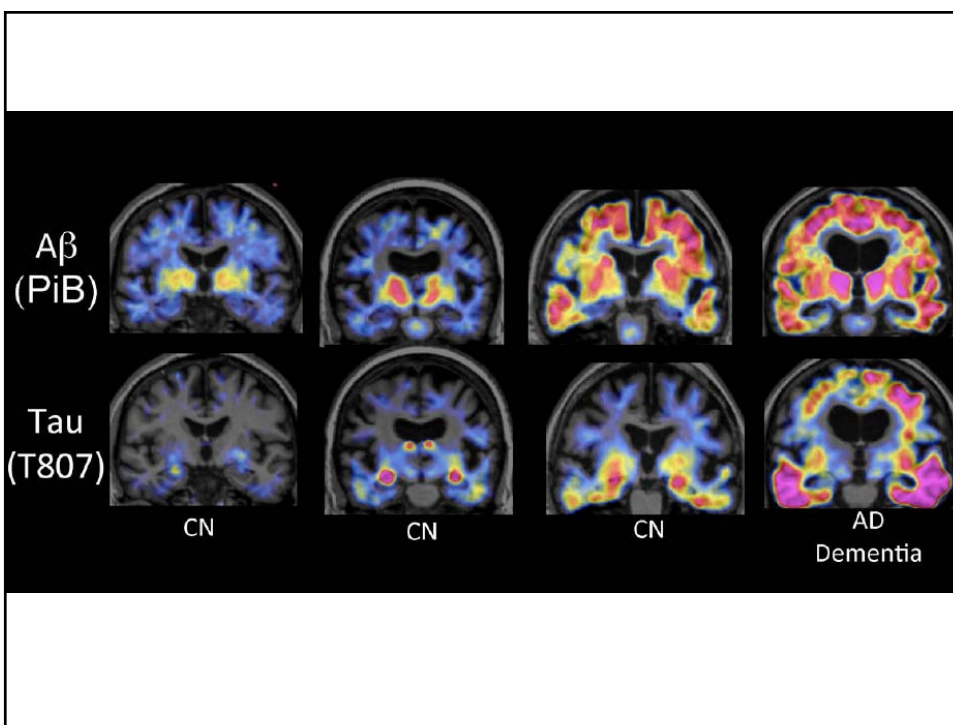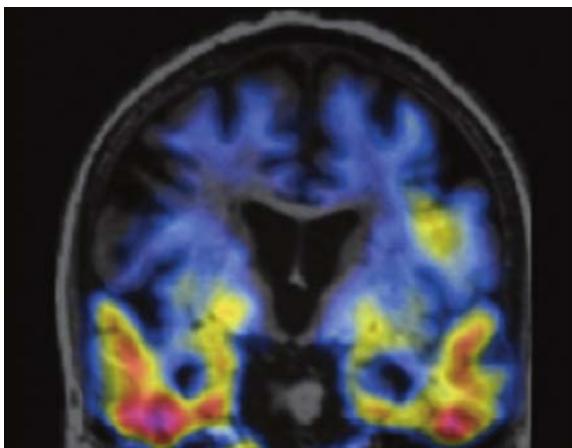 - Hydrocephalus

(In)appropriate Use

- Asymptomatic state
- Solely for positive family history or APOE e4
- Cognitive complaints w/o objective impairment
- To determine dementia severity
- Non-medical usage

Tau PET scans are now a reality
(research only)

Stage III and IV

Aβ (PiB)

Tau (T807)

CN   CN   CN   AD Dementia

Imaging biomarkers

- Offer highly accurate biological diagnosis
- Useful in atypical clinical situations
- Very important to clinical trials

- Amyloid PET: early, prior to symptoms, not sensitive to variability

- Tau PET: early, tightly correlated with symptoms, sensitive to variability, still under development

Different kinds of Alzheimer disease?

- More than one thing goes wrong in Alzheimer disease – more than one mechanism
- Which mechanism is most important may vary with genetic and environmental factors
- More than one mechanism may operate, and more than one disease may be present

Precision medicine for AD

- Stratification by risk
- Early detection (ideally before clinical trouble)
- Alignment of mechanism of intervention with the molecular driver(s) of disease.

Precision Medicine In Cancer
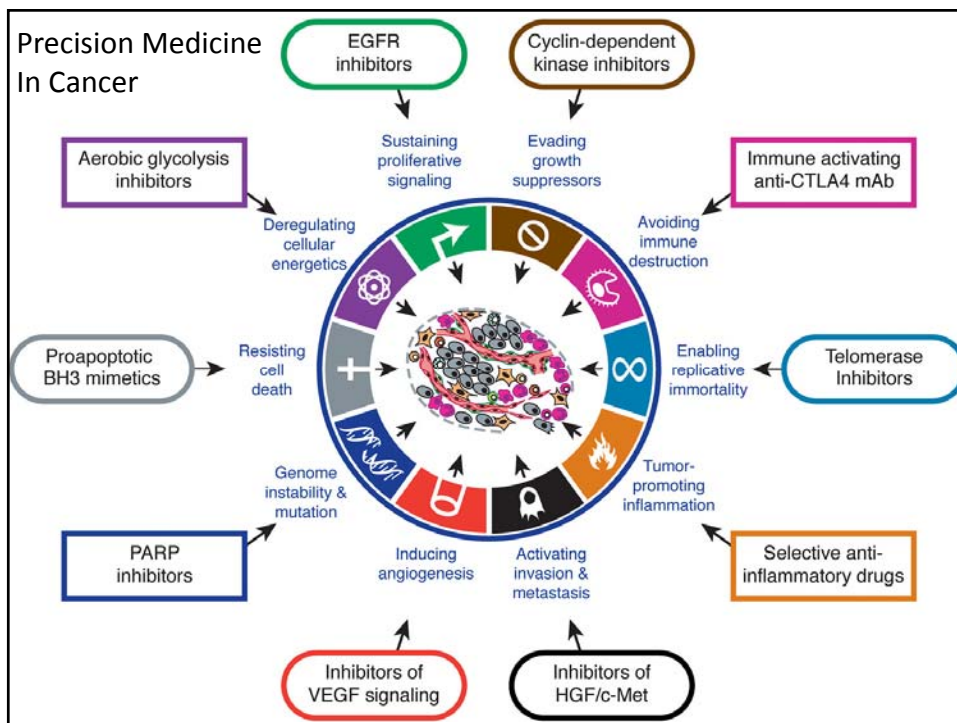
AD mechanisms

- Amyloid toxicity
  - Vascular insufficiency
  - Reduced axonal transport
  - Cortical hyperexcitability
- Neuroinflammation
- Tau spread (prion)
- Mitochondrial insufficiency
- Interaction with primary aging mechanisms

Karch and Goate, 2016
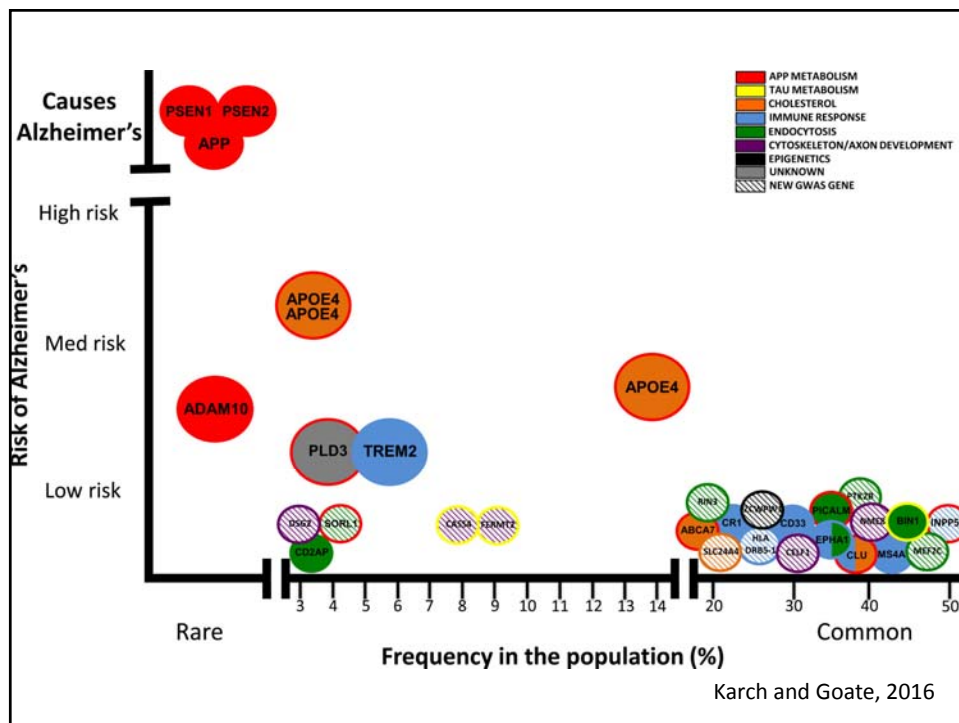
Precision Medicine trial:
DIAN-TU
(for inherited Alzheimer disease)

- Molecular driver: gene mutations increasing amyloid production and toxicity

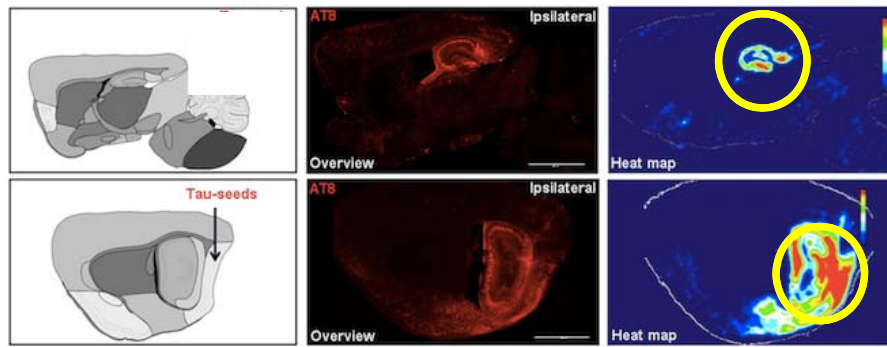- Aligned intervention: antibodies to remove amyloid protein

Amyloid plaque reduction with aducanumab:
example amyloid PET images at baseline and week 54
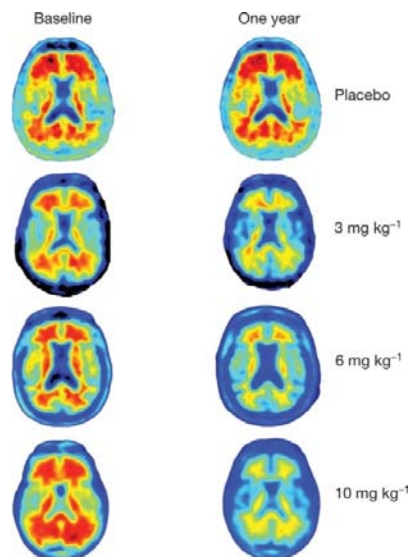
J Sevigny *et al. Nature* **537,** 50–56 (2016) doi:10.1038/nature19323

nature

Spread of tau from cell to cell

Best science paper 2015:

Depletion of microglia and inhibition of exosome synthesis halt tau propagation

Hirohide Asai[1], Seiko Ikezu[1], Satoshi Tsunoda[1], Maria Medalla[2], Jennifer Luebke[2], Tarik Haydar[2], Benjamin Wolozin[1,3,4], Oleg Butovsky[5], Sebastian Kügler[6], and Tsuneya Ikezu[1,3,4]

To advance the day when detection and prevention of threats to memory and brain health is the standard of care

- Early risk stratification (genetics) and intervention for primary prevention
- Or early detection of latent disease (biomarkers) and intervention for secondary prevention

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