Alzheimer Disease: State of the Science and Research Update

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• 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 preclinical Alzheimer disease
• Delivering biomarkers to detect early disease
• Toward precision medicine 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

State of the Science: Alzheimer's Disease and Related Dementias (Thomas Grabowski), Elder Friendly Futures September 2016
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 common
- Alzheimer disease not the same as dementia
- The window for prevention of dementia is wide
Biomarkers:
Amyloid PET

State of the Science: Alzheimer's Disease and Related Dementias (Thomas Grabowski), Elder Friendly Futures September 2016
- 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)
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.
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

Spread of tau from cell to cell

Best science paper 2015:

Depletion of microglia and inhibition of exosome synthesis halt tau propagation

Hirohide Arai\textsuperscript{1}, Seiko Ikozu\textsuperscript{1}, Satoshi Tsunoda\textsuperscript{1}, Maria Medalia\textsuperscript{2}, Jennifer Luebke\textsuperscript{2}, Tarik Haydar\textsuperscript{2}, Benjamin Wolczin\textsuperscript{1,3,4}, Oleg Butovsky\textsuperscript{3}, Sebastian Kügler\textsuperscript{4}, and Tsuneo Ikezu\textsuperscript{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