Knight ADRC
Alzheimer's Disease Research Center
WASHINGTON UNIVERSITY ST. LOUIS

Washington University in St. Louis
SCHOOL OF MEDICINE

American Academy of Insurance Medicine
130th Annual Meeting
October 15-20, 2022, Boston, MA

Alzheimer Disease in 2022: Diagnosis and Treatment

John C. Morris, MD

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Director, Knight Alzheimer Disease Research Center

Disclosure Statement (2021-2022)

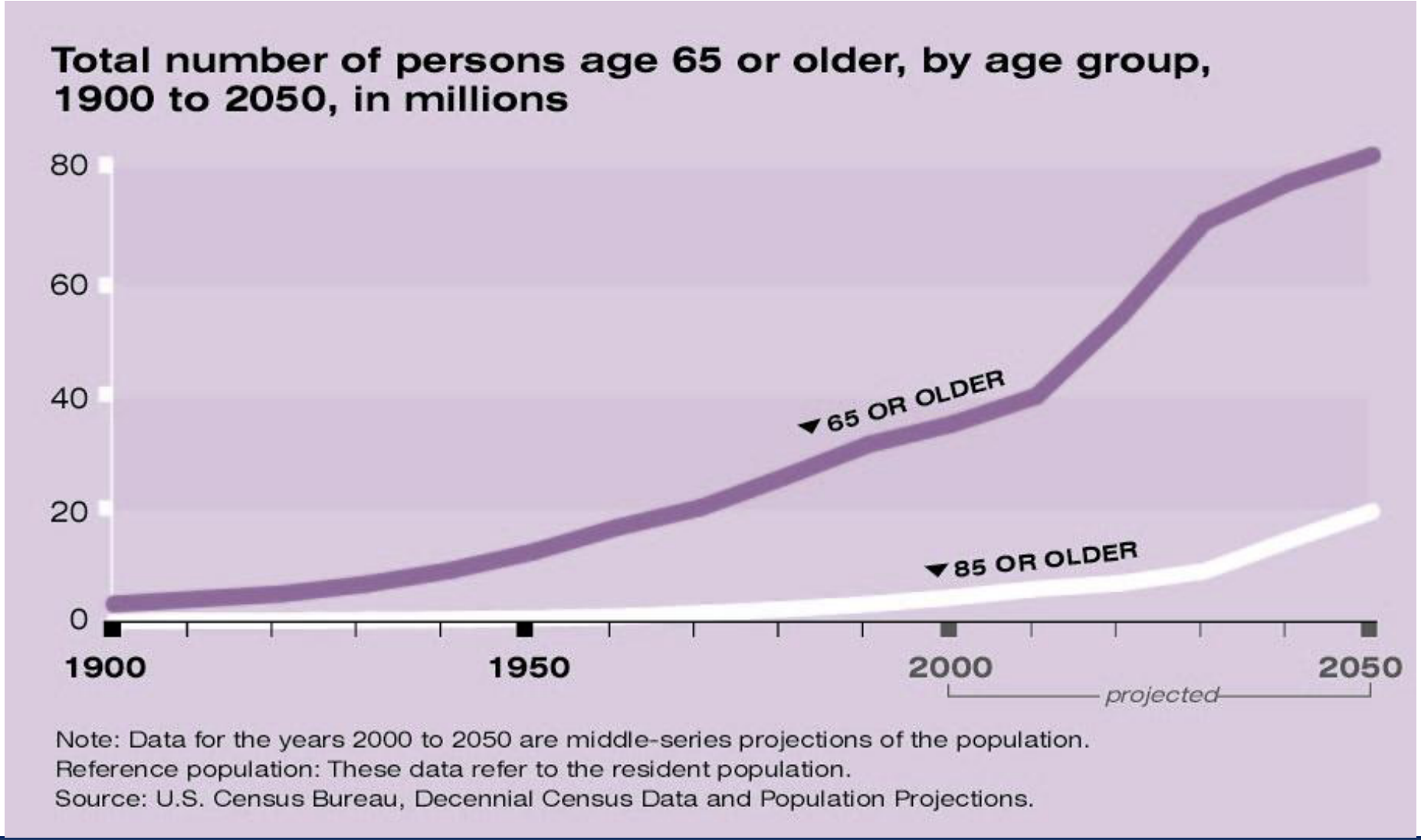
- Sources of Research Support
  1. National Institute on Aging (P01 AG03991; P30 AG066444; P01 AG026276; UF1 AG032438; U19 AG024904)

- Consulting Relationships
  1. BarcelonaBeta Brain Research Foundation Scientific Advisory Board
  2. Diverse VCID Observational Study Monitoring Board
  3. Native Alzheimer Disease-Related Resource Center in Minority Aging Research, External Advisory Board
  4. Cure Alzheimer's Fund Research Strategy Council
  5. Board of Governors, Longer Life Foundation (Reinsurance Group of America and Washington University School of Medicine)

- Industry-Sponsored Trials
  - None
- Fees > $10,000
  - None
- Stock Equity
  - None
- Speaker's Bureaus
  - None
- Editorial Boards
  1. *Brain & Life*
  2. *Alzheimer's & Dementia*

Knight ADRC Faculty, Staff, and Advisors

Aging Population



Aging

- Occurs in every animal that reaches adulthood; occurs after reproductive ability is lost
- Not a disease, but an inexorable loss of physiological capacity
- Fundamental question: Why are old cells more vulnerable to disease than young cells?

Aging in the 21st Century

- Unprecedented numbers of long-lived people
  - Public health
  - Living environments
  - Medical advances
- Economic, political, and societal changes
- Pre-pandemic, life expectancy (# of years remaining for persons at a given age) steadily increased
- Life span (highest documented age at death for a species)
  - Jeanne Calment, 122 years

Jeanne Louise Calment

1875-1997

Myths and Realities

MYTH You can die of old age

REALITY You die of disease, not aging

REALITY The most frequent causes of death are age-associated (heart disease, cancer, stroke, Alzheimer disease)

Cognitive Function in Truly Healthy Aging

- "Diseases commonly occurring in the elderly play a substantial role in the cognitive and functional decline often attributed solely to aging." (Howieson DB et al, Neurology, 1993)

- Hypotheses
  - Longitudinal cognitive performance is relatively stable in unimpaired elderly
  - Cognitive decline is a marker for disease

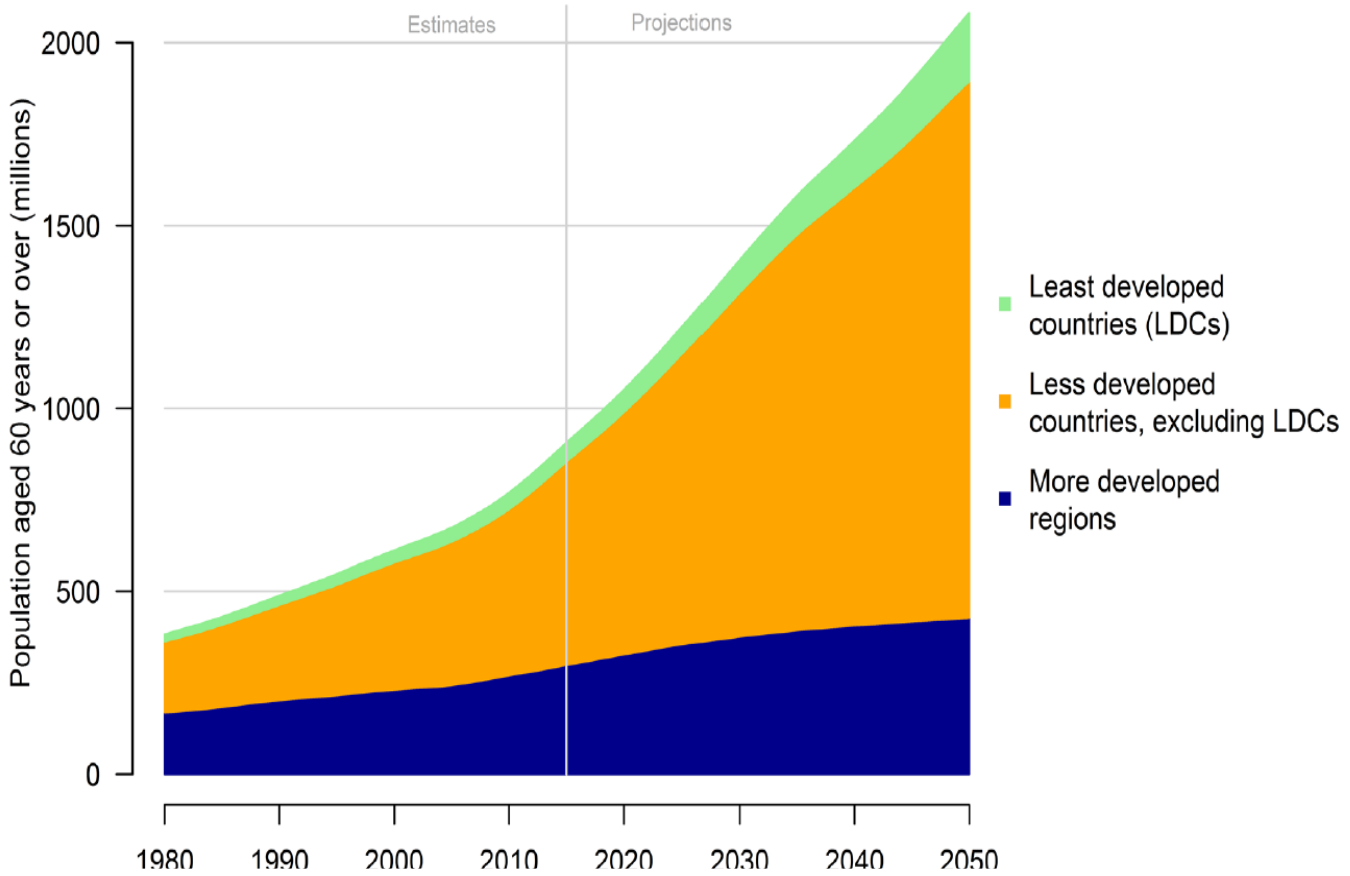
Grow old along with me!
The best is yet to be,
The last of life,
for which the first was made

Robert Browning
1812-1889

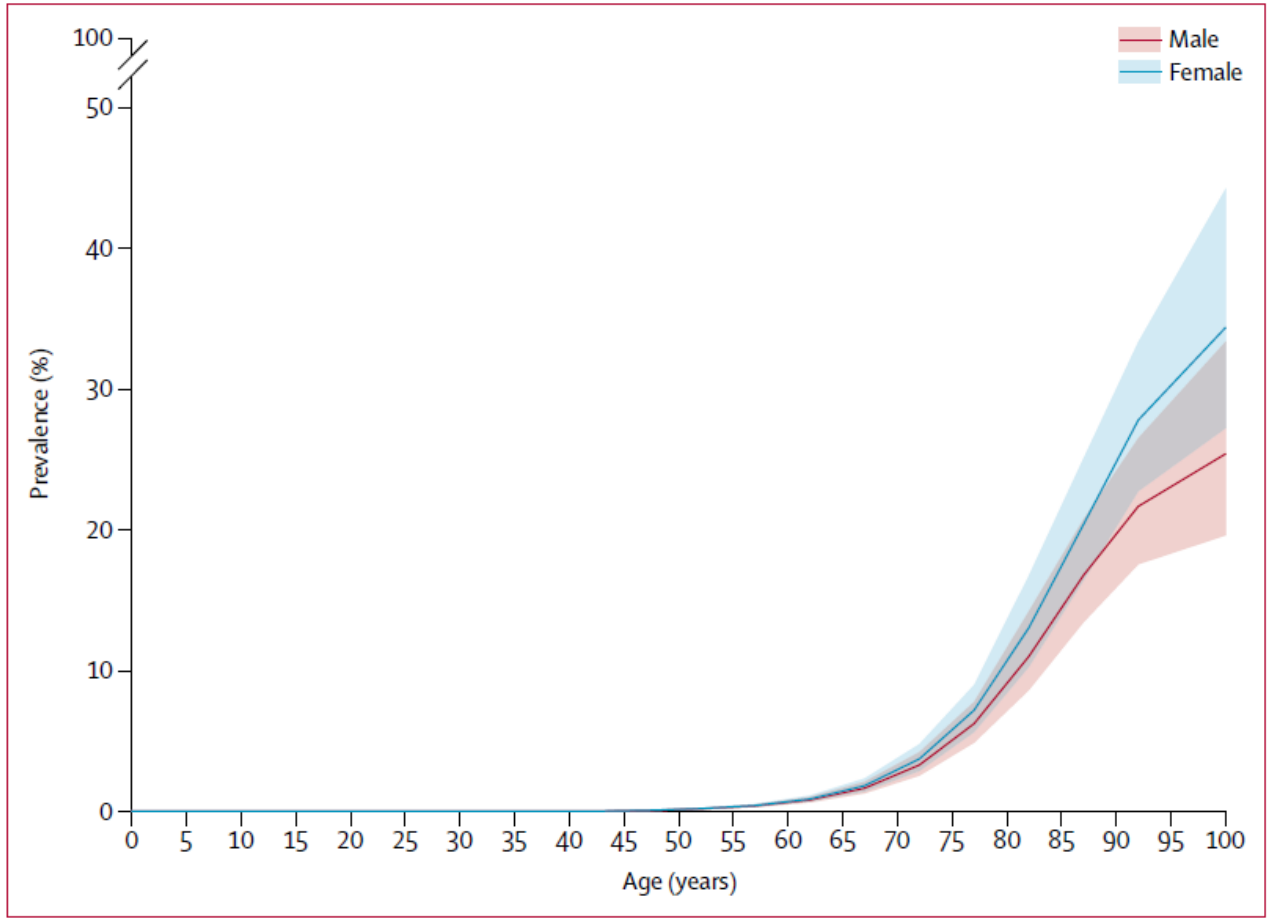
Relentless Aging of Populations

- Declining fertility and rising life expectancy globally result in the number of older persons growing faster than the number of all younger people

- Two-thirds of the world's older persons live in developing regions, where the numbers are growing faster than in developed regions



Global Age-Specific Prevalence of Alzheimer Disease



[1]Global Burden of Diseases, Injuries, and Risk Factors; Lancet Neurology 2019; 18:88-106

Alzheimer Disease and Related Dementias: A Global Challenge

- No group of individuals or place are protected against Alzheimer disease
- The number of individuals worldwide living with Alzheimer disease and related dementias (ADRD) is steadily increasing[1]
  - 20.2 million affected persons in 1990
  - 57.4 million affected persons in 2019
  - Estimate 152.8 million affected persons in 2050
- In the US, the annual direct costs of caring for ~6 million persons with ADRD in 2022 is $321 billion; AD is the only illness in the top ten causes of death in the US that lacks any effective therapy
- The tremendous costs for families, healthcare systems, and government make solving ADRD the biggest challenge currently faced by medical science

[1]Global Burden of Diseases, Injuries, and Risk Factors; AAIC 2021

The Knight ADRC's View of AD

- "Alzheimer disease" (AD) refers to the neurodegenerative brain disorder, regardless of clinical status, representing a continuous process of synaptic and neuronal deterioration
- AD has two major stages:
  - Preclinical (presymptomatic; asymptomatic), undetectable by current clinical methods
  - Symptomatic (clinical)
- Symptomatic AD is defined by intraindividual cognitive decline, from subtle to severe, that interferes with daily function, and can be subclassified on symptom severity:
  - Incipient (prodromal; mild cognitive impairment)
  - Dementia

Morris JC, Arch Neurol 2012;doi:10.1001/archneurol.2011.3152

Dementia

- Clinical Presentation: An acquired syndrome of progressive decline in memory and other cognitive domains (eg, attention, reasoning, language, orientation, spatial abilities) sufficient to affect daily life.

- Etiology: Any disorder causing damage to brain systems involved in memory and cognition. Alzheimer disease is by far the most common disorder causing the dementia syndrome in later life.

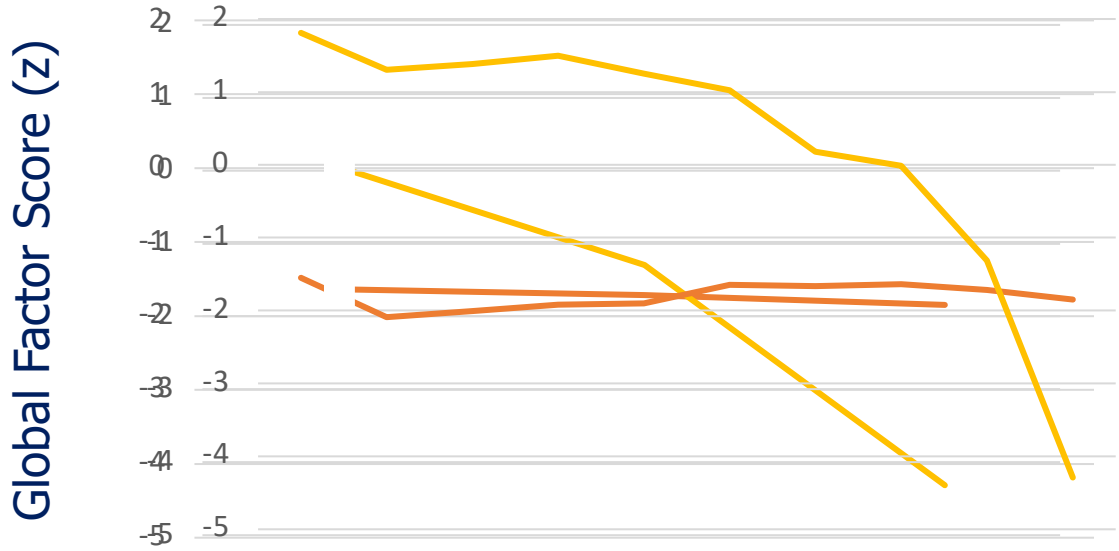
Neurodegenerative Dementias

- Alzheimer Disease
- Dementia with Lewy Bodies
- Vascular Dementia
- Frontotemporal Lobar Dementias
  - FTD
    - Pick Disease
  - Progressive Nonfluent Aphasia
  - Semantic Dementia
- Progressive Supranuclear Palsy
- Corticobasal Degeneration
- Parkinson Disease Dementia
- Multiple System Atrophy
- Huntington Disease
- Prion Disorders
  - Creutzfeldt-Jakob Disease
  - Fatal Familial Insomnia
  - Gerstmann-Straussler Scheinker Disease

Detection of Dementia

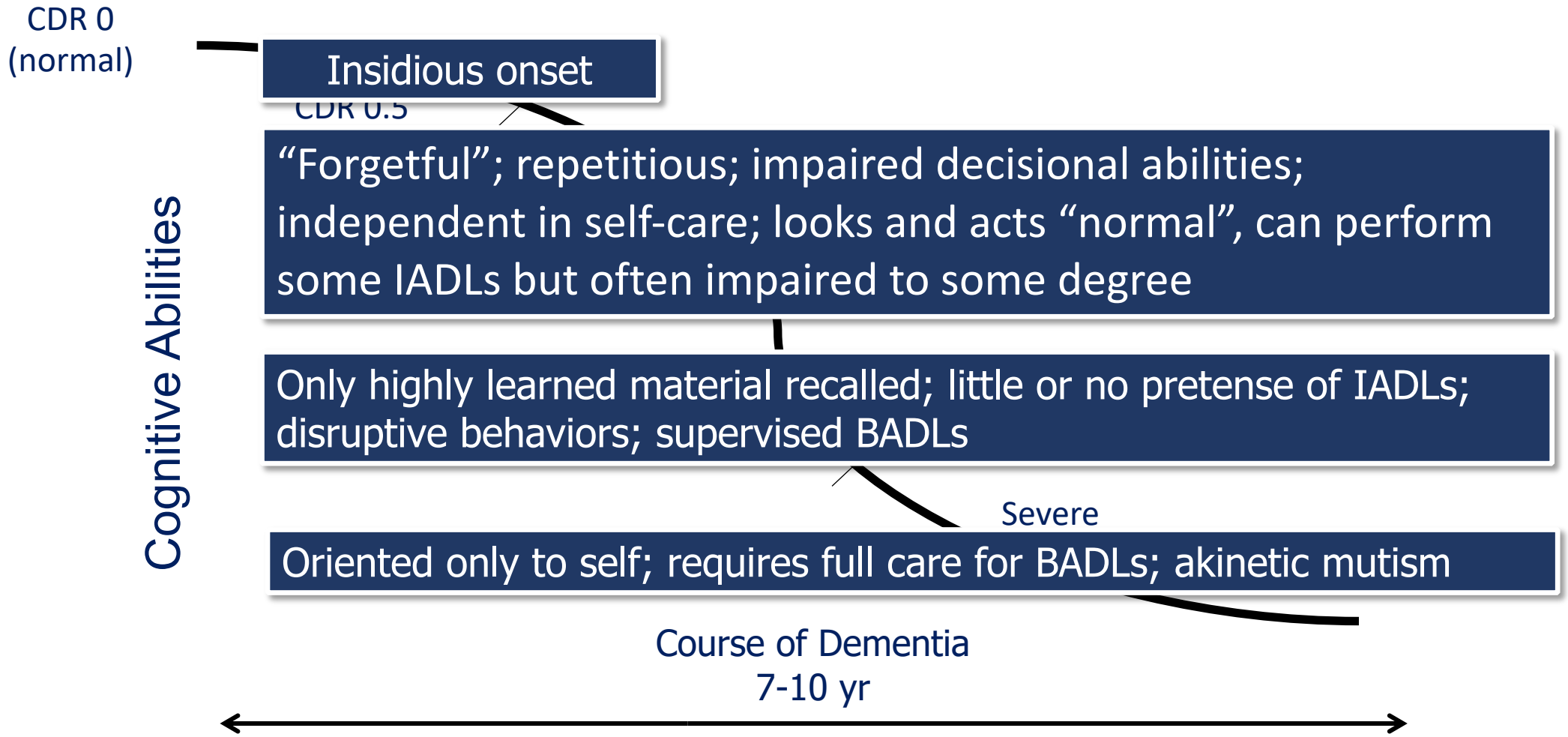
- Intraindividual cognitive change:
  - Serial cognitive testing (prospective); or
  - Informant hx (use patient as own control)
- Interference with activities of daily living
  - Informant hx
- Comparing an individual's cognitive test performance to age-and education-matched norms (interindividual comparison) identifies neither cognitive change nor functional impairment

Intraindividual Decline, Not Test Score, Marks Alzheimer Dementia

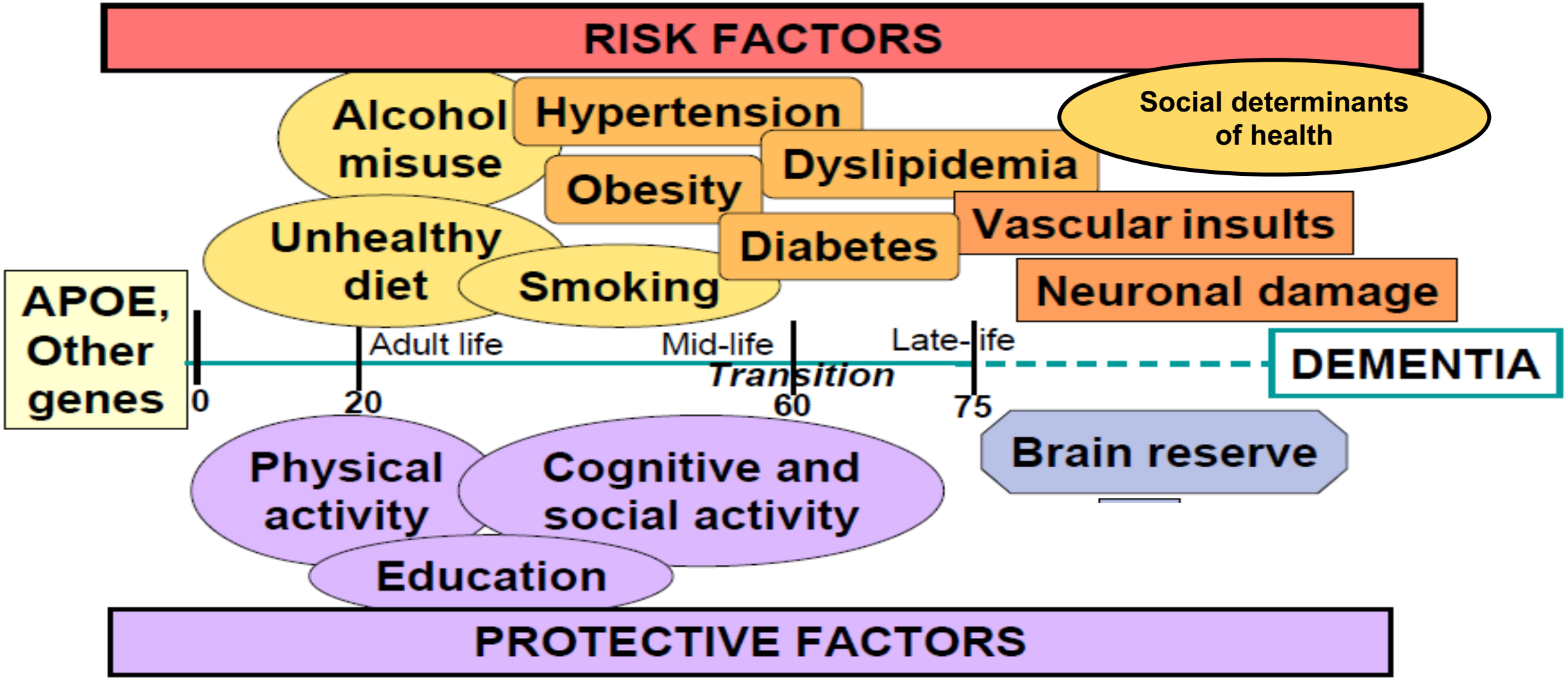


Data courtesy of Martha Storandt

Stages of Alzheimer Dementia (Clinical Dementia Rating)

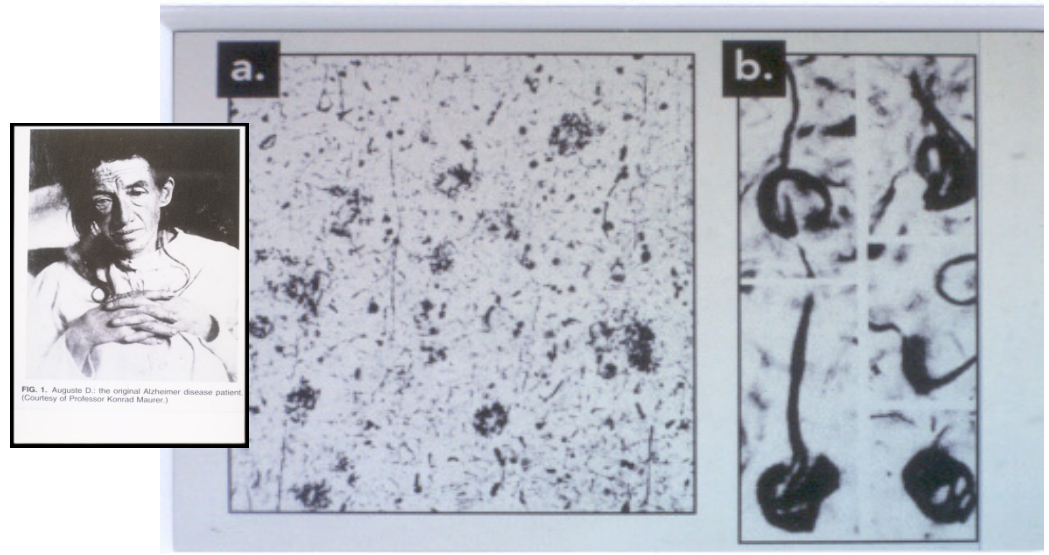


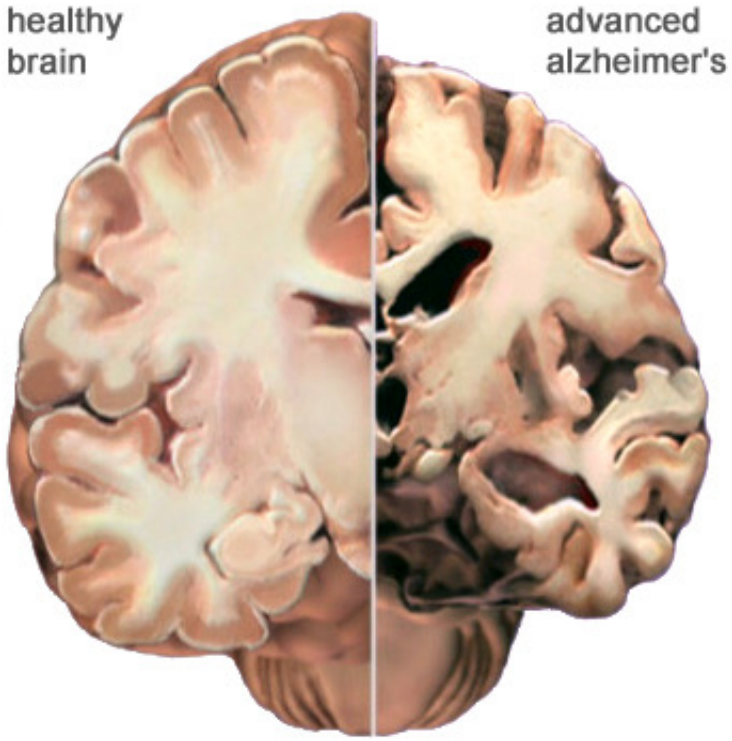
Risk Factors for Alzheimer Disease

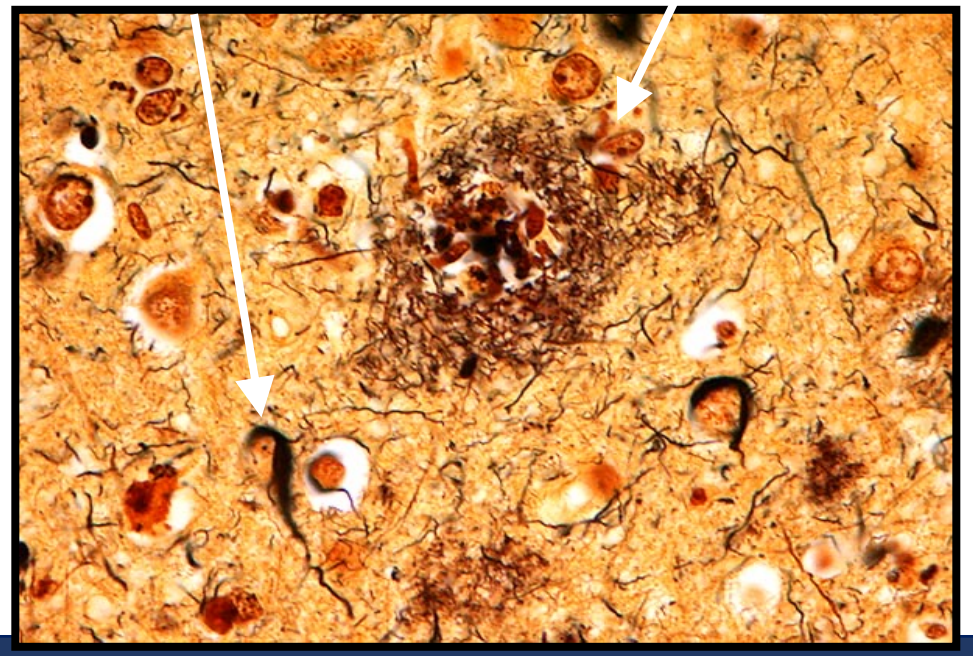


AD Pathologic Hallmarks

- Plaques (diffuse, neuritic, CAA) (Ab)
- Neurofilbrillary tangles (NFT) (tau)
- Neuronal and synaptic dysfunction and loss
- Atrophy of the brain
- Inflammation







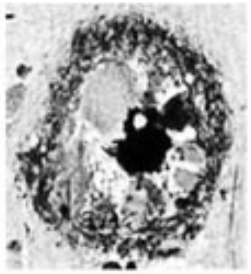
The Amyloid Hypothesis

Factors in clearance and conformation: APOE, APOJ, degrading proteases, anti-Aβ antibodies

Soluble Aβ

Formation of β-sheets; fibrillogenesis

Synaptic and neuronal degeneration



Factors increasing production
- PS1 and PS2 mutations
- APP mutations
- Trisomy 21

Factors decreasing production
- APP mutation (*A673T*)

Neurotoxic and inflammatory responses
- Cytokines
- Glial activation
- Free radical generation

Modified from David M. Holtzman, MD; photomicrographs courtesy of Daniel W. McKeel, MD.

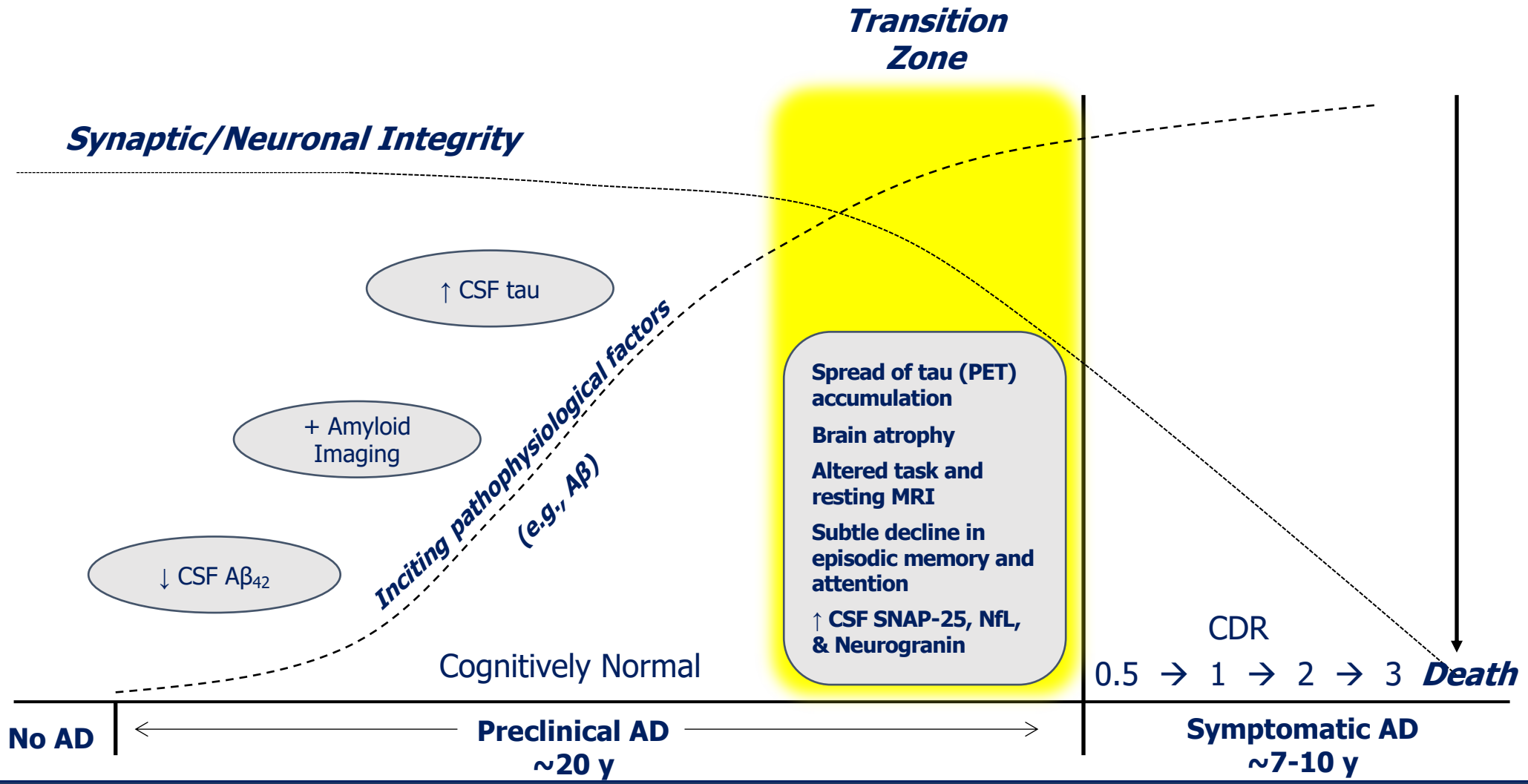
Therapeutic Consequences of the Amyloid Cascade Hypothesis of AD

- In symptomatic AD, Aβ monotherapies are unlikely to provide substantial clinical benefit as they do not address the non-Aβ pathophysiological cascade of multiple co-pathologies

- Combination therapies that target both Aβ **and** other important co-pathologies may improve chances of therapeutic success

- Most compelling rationale: target Aβ **prior** to symptom onset where the goal is to **prevent** AD dementia

Preclinical and Symptomatic AD

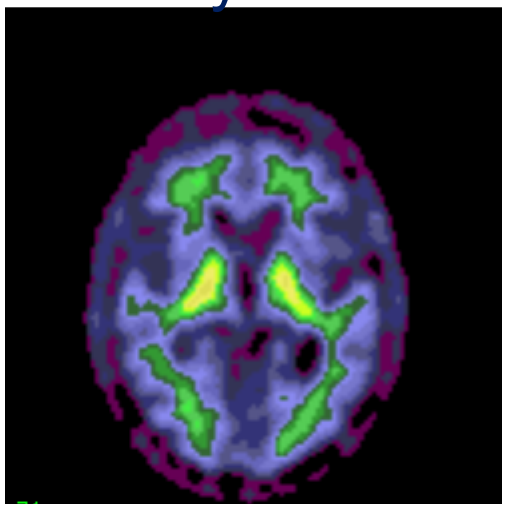
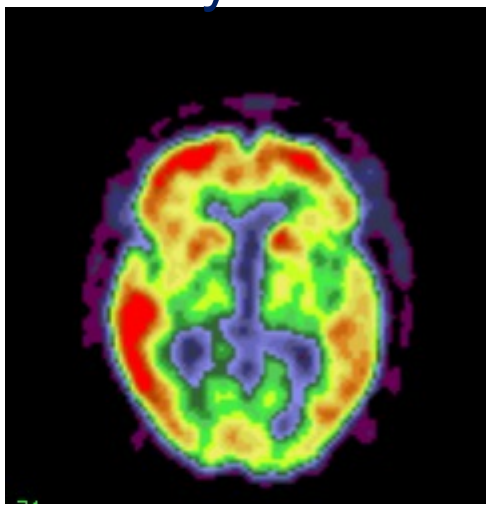
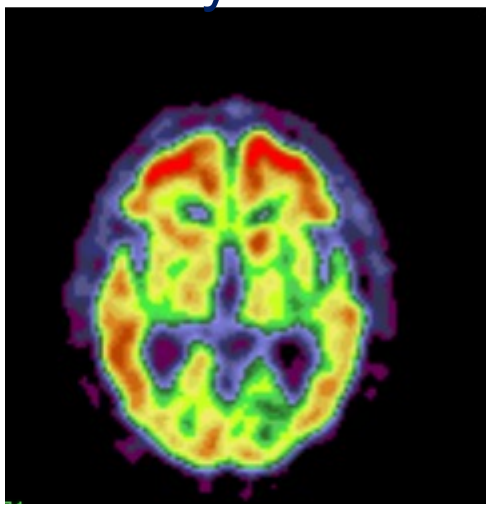


Molecular Biomarkers Detect Symptomatic and Preclinical AD

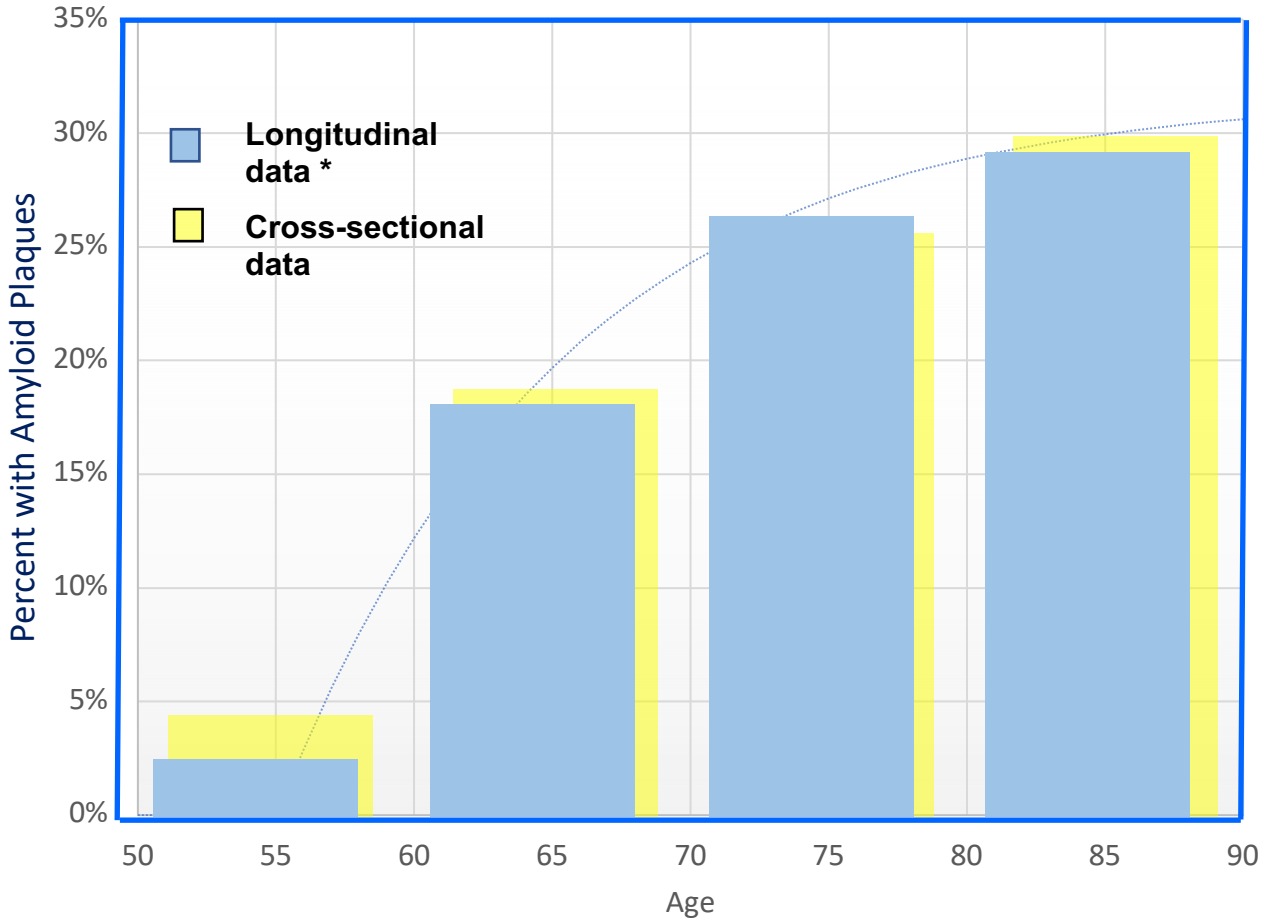
- CSF signature of symptomatic AD: reduced $A\beta_{42}$, elevated tau and p-tau
- Amyloid imaging tracers (e.g., ^{11}C Pittsburgh Compound B, or PIB; ^{18}F AV-45, or Florbetapir)
- PIB amyloid burden increases as a function of the 2 known risk factors for AD, age and *APOE4*

Fagan et al., Ann Neurol 2006; Fagan et al., Arch Neurol 2007; Fagan et al., Ann Neurol 2009; Morris et al., Ann Neurol 2010

Presymptomatic Detection of AD: Biomarkers (PIB Imaging)

Amyloid –	Amyloid +	Amyloid +
		
Cognitively normal	Alzheimer dementia	Cognitively normal
		3 years later, Alzheimer dementia

Percent of Cognitively Normal Participants with Amyloid Plaques



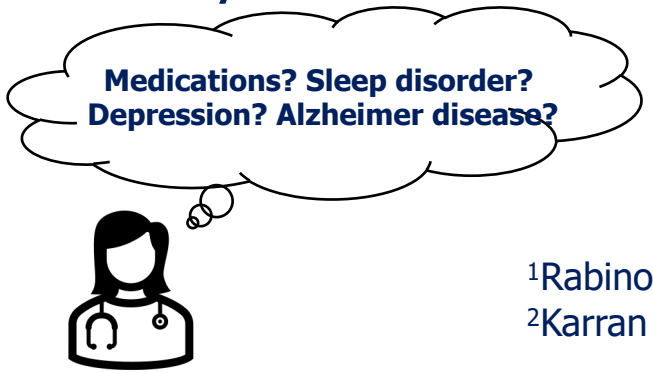
* Courtesy of Mark Mintun, MD, and Andrei Vlassenko, PhD

Why Do We Need Biomarkers?

- Even after a comprehensive clinical evaluation, the diagnosed cause(s) of cognitive impairment is often uncertain or incorrect

- Uncertainty: When dementia specialists say they don't know the diagnosis, they are often right—they often don't know—in one study, the diagnosis was changed 36% of the time after an amyloid PET scan[1]

- Misdiagnosis: In numerous studies, including clinical trials, ~25% of individuals diagnosed with Alzheimer disease dementia by clinical criteria did not have brain amyloidosis[2]



[1]Rabinovici *JAMA* 2019
[2]Karran *NEJM* 2014

Uses of Alzheimer Disease Biomarkers

- **Clinic:**
  - To improve the accuracy of Alzheimer disease diagnosis (currently used in <5% of cases)
  - Appropriate use criteria (AUC) for amyloid PET[1] and cerebrospinal fluid (CSF) biomarker[2] testing in clinical dementia diagnosis have been established that mostly recommend clinical use for atypical, early onset, and uncertain dementia
  - Biomarker confirmation of AD is essential in patients being considered for amyloid-lowering drugs[3]

[1]Johnson *A&D* 2013 [2]Shaw *A&D* 2018 [3]Cummings *JPrevAD* 2021

Threshold for AD Biomarker Testing

- High threshold for amyloid PET and CSF biomarkers due to significant costs/risks/perceived risks
  - Amyloid PET scans cost ~$6,000, is not reimbursed by insurance, involves radiation, and is only available in specialized centers
  - CSF biomarkers cost ~$2,000, are typically reimbursed by insurance, but require a lumbar puncture/spinal tap

- The threshold for AD blood tests may be much lower
  - Patients tolerate blood collection well, AD blood tests may be less expensive to perform, but tests are not currently reimbursed by insurance

- AD blood tests may allow for much broader diagnostic testing for Alzheimer disease, which may improve the speed and accuracy of diagnosis

Blood Biomarkers

- **Pros:**
  - Very well accepted by patients with no major contraindications
  - Potentially much more accessible than amyloid PET or CSF biomarkers, including to diverse groups
  - Much more scalable than imaging or spinal taps

- **Cons:**
  - Only a single test is currently available: PrecivityAD (plasma Aβ42/Aβ40 + apoE proteotype + age)
  - Currently expensive (~$1,250 out-of-pocket) and not reimbursed by insurance, but sliding scale fees are available
  - Accuracy (agreement with amyloid PET) is high, but not as high as CSF biomarkers
  - Not FDA approved yet, not widely used yet

Wash U (Bateman lab) Developed One of the First High Performance Blood Tests for AD

- The test precisely measures concentrations of Aβ42 and Aβ40 in the plasma
- Plasma Aβ42/Aβ40, along with age and *APOE* genotype, is highly predictive of AD brain pathology
- The test was recently validated in three major international cohorts
- C2N Diagnostics commercialized this test, received FDA breakthrough device designation, and the test received approval under CLIA rules
- The test is called PrecivityAD and has been available for clinical use since December 2020. It is currently the ONLY AD blood test that is clinically available.

Amyloid β concentrations and stable isotope labeling kinetics of human plasma specific to central nervous system amyloidosis

Vitaliy Ovod[a,§], Kara N. Ramsey[a,§], Kwasi G. Mawuenyega[a], Jim G. Bollinger[a], Terry Hicks[a], Theresa Schneider[a], Melissa Sullivan[a], Katrina Paumier[a], David M. Holtzman[a,b,c], John C. Morris[a,c], Tammie Benzinger[d,c], Anne M. Fagan[a,b,c], Bruce W. Patterson[e], Randall J. Bateman[a,b,c,*]

High-precision plasma β-amyloid 42/40 predicts current and future brain amyloidosis

Suzanne E. Schindler, MD, PhD, James G. Bollinger, PhD, Vitaliy Ovod, MS, Kwasi G. Mawuenyega, PhD, Yan Li, PhD, Brian A. Gordon, PhD, David M. Holtzman, MD, John C. Morris, MD, Tammie L.S. Benzinger, MD, PhD, Chengjie Xiong, PhD, Anne M. Fagan, PhD, and Randall J. Bateman, MD

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Neurology® 2019;93:e1647-e1659. doi:10.1212/WNL.0000000000008081

Validation of Plasma Amyloid-β 42/40 for Detecting Alzheimer Disease Amyloid Plaques

Yan Li, PhD, Suzanne E. Schindler, PhD, James G. Bollinger, PhD, Vitaliy Ovod, MS, Kwasi G. Mawuenyega, PhD, Michael W. Weiner, MD, Leslie M. Shaw, PhD, Colin L. Masters, MD, Christopher J. Fowler, PhD, John Q. Trojanowski, PhD, Magdalena Korecka, PhD, Ralph N. Martins, PhD, Shorena Janelidze, PhD, Oskar Hansson, MD, PhD, and Randall J. Bateman, MD

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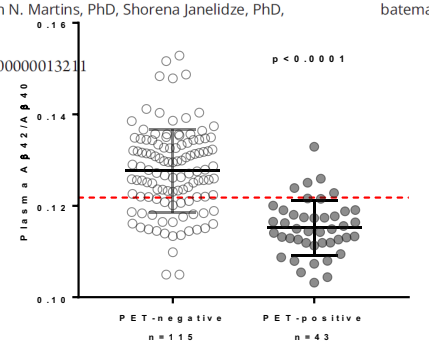
Neurology® 2022;98:e688-e699. doi:10.1212/WNL.0000000000013211



[5]Schindler *Neurology* 2019

A Possible New Paradigm for Dementia Evaluation

- Patients with cognitive impairment potentially caused by AD undergo an AD blood test as part of their work-up

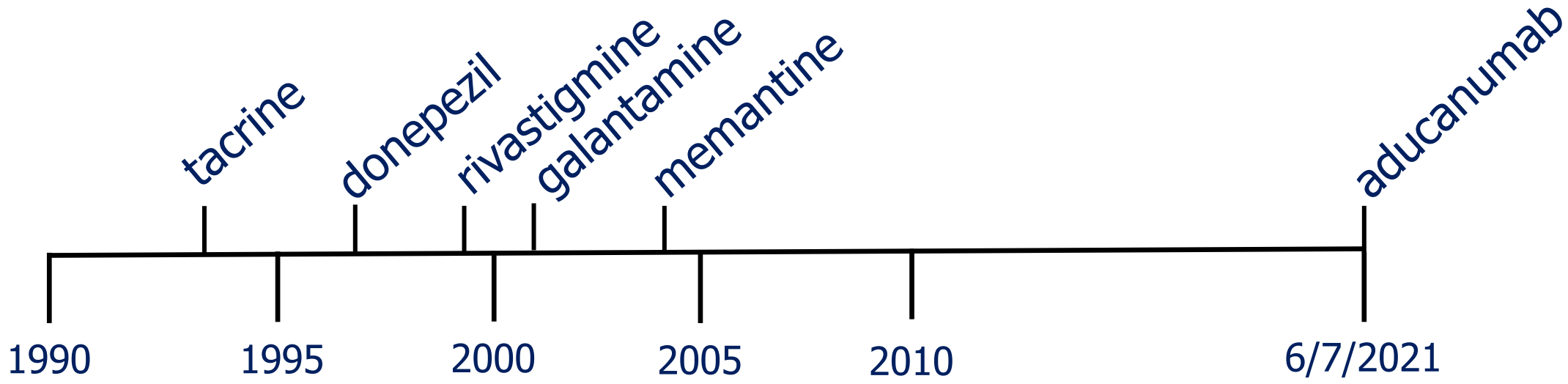
- Clinicians use the results of the AD blood test to guide their evaluation and management
  - The blood test is not assumed to provide the diagnosis
  - Non-AD etiologies of cognitive impairment continue to be considered, even in patients with a positive blood test
  - Amyloid PET or CSF biomarkers are performed if clinicians and patients think it would be helpful to diagnosis and management

- This paradigm could lead to earlier and more accurate AD diagnosis and facilitate more rapid identification of patients who may benefit from AD-modifying drugs

CUBED

Clinical Utility of Blood Tests in Early Dementia Diagnosis

Approved Therapies for Alzheimer Disease



Symptomatic----------to----------disease-modifying

Aducanumab (Aduhelm®)

- High affinity, fully human IgG1 monoclonal antibody against an Aβ epitope (antibodies originally derived from cognitively normal older adults); binds aggregated Aβ

- Two Biogen-sponsored Phase III studies of intravenous Aducanumab failed to meet their pre-specified endpoint for efficacy. Nonetheless, the US Food and Drug Administration (FDA) granted the drug accelerated approval on June 7, 2021, based on the drug's ability to reduce Aβ plaque burden (surrogate endpoint for clinical benefit)

- Biogen establishes price for 1 y treatment with Aducanumab: US $58,000

- In July, 2021, the FDA's acting commissioner asked for an investigation of the relationship of Biogen with the FDA and to assess whether any rules were broken

Aducanumab (Aduhelm®)-2

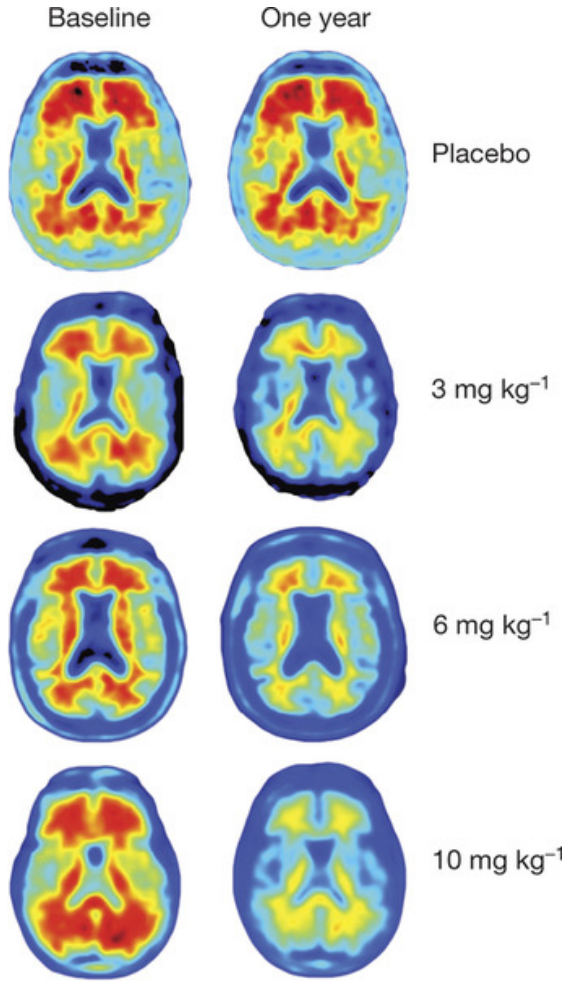
- On December 16, 2021, the European Medicines Agency rejects Biogen's application for Aducanumab
- On December 20, 2021, Biogen reduces its price for Aducanumab from US $58,000 to US $28,000 per year
- In January, 2022, the Centers for Medicare and Medicaid Services agree to reimburse costs of Aducanumab treatment **only** for patients in approved randomized controlled clinical trials
  - Pivotal trial results for gantenerumab (Roche/Genentech) and lecanemab (Eisai) expected in 2022 and for donanemab (Lilly) in 2023

Aducanumab (Aduhelm®)-3

- Difficult to extrapolate the two Phase III study results to the vast majority of AD patients
  - Did not enroll participants reflecting the diversity of the population; e.g., only 19 of the total 3,285 participants (< 1%) were Black, nor did participants have common comorbid disorders
  - Did not enroll participants with more than very mild symptomatic AD
- Amyloid-Related Imaging Abnormalities (edema: ARIA-E; hemorrhage: ARIA-H) occurred in 35% of treated participants in the trials; 25% of participants with ARIA-E were symptomatic, with serious (microbleeds, confusion, seizures, falls) concerns in 3%
- Clinical practice infrastructure unprepared for large scale Aducanumab therapy
  - Inadequate diagnostic capacity: paucity of dementia experts; reimburse the costs of confirmation of the presence of amyloid plaques by PET or CSF (now, possibly plasma)
  - Limited availability of infusion centers
  - How will safety monitoring be supported (e.g., serial MRI to detect ARIA)?

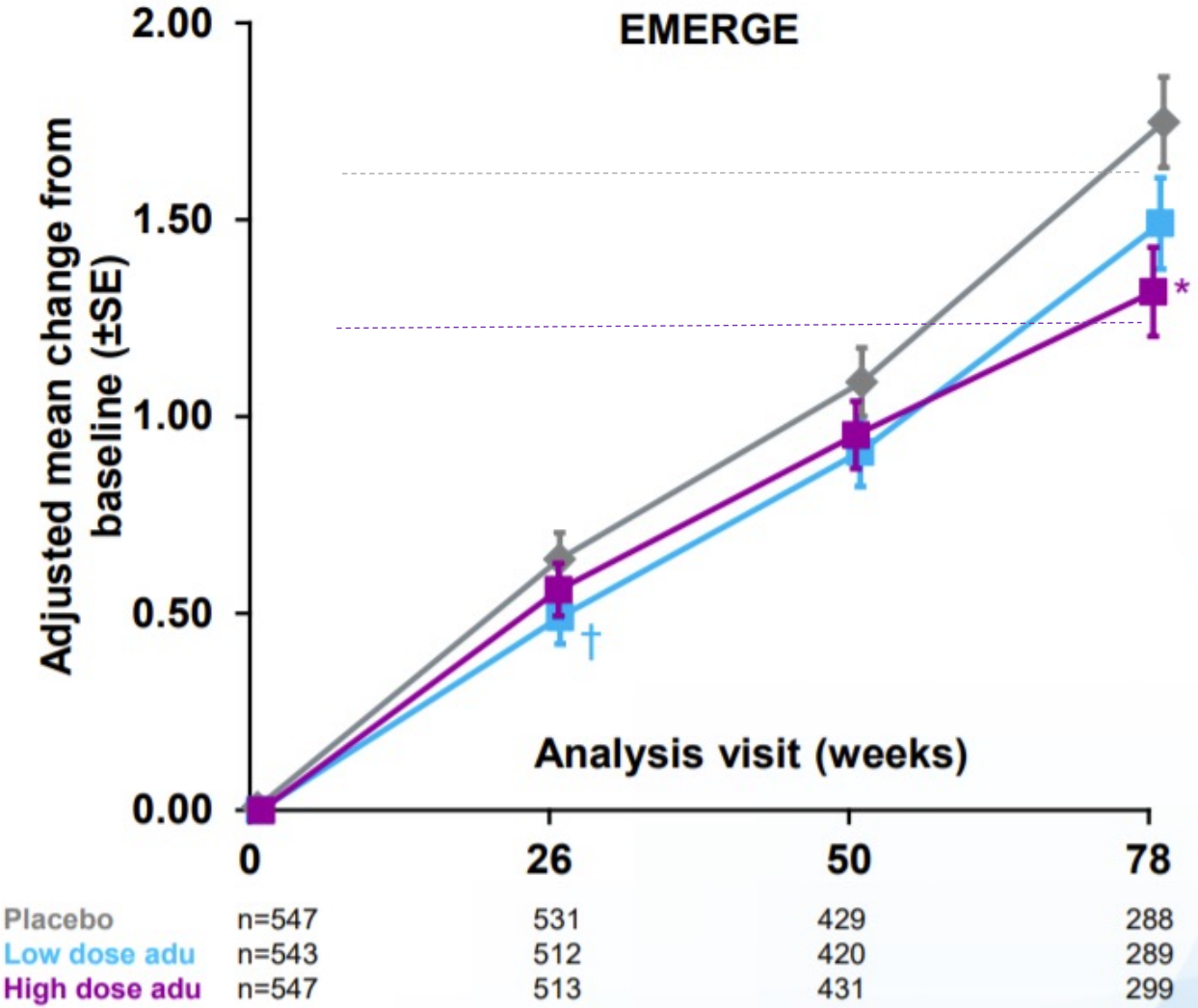
Aducanumab Removes Amyloid Plaques from the Brain

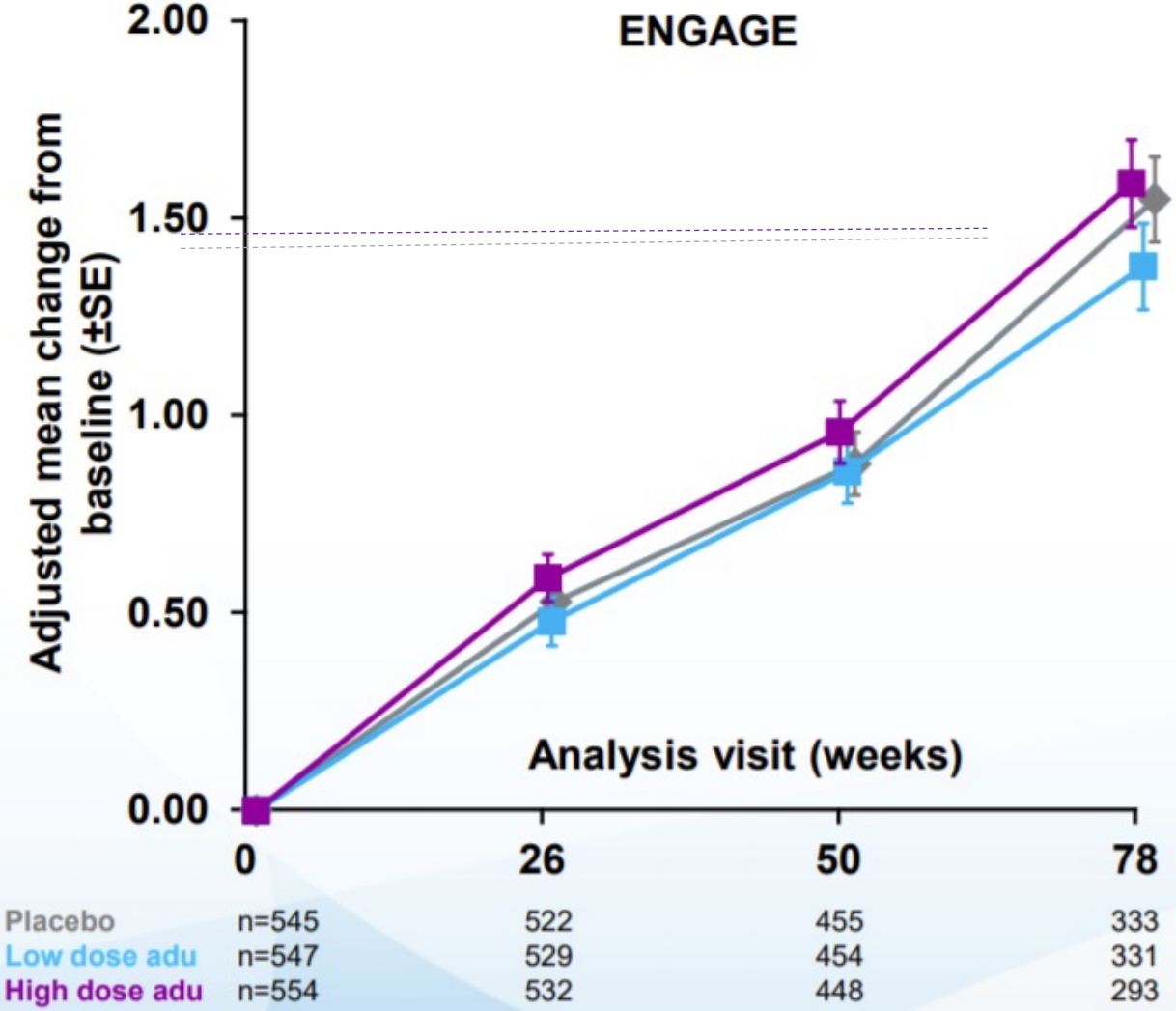
- Amyloid plaques are a hallmark of Alzheimer's Disease
- They form many years before the start of memory problems
- Aduncanumab (Aduhelm) is an antibody that can be infused into the blood stream and can remove amyloid plaques from the brain.



Seivgny, et al., Nature 537:50-56 (2016)

Does Aducanumab slow down Alzheimer Disease?





More Plaque-Removing Antibodies on the Way

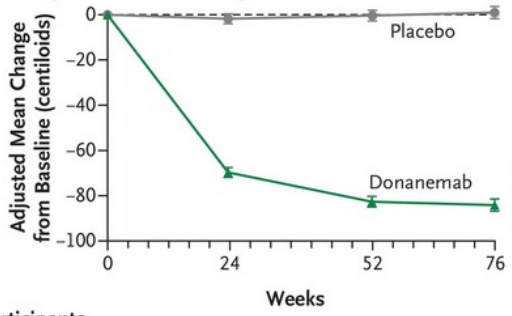
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Donanemab in Early Alzheimer's Disease

Mark A. Mintun, M.D., Albert C. Lo, M.D., Ph.D., Cynthia Duggan Evans, Ph.D., Alette M. Wessels, Ph.D., Paul A. Ardayfio, Ph.D., Scott W. Andersen, M.S., Sergey Shcherbinin, Ph.D., JonDavid Sparks, Ph.D., John R. Sims, M.D., Miroslaw Brys, M.D., Ph.D., Liana G. Apostolova, M.D., Stephen P. Salloway, M.D., et al.

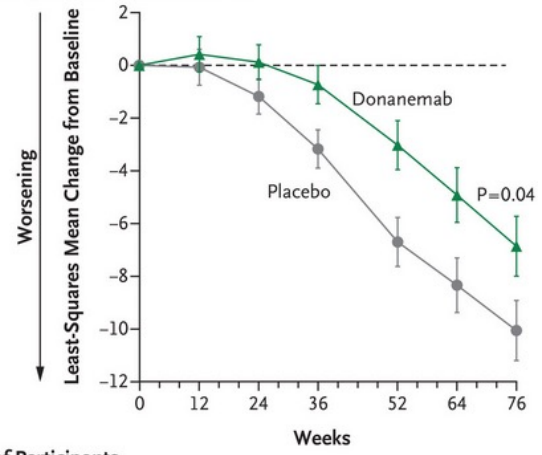
A Amyloid Plaque Level on Florbetapir PET



No. of Participants

Donanemab	121	115	92	90
Placebo	112	111	91	91

A Primary Outcome: iADRS Score



No. of Participants

Donanemab	125	120	112	102	88	89	93
Placebo	120	113	110	103	90	90	91

BMC Part of Springer Nature

Alzheimer's Research & Therapy

A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aß protofibril antibody

Chad J. Swanson, Yong Zhang, Shobha Dhadda, Jinping Wang, June Kaplow, Robert Y. K. Lai, Lars Lannfelt, Heather Bradley, Martin Rabe, Akihiko Koyama, Larisa Reyderman, Donald A. Berry, Scott Berry, Robert Gordon, Lynn D. Kramer & Jeffrey L. Cummings

Alzheimer's Research & Therapy **13**, Article number: 80 (2021) | Cite this article

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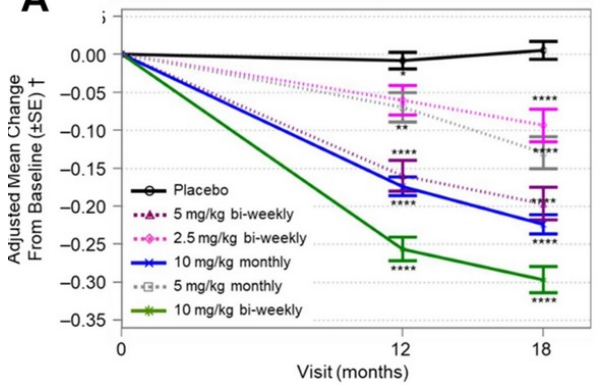

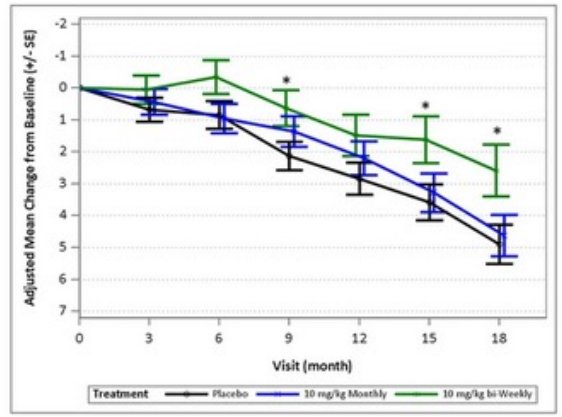

N (ADAS-cog)	0 Months	3 Months	6 Months	9 Months	12 Months	15 Months	18 Months
Placebo	238	227	214	201	186	172	158
10 mg/kg monthly	246	233	209	176	164	152	146
10 mg/kg biweekly	152	144	130	104	94	90	79

Lecanemab: Phase 3 CLARITY Alzheimer Study– Press Release 9/27/2022

- Anti-amyloid beta protofibril antibody
- Enrolled persons with very mild to mild Alzheimer dementia
  - Of 1795 persons enrolled, ~25% were from groups underrepresented in research
- 50% received active drug, 50% received placebo
  - Intravenous dose of 10mg/Kg bi-weekly for 18 months
- Primary endpoint: reduced clinical decline by 27% as measured by CDR-SB
  - Treatment difference between drug and placebo of ~0.5 points
  - Non-treated very mild AD Alzheimer persons decline by about 1.5 CDR-SB points per year
- ARIA-E occurred in 12.5% (vs 1.7% in placebo); ARIA-H occurred in 17% (vs 8.7% in placebo)

Conclusion

- The outlook regarding Alzheimer disease in 2022 has been considerably boosted by
  - Blood-based biomarker tests to notably improve accurate diagnosis
  - Apparent success of some anti-amyloid immunotherapies that may provide modest clinical benefit

- To come:
  - Combination therapies for persons with symptomatic AD
  - Prevention therapies for preclinical AD