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2023 Brock Institute - Glennan Center

Internal Medicine Grand Rounds

"Alzheimer's: Quest for Cure vs. Patient Prioritized Population Health: Rekindling the Conversation"

Ardeshir Hashmi, MD, FACP, FNAP, AGSF

Endowed Chair of Geriatric Innovation, Section Chief

Center for Geriatric Medicine, Cleveland Clinic

October 25, 2023

12 noon-1:00 pm

The Brock Institute - Glennan Center Lecture established by the Cooke Fund of the Hampton Roads Community Foundation

EVMS GLENNAN CENTER FOR GERIATRICS AND GERONTOLOGY | 25TH ANNIVERSARY | EVMS M. FOSCUE BROCK INSTITUTE FOR COMMUNITY AND GLOBAL HEALTH

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Community focus.
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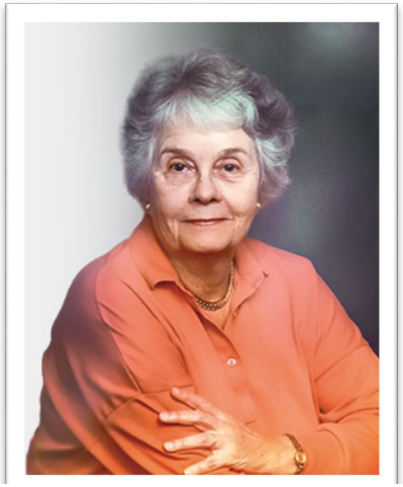
M. Foscue Brock Institute for Community & Global Health

M. Foscue Brock, MD, was a tuberculosis specialist in charge of Norfolk's Grandy Sanitorium for 29 years before he entered private practice. Dr. Brock volunteered at the public health center in Norfolk throughout his career and was a popular family doctor. It was Dr. Brock's involvement with the community that inspired Dr. Brock's son, Macon F. Brock Jr., and wife, Joan, to establish the M. Foscue Brock Institute for Community and Global Health at EVMS in 2012. The M. Foscue Brock Institute for Community and Global Health honors the values that led Dr. Brock in his life and career.

M. Foscue Brock, MD



Virginia Glennan Ferguson

Glennan Center for Geriatrics and Gerontology

The Glennan Center for Geriatrics and Gerontology was established in 1995 through a generous gift from Virginia Glennan Ferguson in honor of her father and grandfather. The Glennan Center aims to promote the health, well-being, independence, and quality of life of older adults; and to enhance the knowledge base and standards of practice in geriatrics and gerontology through clinical practice, education, research and advocacy especially in the areas of cognition, healthy aging and palliative care.

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Brock Institute - Glennan Center Lecture

The Cooke Fund of the Hampton Roads Community Foundation established in 2015 highlights the latest in geriatric academic research and brings world-renowned leaders in geriatric care to EVMS to share their knowledge with the students, faculty, community physicians and leaders in healthcare throughout Hampton Roads.

Since 2015, the year of the first Brock Institute Glennan Lecture, leveraging the experience and network of Dr. Bob Palmer, now professor emeritus and former director of the Glennan Center, and the current director, Dr. Marissa Galicia-Castillo, the partnership between the Brock Institute and the Glennan Center is pleased to present this evening's program.

We thank Mr. Robert Goodman, Esq. for your support and guidance in the development of these series of presentations.

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Continuing Medical Education

ACCME Accreditation

Eastern Virginia Medical School is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

AMA Credit Designation

Eastern Virginia Medical School designates this live activity for a maximum of 1.0 *AMA PRA Category 1 Credit* ™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Disclosure

Dr. Ardeshir Hashmi has disclosed he is member of the advisory board for Cognivue, Inc.

All other planning committee members have no relevant financial relationships with ineligible companies to disclose.

Target Audience

Physicians, Physician Assistants, Residents, Nurses, and other healthcare providers

Learning Objectives

- Assess current evidence for Alzheimer's Dementia (AD) pharmacotherapy efficacy & risks and its underlying constructs; Amyloid cascade and other pathogenetic pathways.
- Evaluate AD's medical, psychosocial and economic impact on population health and the national caregiver crisis.
- Propose the Patient Priorities Care & Social Prescribing global paradigms as a practical, low cost strategy to counter the AD pandemic and reframe AD quality metrics and goals of care.

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Alzheimer's: Quest for Cure vs. Patient Prioritized Population Health: Rekindling the Conversation"

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Cleveland Clinic

Alzheimer's Dementia:
Quest for Cure vs. Patient Prioritized Population Health
- "Rekindling the Conversation"

Brock Institute - Glennan Center Lecture

October 2023

Ardeshir Z. Hashmi MD, FACP, FNAP, AGSF

Enterprise Chief: Center for Geriatric Medicine

Endowed Chair for Geriatric Innovation

Cleveland Clinic

Cleveland Clinic

Financial Disclosures: Physician Advisory Board Cognivue Inc.

This bears no relationship to any content of this talk

Agenda

1. Alzheimer's –The Global Pandemic:
   - Demographics & Definition

2. Search for the Holy Grail of a Cure:
- Review of Treatment & Therapeutics to date

3. AD Research Re-Focus

4. Redefining Alzheimer's: Current Ground Realities

5. Alzheimer's: Care Reimagined for Populations

Alzheimer's: The Global Pandemic

Someone in the United States develops Alzheimer's disease

- Aging Demographic – "Silver Tsunami" will see a surge of Geriatric Patients Nationally;

  80 million by 2050

- **2023: 6.7 million AD** patients nationally

- By **2050**:: Projected **16 million will have Alzheimer's Dementia**

- **Annual Dementia Costs:**

  Globally - $ 818 Billion

  - U.S: $ 215 Billion

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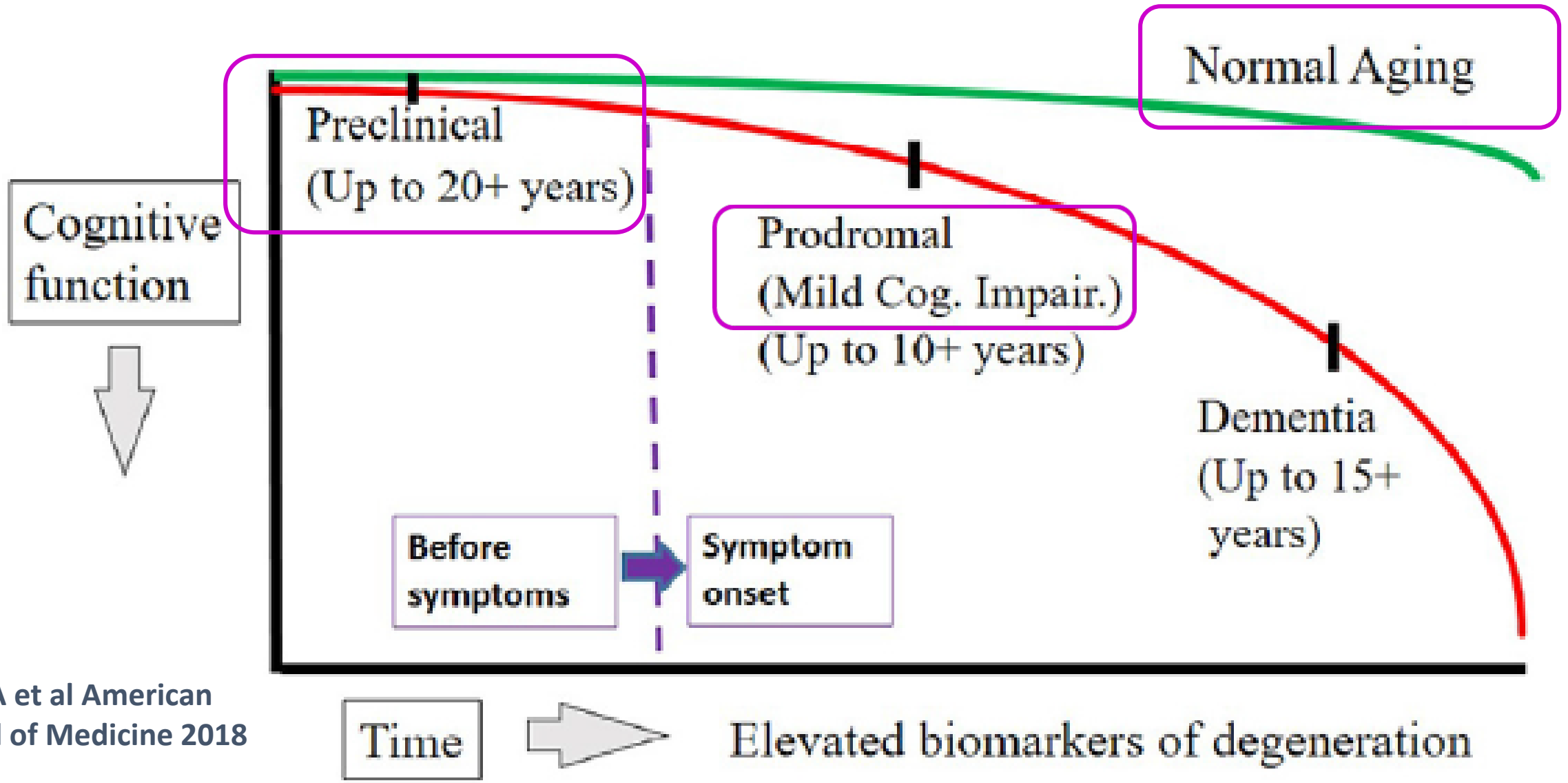
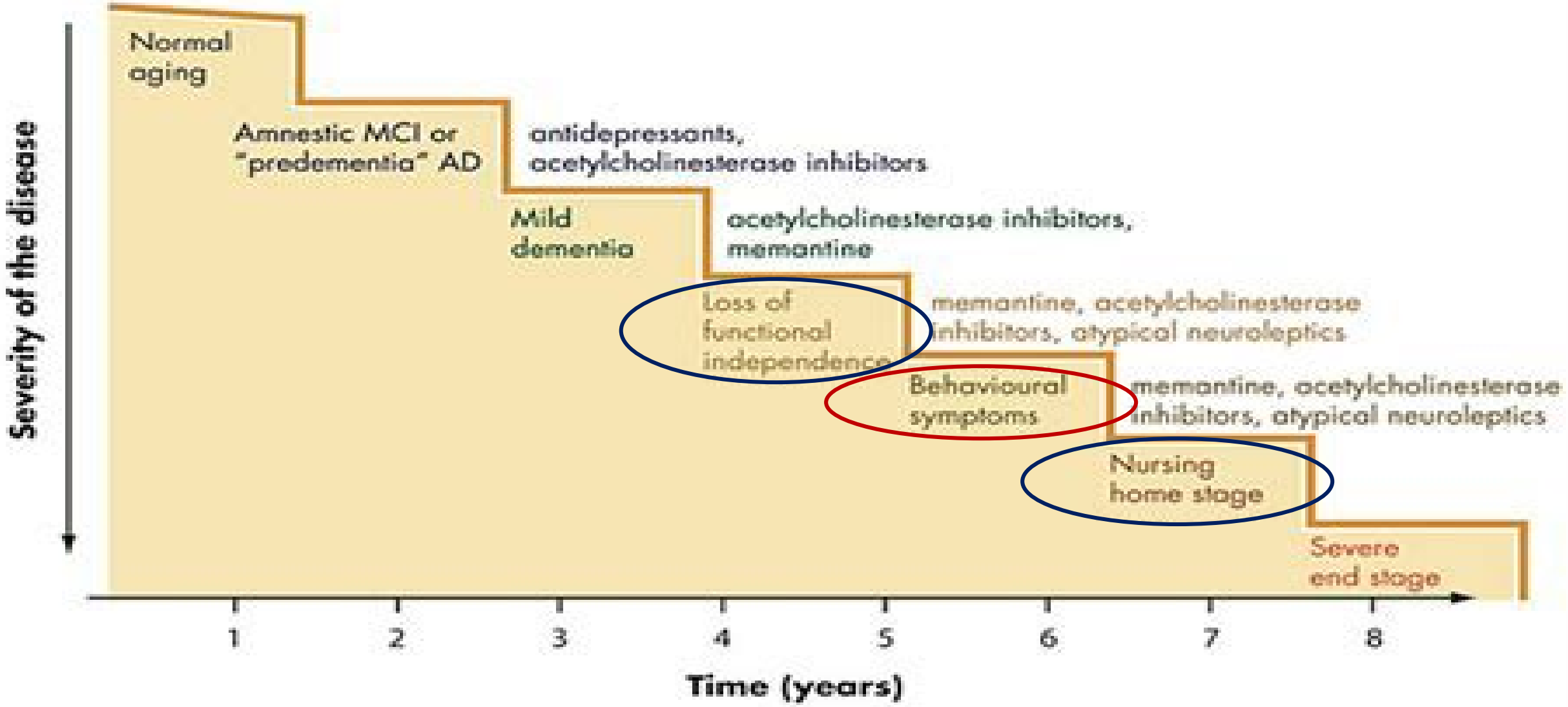
The Continuum of Alzheimer Disease (AD)



Gale SA et al American Journal of Medicine 2018

Natural History of Alzheimer's Disease and Stage-specific Symptomatic Drugs



Agenda

1. Alzheimer's –The Global Pandemic:
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2. Search for the Holy Grail of a Cure:
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3. Review of Evidence for Prevention Strategies

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5. Alzheimer's Care: Reimagined for Populations

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AD Therapeutics: Current State

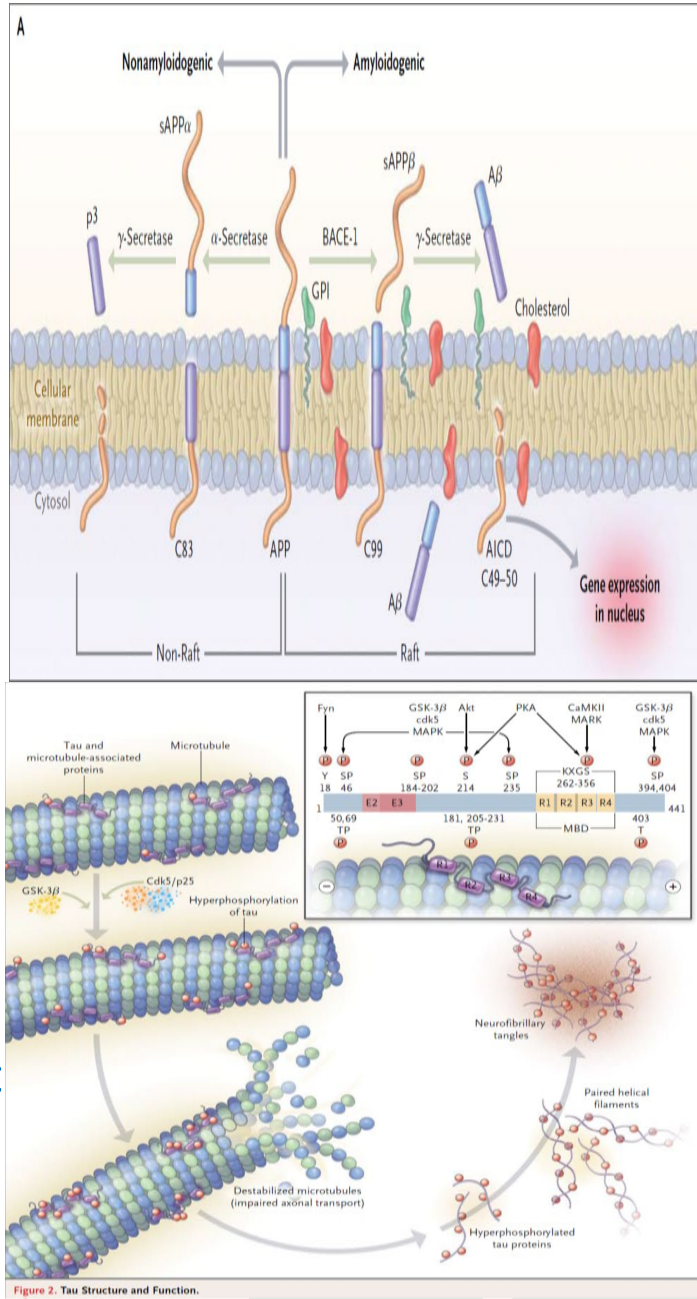
- Alois Alzheimer first described pathognomonic signs of AD in 1907
- Only 6 medications approved by FDA for AD treatment over the last 111 years!
- **Amyloid beta peptide: Therapeutic "target" for AD research over last 20 years**
- These medications which include Cholinesterase inhibitors and NMDA antagonists CANNOT reverse cognitive decline, have modest benefit on stabilization of cognition/function in clinical trials; do NOT impact institutionalization or quality of life and lose efficacy over time
- Acetylcholinesterase inhibitors include **Donepezil** ("Aricept"), **Rivastigamine** ("Exelon") and **Galantamine** ("Razadyne")
- NMDA Antagonist is **Memantine** ("Namenda)-Reduces Ca influx/excitotoxicity

Kim LD, Factora RM CCLJM 2018

Amyloid Cascade Hypothesis

Querferurth HW LeFerla FM NEJM 2010

- Imbalance between neurotoxic Amyloid beta-42 peptide production and clearance is a very early initiating/trigger factor
- Amyloid beta 42 peptide generated by proteolytic cleavage (by BACE 1 (beta site APP cleaving enzyme) and sequentially gamma secretase) of Amyloid Precursor Protein (APP)
- Early onset amyloid beta deposition/aggregation forming extracellular amyloid plaques
- Amyloid beta oligomers impair synaptic function (including long term potentiation) and structure and is a potent mitochondrial poison
- Followed by accumulation of intracellular tangles/neuritis containing wild type hyperphosphorylated Tau filaments-This interferes with axonal transport and leads to cell death



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Amyloid based AD Therapeutics: Evidence to Date

- **Antibodies targeting Amyloid beta**: Bapineuzumab, Crenezumab, Ponemab, Verubecestat and Solanzeumab **(EXPEDITION Trials 1 and 2)** have all **FAILED** in clinical trials

- **Small molecule amyloid beta binder** scyllo-inistol and tramiprosate have also **Failed**

- **Gamma secretase inhibitors** also concomitantly inhibit Notch signaling protein which is essential for normal physiological function;

-Semagecestat **"IDENTITY" trials** terminated at 12 months due to adverse events, **failed to improve cognition scores and had worsened functional scores at higher dose!**

- First active AD vaccine AN1792 **suspended s/p meningoencephalitis adverse effect!**

Honig et al NEJM 2018

Egan MF et al NEJM 2018

Gilman S. et al Neurology 2011

Holmes C et al. Lancet 2012

Salloway S et al. 2009

Salloway S Neurology 2011

Aisen PS Arch med Sci 2011

Bouter Y et al, Acta Neuropathol 2015

Gandy S Nat Rev Neurol 2015

Doody RS et al. NEJM 2013

Doody RS NEJM 2014

Landen JW et al. Clini Neuropharmacol, 2013

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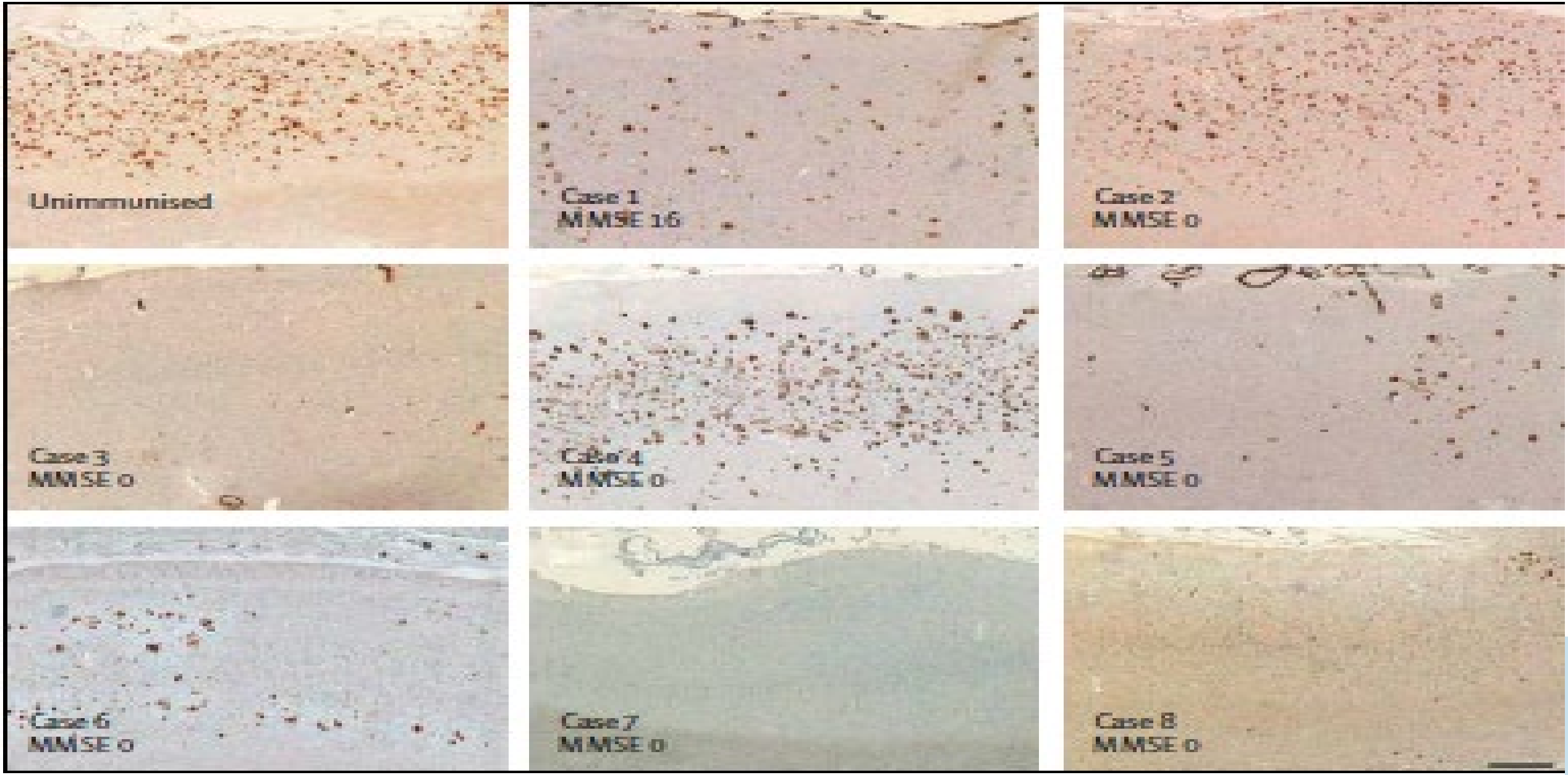

Figure 2: Histological patterns of Aβ in the temporal lobe neocortex after immunisation with AN1792

Holmes C et al 2008

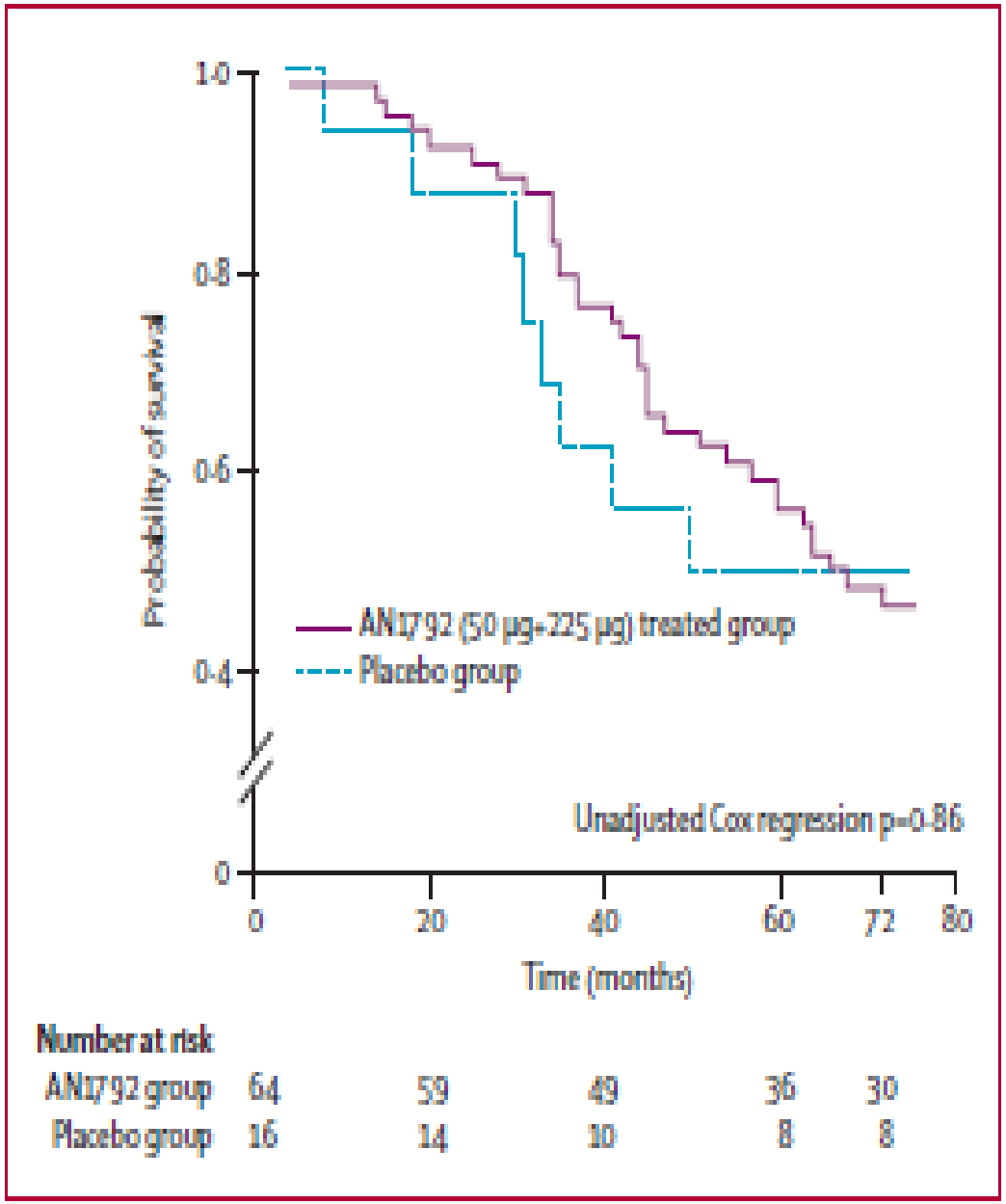

Figure 4: Kaplan-Meier estimates of survival time to death by treatment group

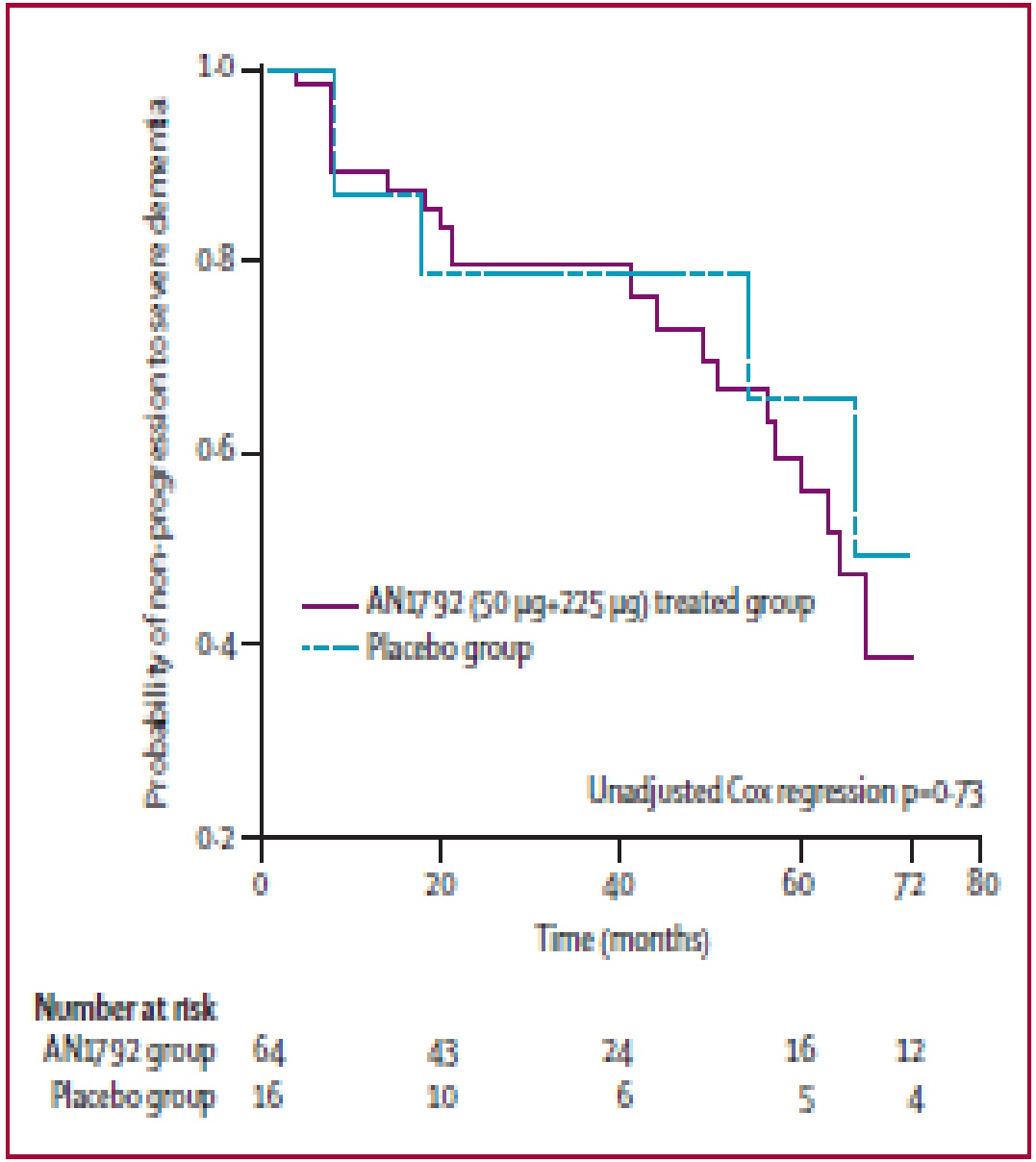

Figure 5: Kaplan-Meier estimates of time to severe dementia by treatment group

Holmes C et al 2008

Tau based AD Therapeutics: Evidence to Date

- Tau treatment strategies have included (i) Directly blocking aggregation (ii) vaccines (iii) Indirectly stabilizing microtubules (iv) manipulating kinases and phosphatases

- Tau Aggregation blockers Trx0237 failed to show benefit in Phase III trials

- Methylene blue failed to show a benefit in Phase III trials

- IVIG failed to meet primary end points in Phase III trials

- Tau targeted active vaccines, Tau oligomer specific antibody (TOMA) & strategies for stabilizing microtubules and manipulating kinases and phosphatases currently being studied

Gauthier S. et al-Lancet 2016

Li C, Gotz J Nat Rev. Drug Discov 2017

Challenges to the Amyloid Cascade Hypothesis

- Majority of AD patients do NOT over produce Amyloid Precursor Protein (APP)
- *Autopsy studies* show abundant Amyloid beta deposits in individuals who did NOT manifest AD clinically
- *Amyloid PET and CSF studies* evidence approx. one third of clinically normal older individuals harbor amyloid plaque accumulation
- Deposition of Amyloid beta does NOT consistently correlate with neurofibrillary tangles, cell loss or dementia

AD Pathogenesis Hypotheses

- Amyloid Cascade Hypothesis and Cholinergic Neuron damage-Basis of use of Cholinesterase Inhibitors in AD
- Tau-Microtubule associated "scaffolding" protein-Pathological states: Impairs axons causing neurodegeneration; Hyperphoshoprylated Tau-Renders protein aggregation prone reducing neuroplasticity
- Oxidative stress-ROS exposure can directly increase APP or indirectly modulate BACE and gamma secretase enzymes
- Inflammation: Microglial dysfunction in synaptic pruning and pro-inflammatory cytokines
- Glucose Hypometabolism (basis for FDG PET scanning)-Insulin resistance, IGF-1 and insulin degrading enzyme modulate amyloid beta clearance and Insulin transport is highest in Olfactory bulb
- Newer/Other Pathways: Gut Microbiome/Immune Pathway/Cholesterol/CATCH Vascular

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“Pre-Clinical” Alzheimer’s

- **Begins at least 20 years prior to first symptom onset!**

- **“Prevention” trials** focused on this “pre-clinical” AD phase are **currently underway** exploring **potential “theragnostic markers”** including :

- The international **“A4” (“Anti-Amyloid Treatment in Asymptomatic Alzheimer’s Disease”)** RCT (based on abnormal *PET –amyloid scans*);

- The **“API”** study examining the *world’s largest Presenelin-1 kindred in rural Medellin Colombia* and

- The “**DIAN” (“Dominantly Inherited Alzheimer’s Network”)** trials enrolling younger individuals from *families with APP, Presenelin-1, Presenelin 2 mutations*

- AHEAD Trial – Lecanemab and Pre-Clinical AD

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ELSEVIER

CrossMark

Alzheimer's & Dementia 14 (2018) 535-562

Alzheimer's & Dementia

2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

Clifford R. Jack, Jr.,[a,*], David A. Bennett[b], Kaj Blennow[c], Maria C. Carrillo[d], Billy Dunn[e], Samantha Budd Haeberlein[f], David M. Holtzman[g], William Jagust[h], Frank Jessen[i], Jason Karlawish[j], Enchi Liu[k], Jose Luis Molinuevo[l], Thomas Montine[m], Creighton Phelps[n], Katherine P. Rankin[o], Christopher C. Rowe[p], Philip Scheltens[q], Eric Siemers[r], Heather M. Snyder[d], Reisa Sperling[s]

Contributors[†]: Cerise Elliott, Eliezer Masliah, Laurie Ryan, and Nina Silverberg

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[b]*Department of Neurological Sciences, Rush University, Chicago, IL, USA*
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[d]*Medical & Scientific Relations, Alzheimer's Association, Chicago, IL, USA*
[e]*Office of Drug Evaluation, FDA, Silver Spring, MD, USA*
[f]*Biogen, Cambridge, MA, USA*

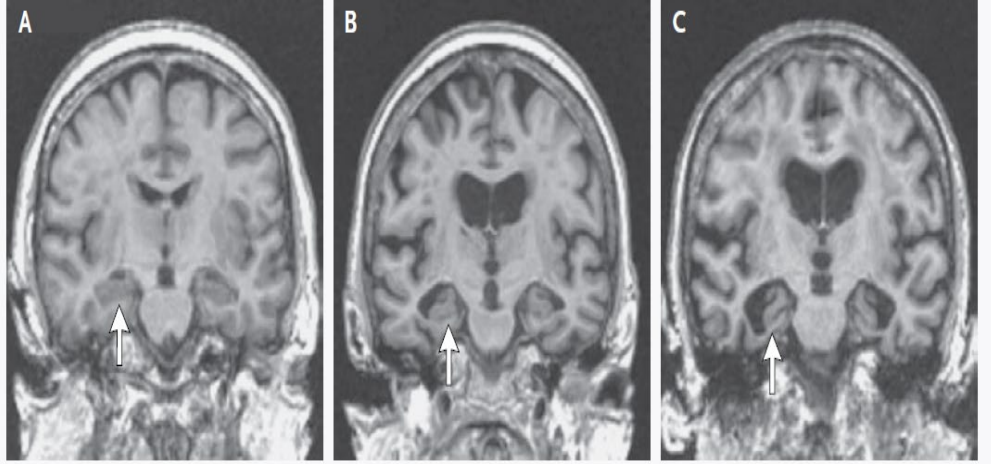


Figure 2. Coronal MRI Scans from Patients with Normal Cognition, Mild Cognitive Impairment, and Alzheimer's Disease.

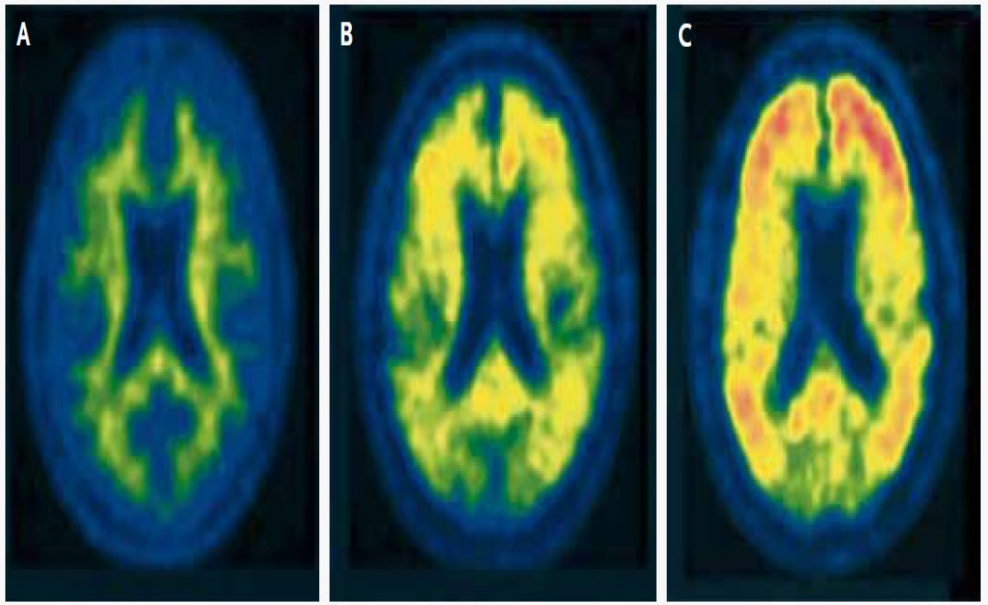
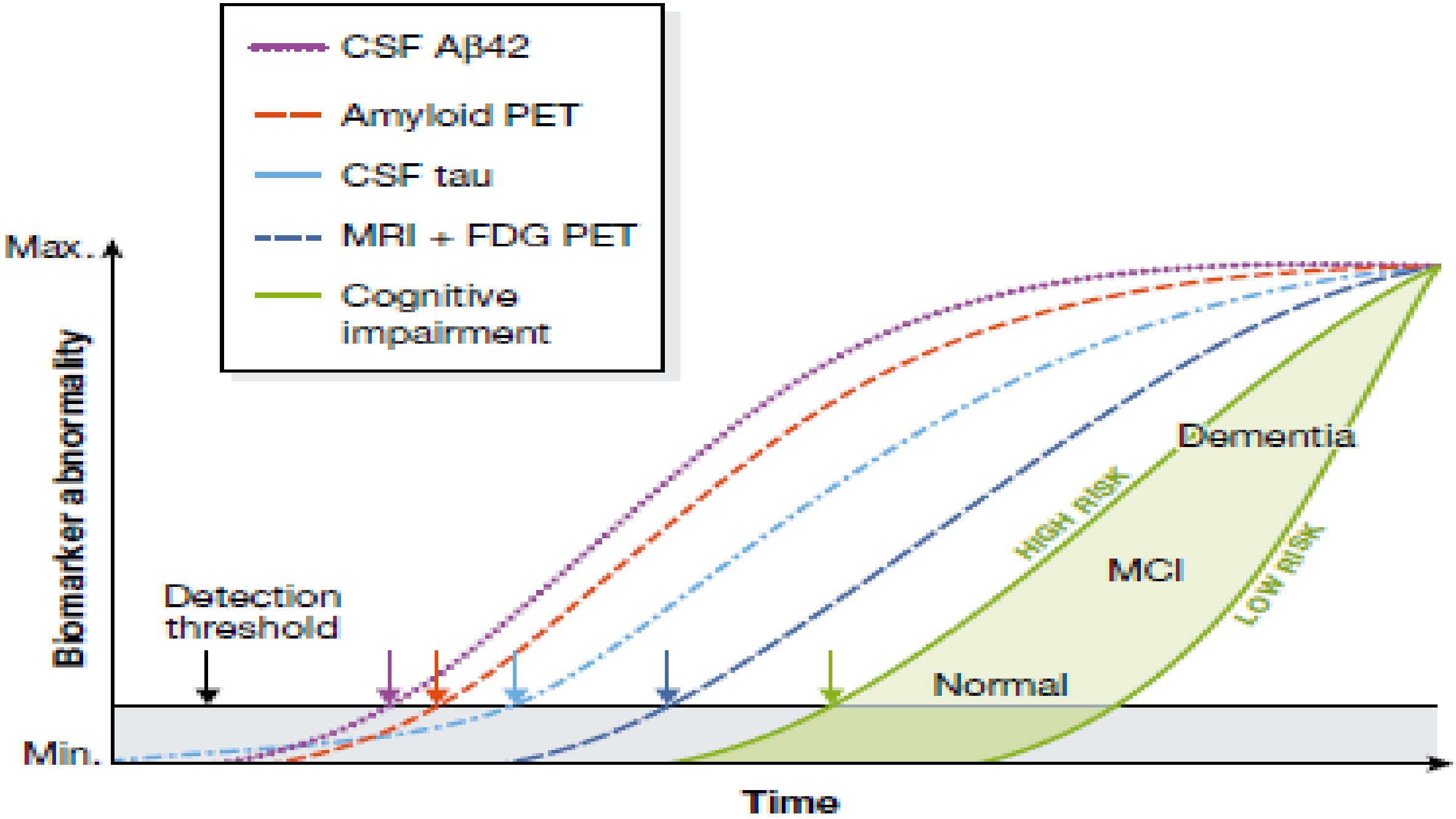


Figure 3. Axial Scans of the Brain Obtained with Positron-Emission Tomography and the Use of Amyloid-Binding Carbon 11–Labeled Pittsburgh Compound B.

Petersen RC NEJM 2011



Selkoe D Hardy J EMBO Molecular Medicine 2016

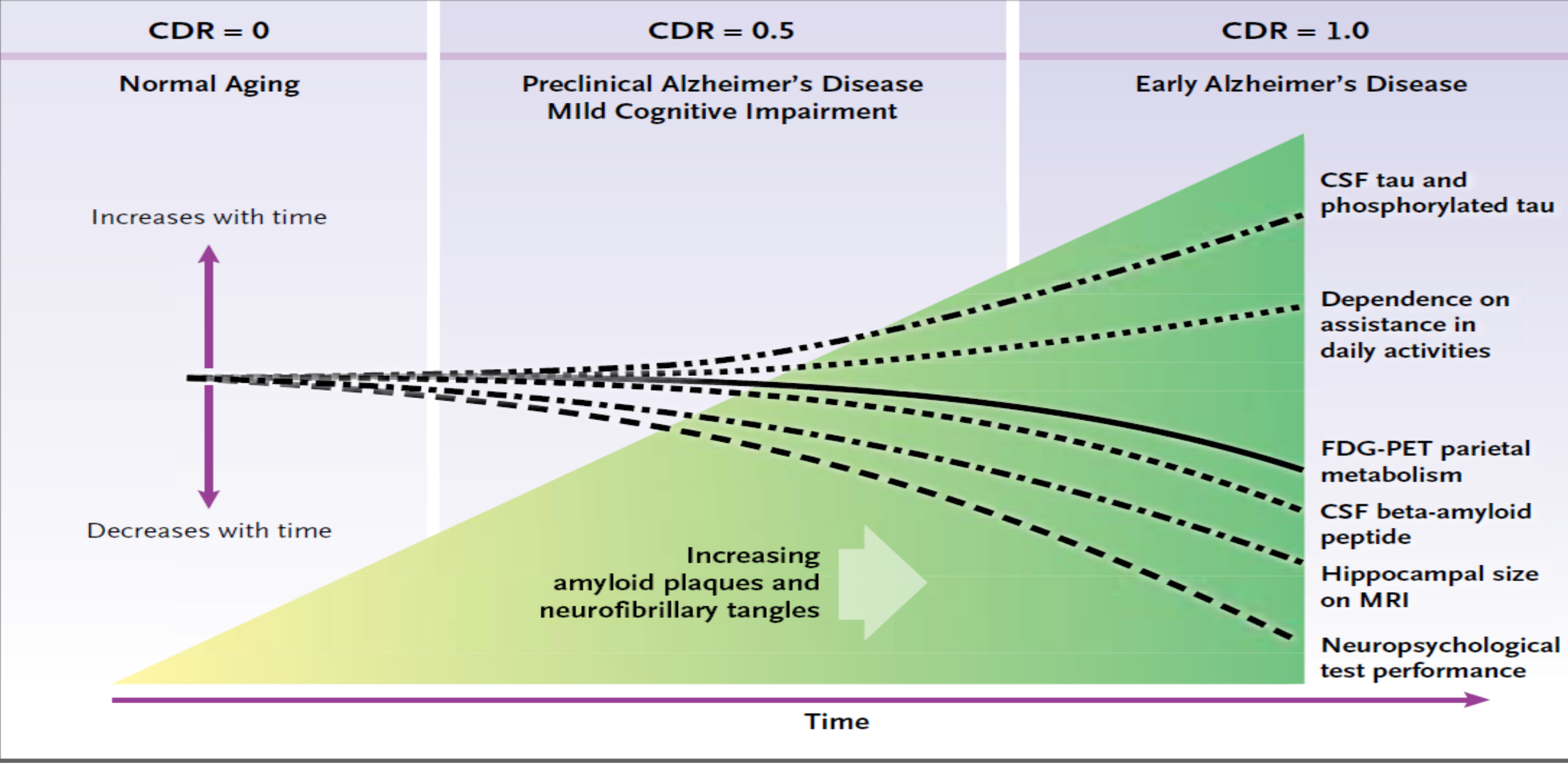


Figure 1. Sequence of Pathological, Clinical, Physiological, and Radiologic Changes from Normal Aging to Early Alzheimer's Disease.

Mayeux M NEJM 2010

Alzheimer's Biomarker "Signatures" (Unchanged since 2010!*):

- **MRI Brain: Hippocampal/Medial temporal lobe atrophy**

- **FDG-PET Scan: Bilateral temporo-parietal hypometabolism**

  - Hypometabolism in temporo-parietal regions=11 times more likely AD incidence in next 2 years (ADNI-Alzheimer's Disease Neuro-Imaging Initiative)

- **Amyloid PET: Plaque deposition** evaluated-*Cost Not currently covered by CMS

  - (**IDEAS study** "Imaging Dementia Evidence for Amyloid Scanning) will study impact of Amyloid PET on diagnostically challenging cases, ED visits and Hospitalizations-18,000 patients across the U.S)

- **CSF Markers:** - Decreased beta-amyloid-42 residue protein (as inc. bound to plaques)

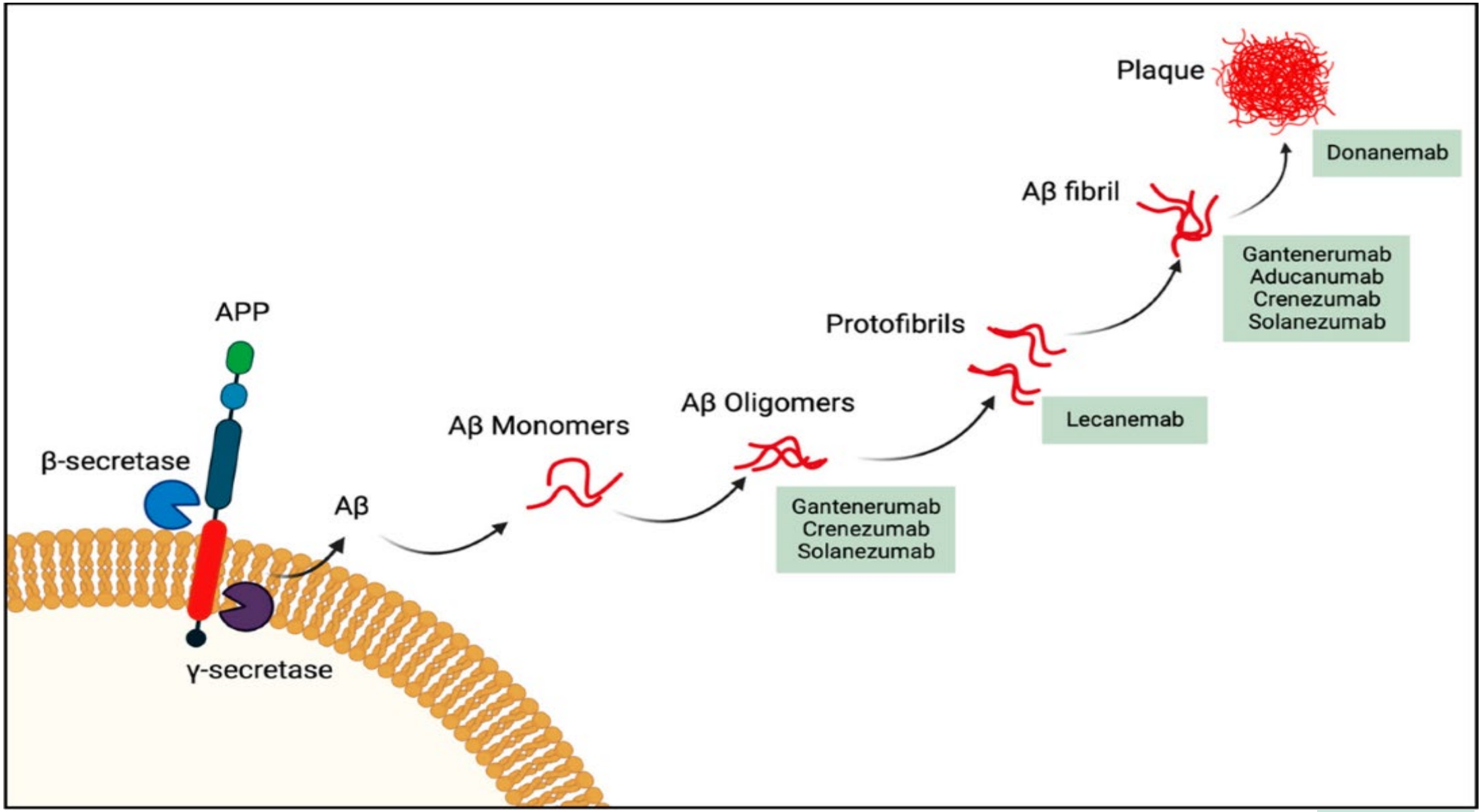
  - Increased Phosphorylated Tau

- **CSF Amyloid beta 42/Phosphorylated Tau Ratio** (Sensitivity 83% Specificity 72%, PPV 62%, NPV 88 % - **"Not.. appropriate for clinical use**..not currently possible to alter..development of AD)

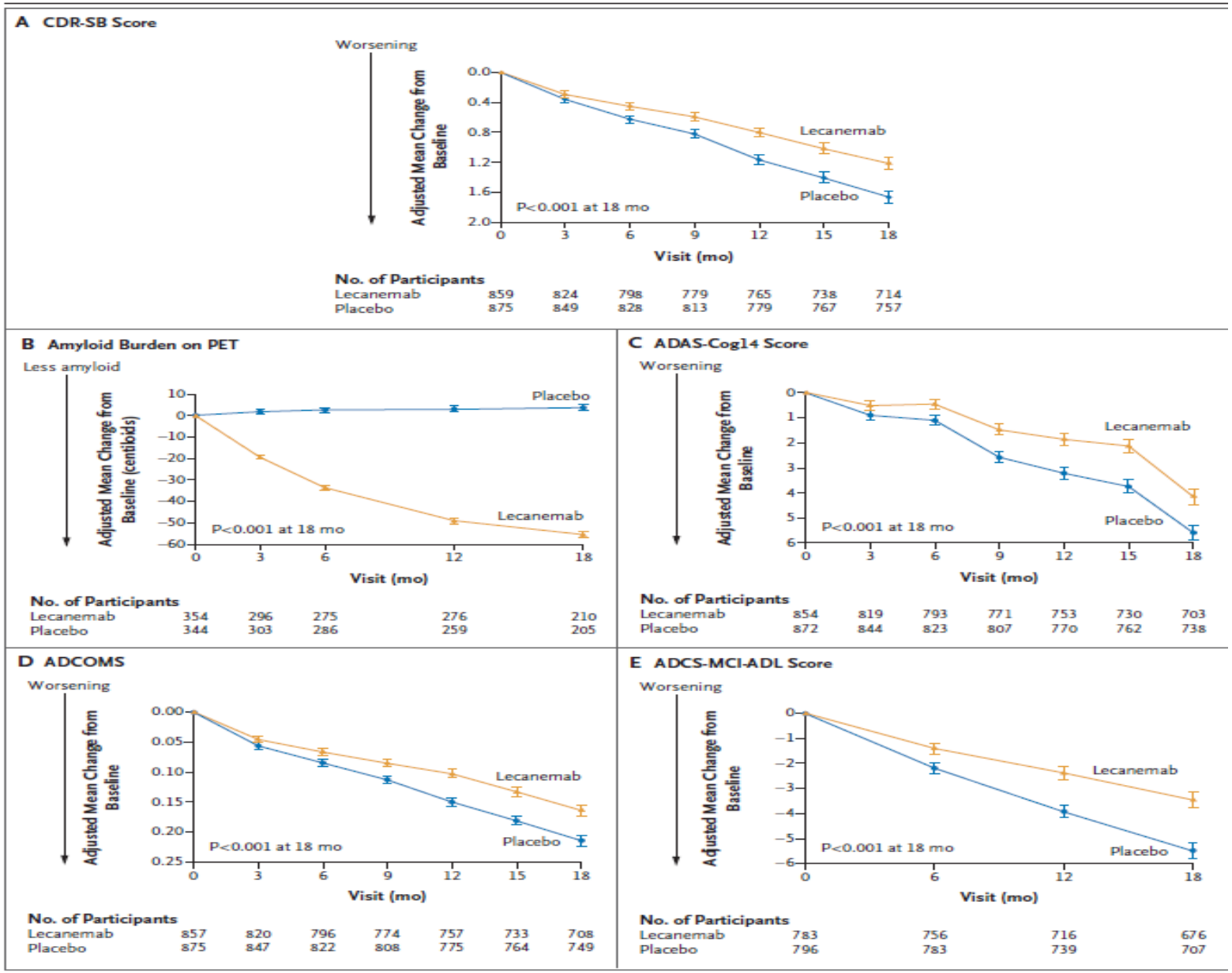
*Blood Based Biomarkers under investigation since 2020

Mattsson et al –JAMA 2009

New AD Monoclonal Antibody Infusions on the horizon



Clarity-AD Trial – van Dyck et al. Lecanemab in early AD-NEJM Jan 2023



- Lecanemab-Humanized IgG1 monoclonal antibody that binds with high affinity to Amyloid beta soluble protofibrils (toxic to neurons)

- 18 month multi-center double blind phase 3 trial age range 50 to 90 with mild AD or MCI

- **Primary End point-Clinical Dementia Rating –Sum of Boxes (CDR-SB)**
- **With Lecanemab:**
- **CDR-SB difference -0.45**

- Greater reductions in amyloid burden

- ADAS-cog14 score -1.44

- ADCOMS -0.05

- ADCS-MCI-ADL score + 2

All statistically significant p < 0.001

Clarity AD: Further Clarity re: Lecanemab…..

- **Infusion related reactions:** 26.4% Headaches 10 % Falls 10 %
- **Amyloid Related Imaging Abnormalities (ARIA):** 12.6% - APO-E4 homozygotes at higher risk

- Primary end point CDR-SB- **Score range 0 to 18** (CDR SB **difference -0.45** at 18 months)
- 27 % less decline in cognitive function? 5-month delay in symptom progression after 18 months?

- ADAS COG14 **score range 0 to 90**: **Difference - 1. 44** at 18 months
- ADCOMS **score range 0 to 1.97**: **Difference - 0.05**
- ADCS-MCI-ADL score **range 0 to 53**: (lower scores = greater impairment): **Diff. +2**

- **African American patient recruitment:** 2.3 % in intervention and 2.7 % in placebo arms

- **Drop out rate:** 17.2%

Clarity AD: Crystal Clarity still needed on….

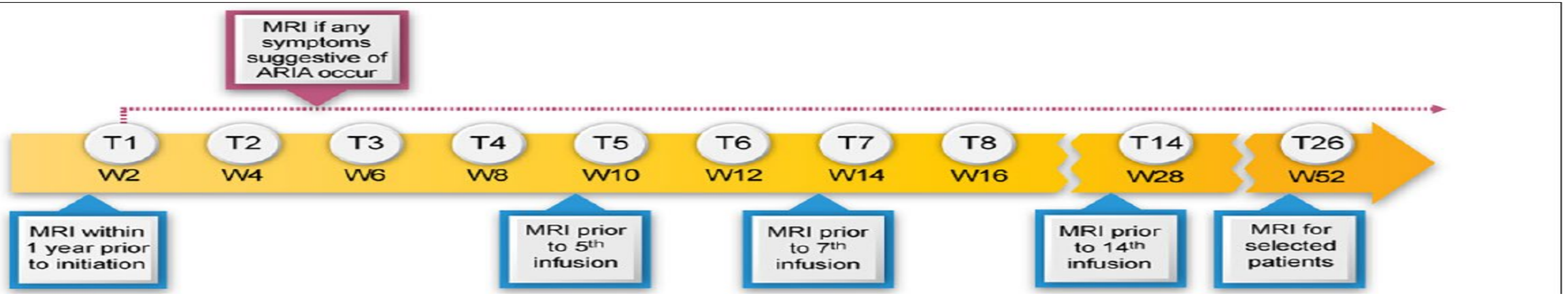
- **Is statistical significance the same as clinical significance and meaningfulness to patient and care partner quality of life? – MCID (Minimally clinically important differences) (CDR-SB 0.98 MCI and 1.63 for AD) Clarity -0.45 difference in CDR-SB does Not meet MCID criteria**

- From the authors of and in the Clarity AD manuscript: *"A definition of clinically meaningful effects in the primary end point of the CDR-SB score has **Not** been established…..*

- **Inclusion criteria: MMSE scores 22-30 (scale is out of 30-Does this include patients with age related** physiological changes in cognition?)
- Allowed concurrent cholinesterase inhibitor and memantine therapies- **? Exclusivity of Lecanemab effect**

- **Exclusion criteria:** Patients on anticoagulation, with immunological disorders or on immunoglobulins, monoclonal antibodies, systemic immunosuppressants, plasmapheresis, patients with CVA, TIA, bleeding disorders, seizures in past 12 months , Depression (GDS >8), patients with hallucinations/delusions BMI > 35 or < 17, H/o CVD,CA,PVD
- – **Only 8 %% of MCI/early AD "real world" patients Mayo Clinic Study of Aging" would be eligible for Lecanemab (5% for Aducanumab)(Pittock et al. Neurology - August 2023)**

Clarity AD: Crystal Clarity still needed on….



- **Operational:** Baseline CSF or PET confirmation of AD
- Lecanemab administered IV every two weeks - Caregivers 8 hours availability per week'

- **Cost**: Medicare: **Annual out of pocket costs: USD 6,636 with 80 % coverage by CMS (Arbanas et al. JAMA-IM August 2023) CMS Annual costs USD 2 to 5 billion**

- What happens if MCI / early AD progresses / What happens beyond 18 months? Trials ongoing
- - Atypical AD ? e.g. Primary Progressive Aphasia

- Pre-Clinical AD: **AHEAD 3-45** study

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Cleveland Clinic

Dementia Prognostication

- **Current State: Irreversible and Progressive**

- **Median Survival Post Diagnosis: 3 to 12 years**

- Most Common sites of AD deaths: Skilled Nursing Facility/"Nursing Homes" (19%)

- **Hospitalizations** in last 3 days of life, multiple hospitalizations last 90 days of life

-75 % of which are medically unnecessary or discordant with patient/family wishes

- Inappropriate medication use in SNF AD patients Prevalence 54% C**holinesterase Inhibitor*** (36%); **Memantine*** (25%) Statins (22%)

Stage	Stage Name	Characteristic	Expected Untreated AD Duration (months)	Mental Age (years)	MMSE (score)
1	Normal Aging	No deficits whatsoever	--	Adult	29-30
2	Possible Mild Cognitive Impairment	Subjective functional deficit	--		28-29
3	Mild Cognitive Impairment	Objective functional deficit interferes with a person's most complex tasks	84	12+	24-28
4	Mild Dementia	IADLs become affected, such as bill paying, cooking, cleaning, traveling	24	8-12	19-20
5	Moderate Dementia	Needs help selecting proper attire	18	5-7	15
6a	Moderately Severe Dementia	Needs help putting on clothes	4.8	5	9
6b	Moderately Severe Dementia	Needs help bathing	4.8	4	8
6c	Moderately Severe Dementia	Needs help toileting	4.8	4	5
6d	Moderately Severe Dementia	Urinary incontinence	3.6	3-4	3
6e	Moderately Severe Dementia	Fecal incontinence	9.6	2-3	1
7a	Severe Dementia	Speaks 5-6 words during day	12	1.25	0
7b	Severe Dementia	Speaks only 1 word clearly	18	1	0
7c	Severe Dementia	Can no longer walk	12	1	0
7d	Severe Dementia	Can no longer sit up	12	0.5-0.8	0
7e	Severe Dementia	Can no longer smile	18	0.2-0.4	0
7f	Severe Dementia	Can no longer hold up head	12+	0-0.2	0

Mitchell SL NEJM 2015 Givens JL et al: JAGS 2012

TABLE 2

Alzheimer disease: Severity, associated symptoms, and recommended treatment

Dementia category	Global Deterioration Scale (stages 1–7)	Medications
Not demented	**1** No cognitive impairment **2** Very mild decline: age-associated cognitive impairment **3** Mild cognitive impairment, minor neurocognitive decline	No indication for cognitive enhancers
Mild dementia	**4** Decreased knowledge of current and recent events Decreased ability to travel, handle finances, and manage basic activities of daily living	Cholinesterase inhibitors
Moderate dementia	**5** Unable to recall a major relevant aspect of their current life, an address or telephone number of many years, or the names of close family members Basic activities of daily living begin to be impaired	Cholinesterase inhibitors with or without an NMDA receptor antagonist
Severe dementia	**6** Occasionally forgets the name of the spouse or caregiver on whom he or she is entirely dependent Unaware of all recent events and experiences in their lives Most basic activities of daily living impaired	Cholinesterase inhibitor (donepezil) with or without an NMDA receptor antagonist
Advanced dementia	**7** Cannot speak or walk, has incontinence and difficulty swallowing	No randomized controlled trials in stage 7

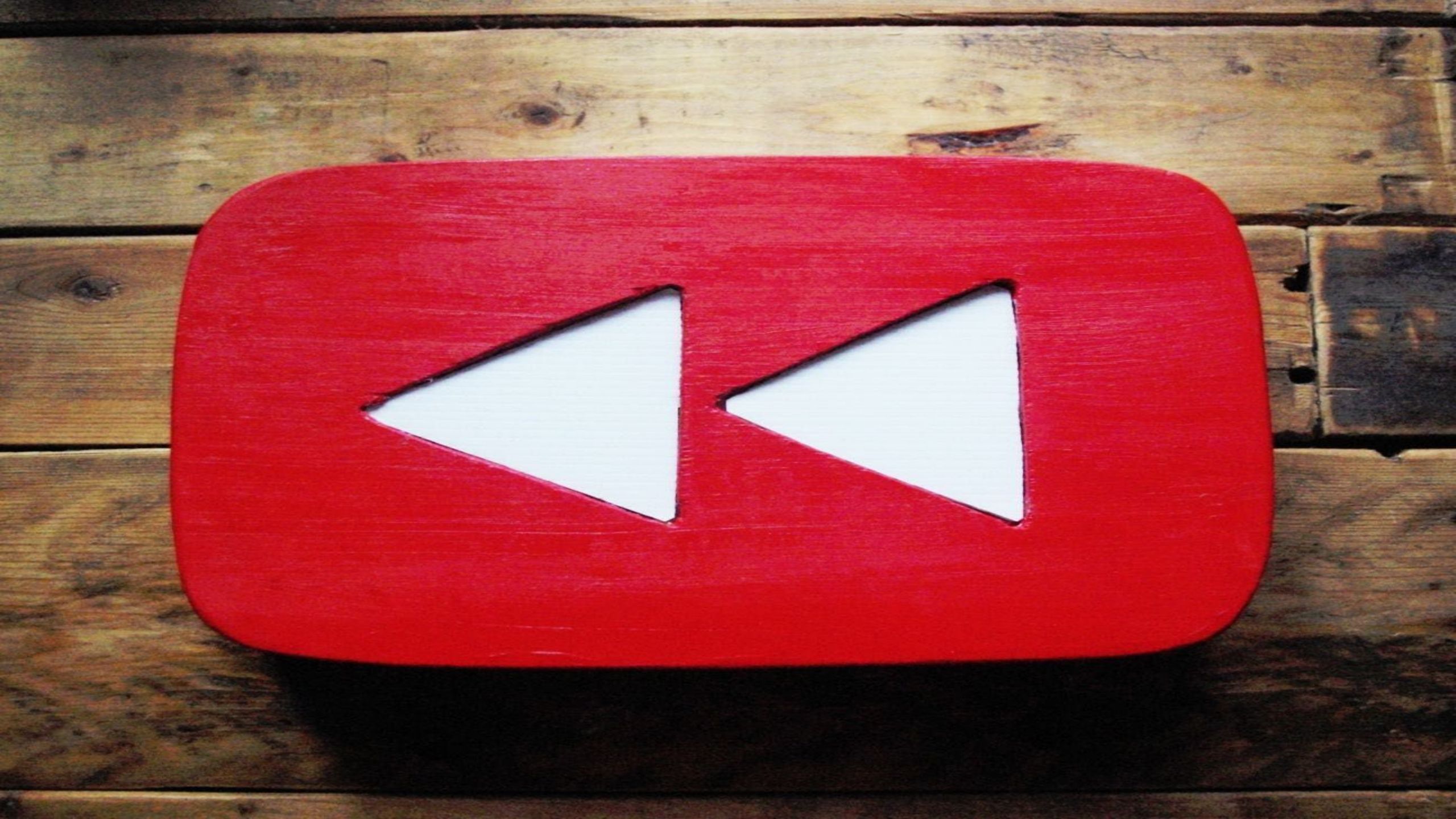
NMDA = *N*-methyl-D-aspartate

Kim LD Factora RM CCLJM 2018

Dementia hospice eligibility

- Stage 7 or beyond according to the FAST scale
- Unable to ambulate without assistance
- Unable to dress without assistance
- Unable to bathe without assistance
- Urinary or fecal incontinence, intermittent or constant
- No meaningful verbal communication, stereotypical phrases only, or ability to speak limited to six or fewer intelligible words
- Plus one of the following within the past 12 months:
  - Aspiration pneumonia
  - Pyelonephritis or other upper UTI
  - Septicemia
  - Multiple stage 3 or 4 decubitus ulcers
  - Fever that recurs after antibiotic therapy
  - Inability to maintain sufficient fluid and calorie intake, with 10 percent weight loss during the previous six months or serum albumin level less than 2.5 g per dL (25 g per L)

Schonwetter RS, Han B, Small BJ, Martin B, Tope K, Haley WE. Predictors of six-month survival among patients with dementia: an evaluation of hospice Medicare guidelines. Am J Hosp Palliat Care 2003;20:105-13.



Alzheimer's & Population Health Ramifications

- "No Show Rates / Missed Appointments 
- Medication non adherence and linked to frequent ED visits 
- Medication Adverse Effects and lack of affordability (in setting of financial exploitation) 
- Food & Financial Security and Home Safety including Fire Hazards as well as Shelter 
- Road Safety and MVAs and transportation to clinical appointments 
- Cost of PET scanning the entire population 
- Feasibility & Invasiveness of CSF analysis by mass lumbar punctures

Clinical Frailty Scale

1. **Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

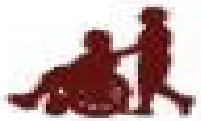
2. **Well** – People who have no active disease symptoms but are less fit than Category 1. Often, they exercise or are very active occasionally, e.g. seasonally.

3. **Managing Well** – People whose medical problems are well controlled, but are not regularly active beyond routine walking.

4. **Vulnerable** – While not dependent on others for daily help, often symptoms limit activities. A common complaint is being "slowed up," and /or being tired during the day.

5. **Mildly Frail** – These people often have more evident slowing, and need help in high order IADLs (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6. **Moderately Frail** – People need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing.



7. **Severely Frail** – Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8. **Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. **Terminally Ill** – Approaching the end of life. This category applies to people with a life expectancy < 6 months, who are not otherwise evidently frail.

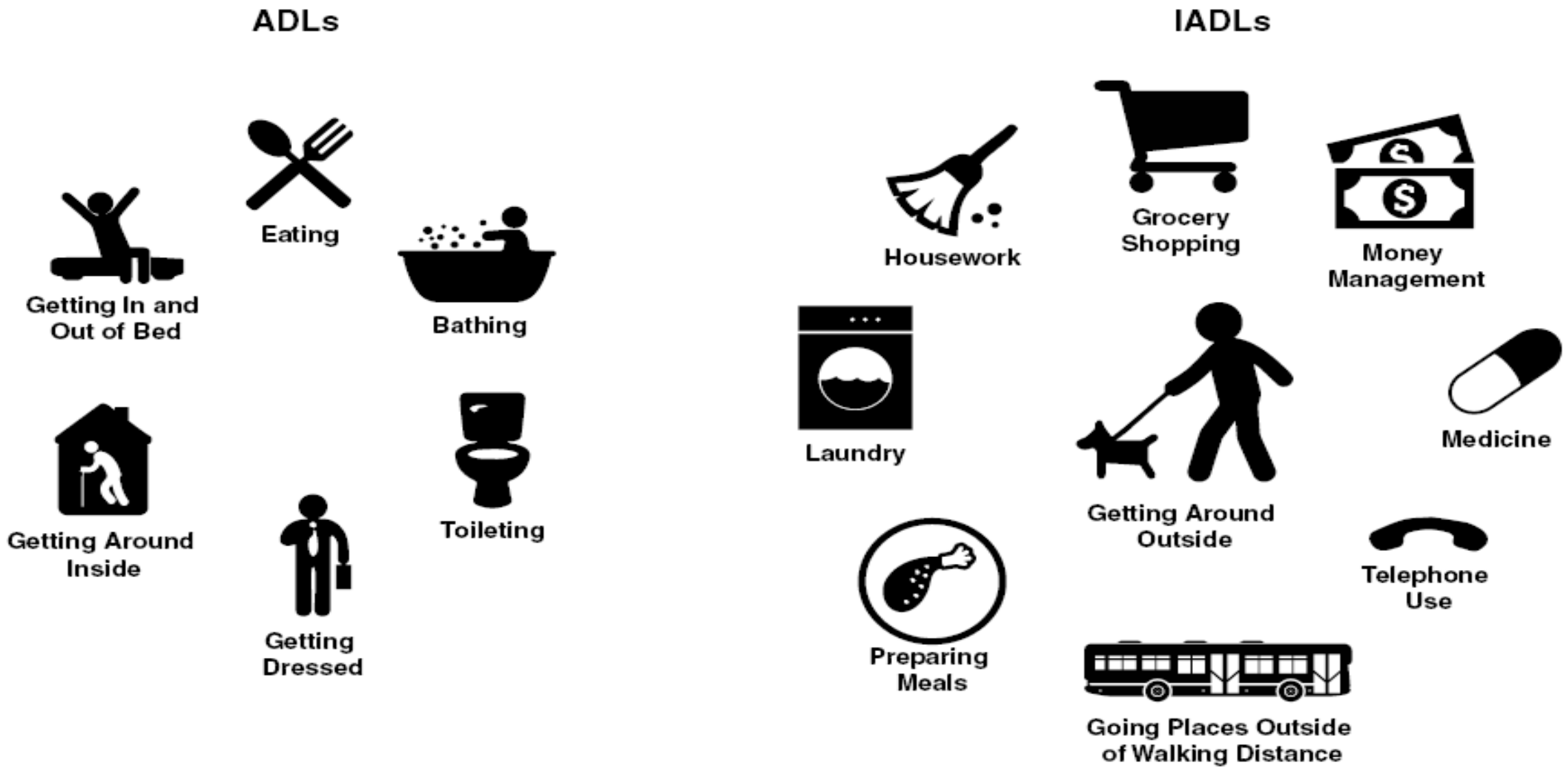
Where dementia is present, the degree of frailty usually corresponds to the degree of dementia:

- **Mild dementia** – includes forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.
- **Moderate dementia** – recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.
- **Severe dementia** – they cannot do personal care without help.

K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489–495

Figure 1

Activities of Daily Living (ADLs) and Instrumental Activities of Daily Living (IADLs)



Instrumental Activities of Daily Living (IADLs): An Early Clinical Marker of Dementia-The PAQUID study

- 104 incident dementia cases and 882 healthy controls followed prospectively over 10 years in southwest France
- Restriction in 4 IADLs studied: Telephone, Transportation, Medication management, Finances
- Restrictions in at least 2 IADLs at baseline had a higher risk of dementia 10 years later (OR 2.59 C.I 1.24-5.38)
- Also associated with a more rapid functional deterioration over time
- Finances IADL limitations at baseline predictive of dementia 10 years later (O.R 2.15 (C.I 1.13-4.08)

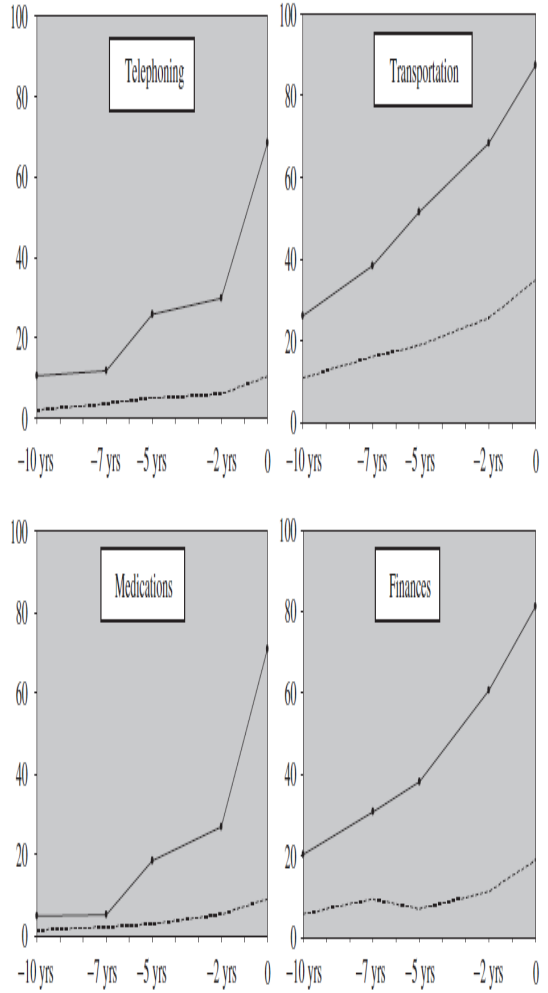
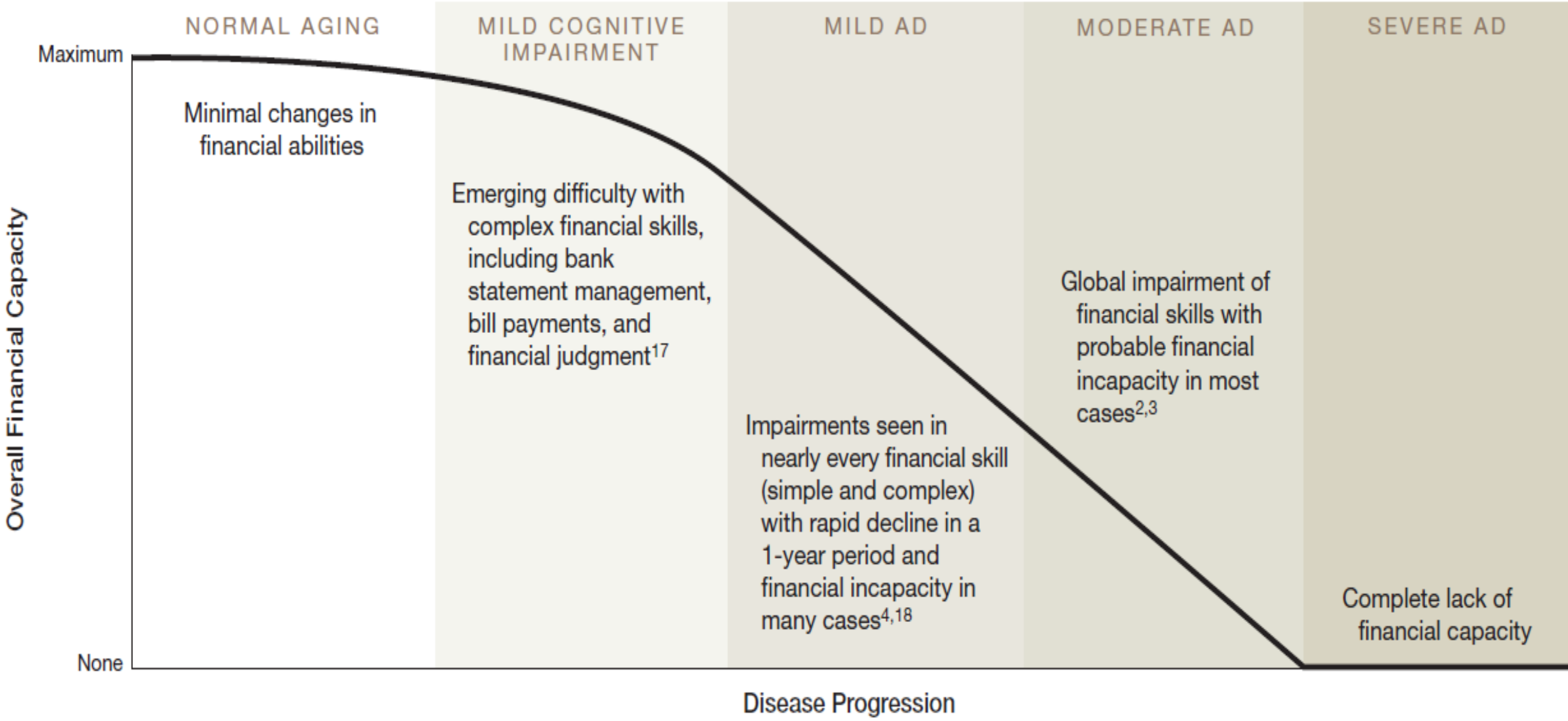


Figure 2. Cross-sectional prevalence of restriction in the four specific instrumental activities of daily living over the 10 years preceding dementia, at each time of follow-up available—the PAQUID Cohort. —•— Incident dementia cases at the T10 visit (0). ---- Subjects free of dementia at the T10 visit (0). On the abscissa: time before the clinical diagnosis of dementia (0), i.e., 2, 5, 7, and 10 years.

Peres et al JAGS 2008

IADL Impairment I: Financial Incapacity

Figure 1. Conceptual Schematic of Progressive Decline in Financial Capacity in a Person With Alzheimer Disease (AD)



Widera E et al JAMA 2011

IADL Impairment I: Financial Incapacity

- **One of the first IADLs in AD to be impacted** occurring very early in course of AD — Peres K et al. JAGS 2008
- **Financial Capacity:** Ability to independently manage one's financial affairs in a manner consistent with personal self interest — Ravio MM et al J Med Ethics 2008
- Underscores **importance of advanced financial planning**, recognizing clinical signs of financial incapacity and establishing effective financial protections — Wald C et al Int J Geriatr Psych 2003
- Finnish and U.K studies evidence 48 % to 94 % of families wish to have discussions re: financial planning with their PCP but only 10 % actually have one — Lachs MS and Pillemer KA NEJM 2015
- **AD is a documented risk factor for financial exploitation** — Widera e et al. JAMA 2011

Reporting Requirements Resource: National Center for Elder Abuse Website

IADL Impairment II: Driving Impairment

IADL Impairment II: Driving Impairment

- 81% of adults aged > 65 hold a driver's license

- Early AD patients at 2.5 to 4.7 times increased risk of MVA

- American Academy of Neurology*: "There is insufficient evidence to support or refute the use of neuropsychological testing to evaluate driving risk after controlling for the presence and severity of dementia"*

Papandonatos et al
JAGS 2015

Chihuri S et al
JAGS 2016

- Meta-analysis pooled from 5 studies: Driving Cessation almost doubles risk of depression
- - Of note; NOT mitigated by presence of alternative means of transportation

- Driving cessation associated with declines in general health, physical, psychological and social functioning

- Driving cessation also associated with greater risk of admission to long term care facilities (HR 4.85 (CI 3.26-7.21)

IADL Impairment III: Medication Adherence

IADL Impairment III: Medication Management: Deprescribing/Reducing Anticholinergic Burden

- Case control study of 40,770 patients aged 65-99 seen at general practices across the UK between April 2006 and July 2015
- Anticholinergic Burden Scale (ACB) correlated with risk of Dementia and evaluated by medication sub-types
- Dementia associated with an increasing ACB score
- Risk of dementia increased with antidepressant , urologic and anti-Parkinsons drugs with an ACB score of 3 – Exposure up to 15-20 years prior to diagnosis (O.R 1.17 (1.1-1.24) with a dose-response effect observed
- Five most common ACB level 3 medications: Amitriptyline, Dothiepin, Paroxetine, Oxybutynin, Tolterodine

Richardson K et al- BMJ March 2018

Caregivers of Older Adults: A Focused Look at Those Caring for Someone Age 50+

Conducted by

AARP Real Possibilities Public Policy Institute

National Alliance for Caregiving

Figure 1: Gender of Care Recipient and Caregiver

Q9. And is/was the person you care/cared for …
Caregiver gender provided by panel or recorded by interviewer.

Base: Caregivers of Recipient
Age 50+ (n=1,087)

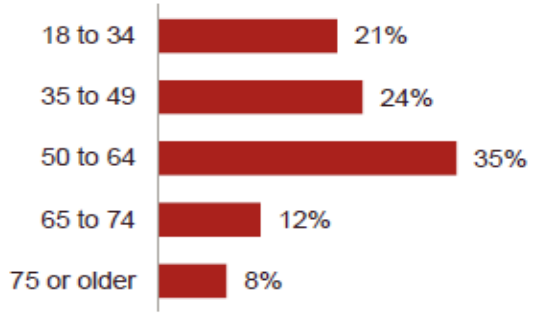
Age of Caregiver and Care Recipient

On average, caregivers of someone 50+ are themselves 50.3 years old.

Figure 2: Age of Caregiver

Caregiver age provided by online panel.
SC2. [phone only] How old were you on your last birthday?

Base: Caregivers of Recipient
Age 50+ (n=1,087)



On average, the care recipient is 74.7 years old. More than half (55%) of caregivers of someone 50+ are caring for someone age 75 or older.

"Family Caregivers are an invisible, isolated army carrying out increasingly complex tasks.. without adequate recognition, support or guidance, and at great personal cost. Despite the extent of involvement in everyday care.. Often ignored by payers and providers with no.. Acknowledgment of interdependence of their situation and that of the ..care recipient"

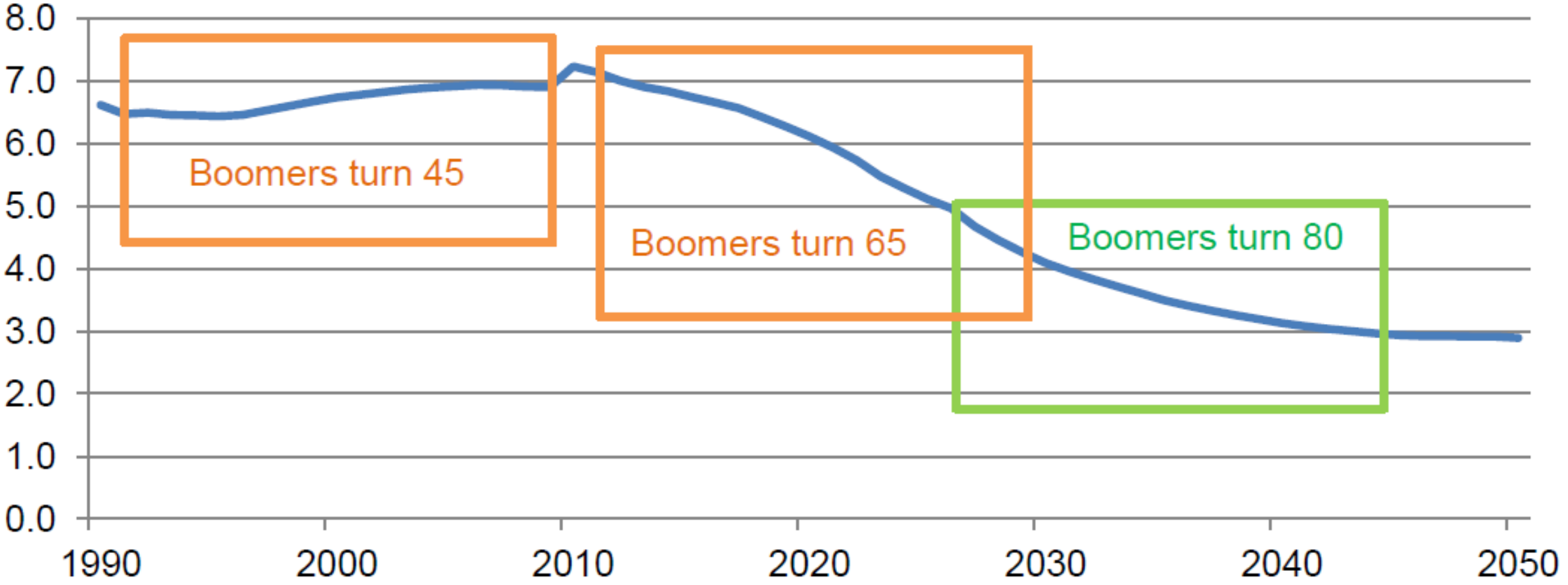
("Valuing the Invaluable-2015 Update)

AARP

AARP Real Possibilities

Figure 1

Caregiver Support Ratio, United States



Source: AARP Public Policy Institute calculations based on REMI (Regional Economic Models, Inc.) 2013 baseline demographic projections.

Note: The caregiver support ratio is the ratio of the population aged 45–64 to the population aged 80-plus.

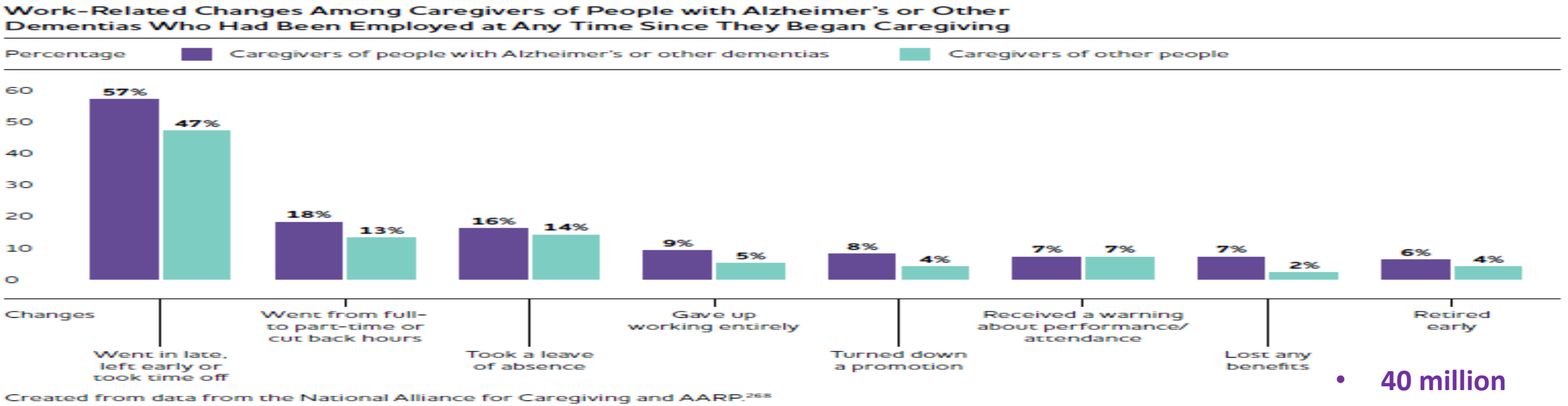
Financial & Emotional Cost of Caregiving for BPSD: A Population Health Challenge-"The Invisible Workforce"

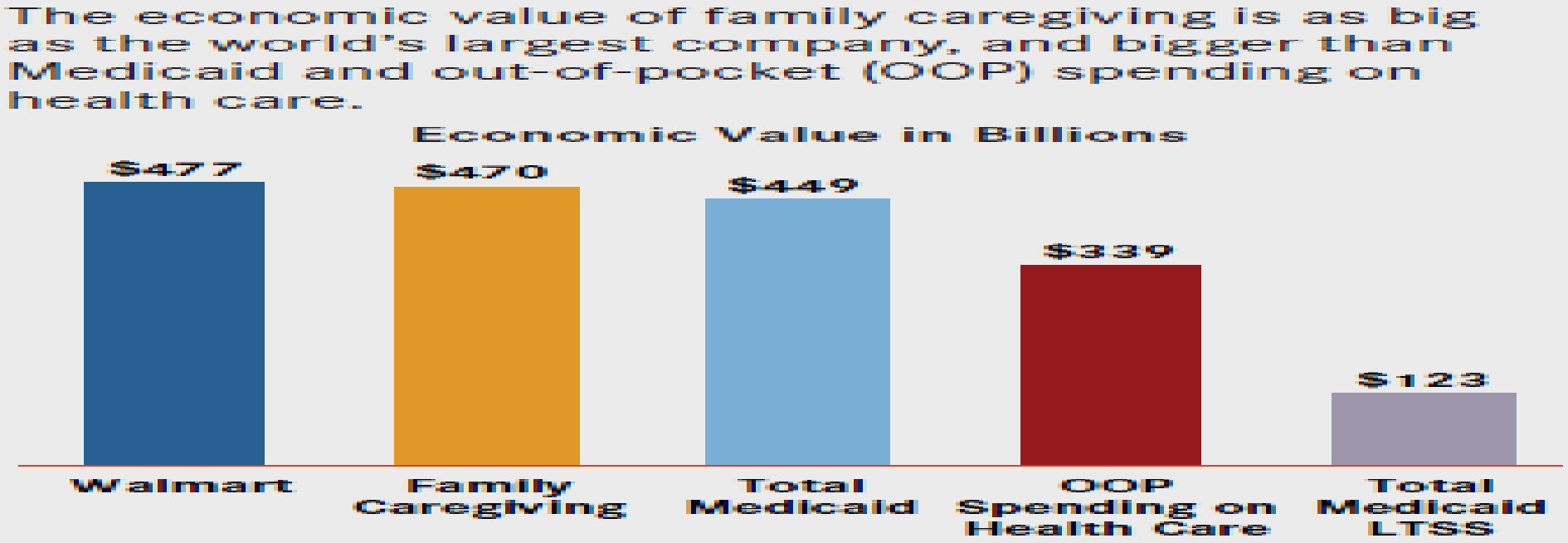
- **37 billion caregiving hours per year**
- **-43.5 million caregivers provide informal, unpaid care to geriatric patients**
- **15.5 million care for dementia patients**

- Dementia caregivers spend more caregiving hours, report **greater emotional distress and burden**
- **"Role Captivity"**

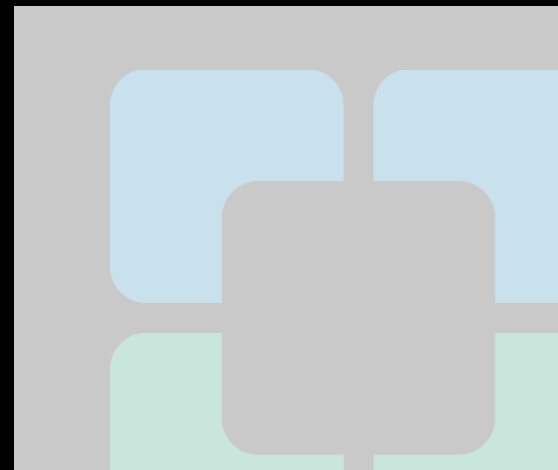
- **Caregiver stress** for caregiver of dementia BPSD a **predictor of SNF placement**

- **Dementia caregivers** report twice as much **out of pocket costs ($10,697** vs . Non-dementia caregivers $ 5,758
- Economic burden: **$ 470 billion in 2013** – By **2050, $ 1.2 trillion annually (20% of income on caregiving expenses)**





- 40 million Caregivers x 18 caregiver hours per week x $ 12.51 per hour (Meta-Analysis- 11 studies)
- Equivalent to combined annual sales of Apple, IBM, Hewlett Packard and Microsoft



Agenda

1. Alzheimer's –The Global Pandemic:
   - Demographics & Definition

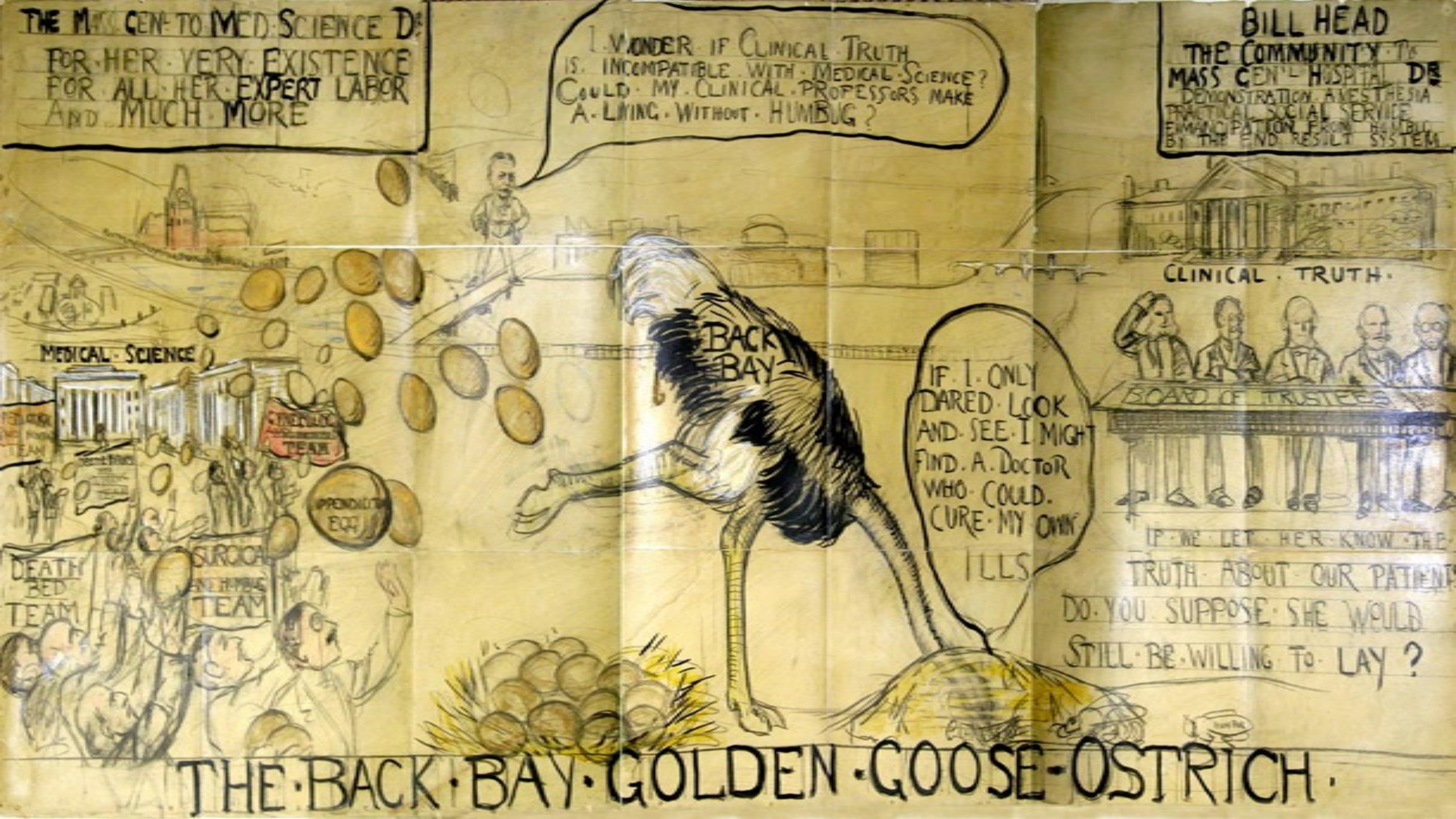
2. Search for the Holy Grail of a Cure:
- Review of Treatment & Therapeutics to date

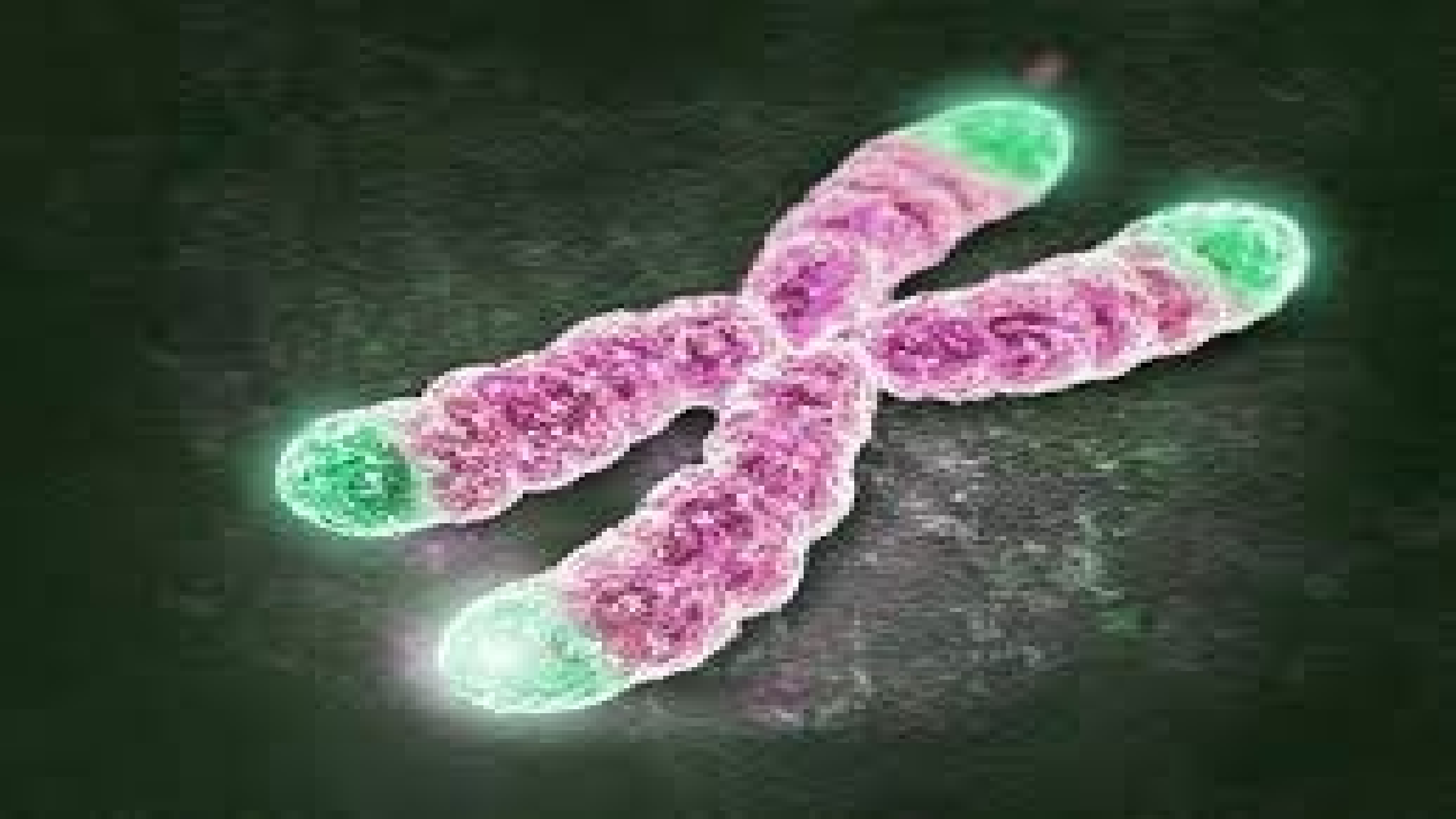
3. AD Research Re-Focus

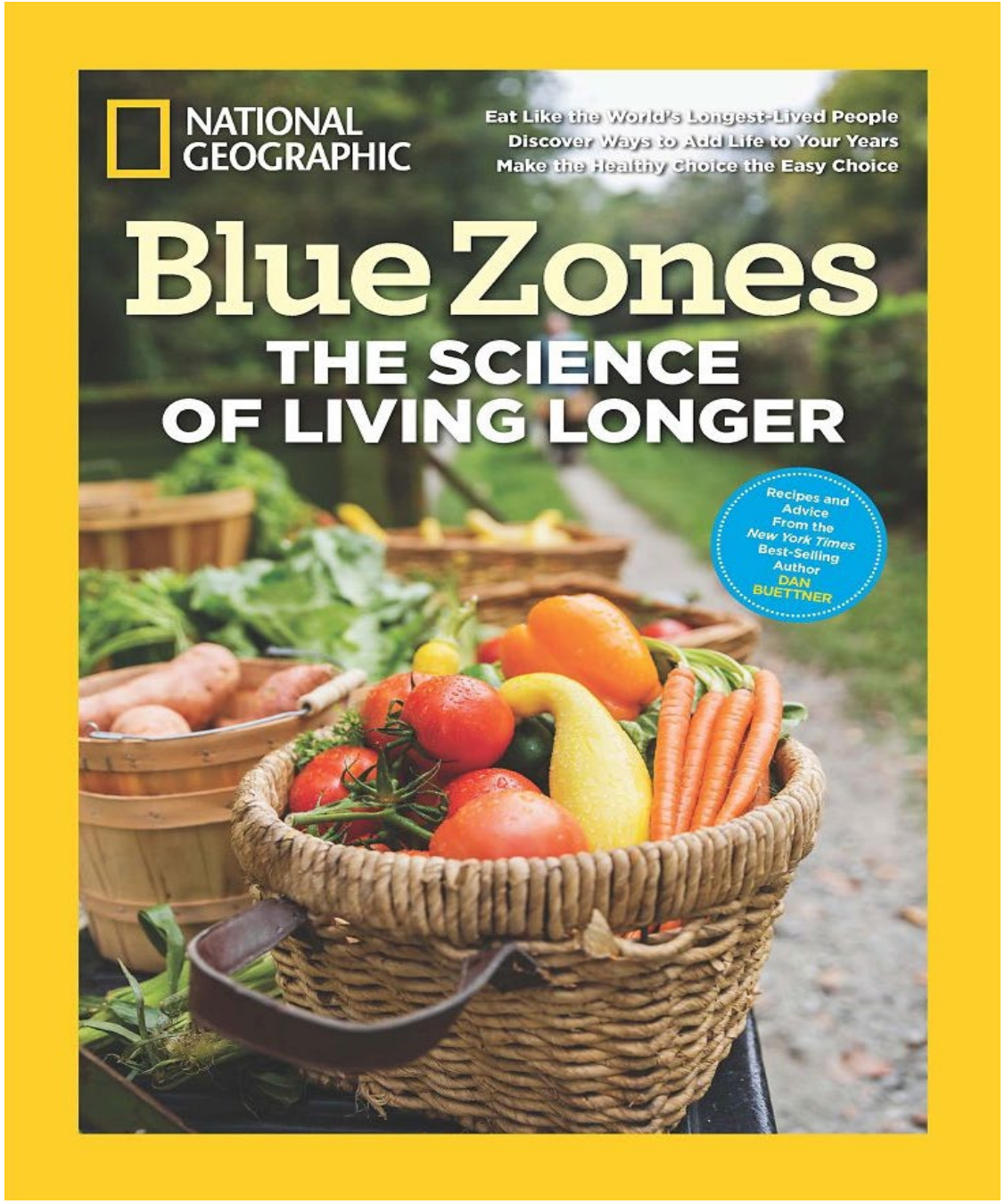
4. Redefining Alzheimer's: Current Ground Realities

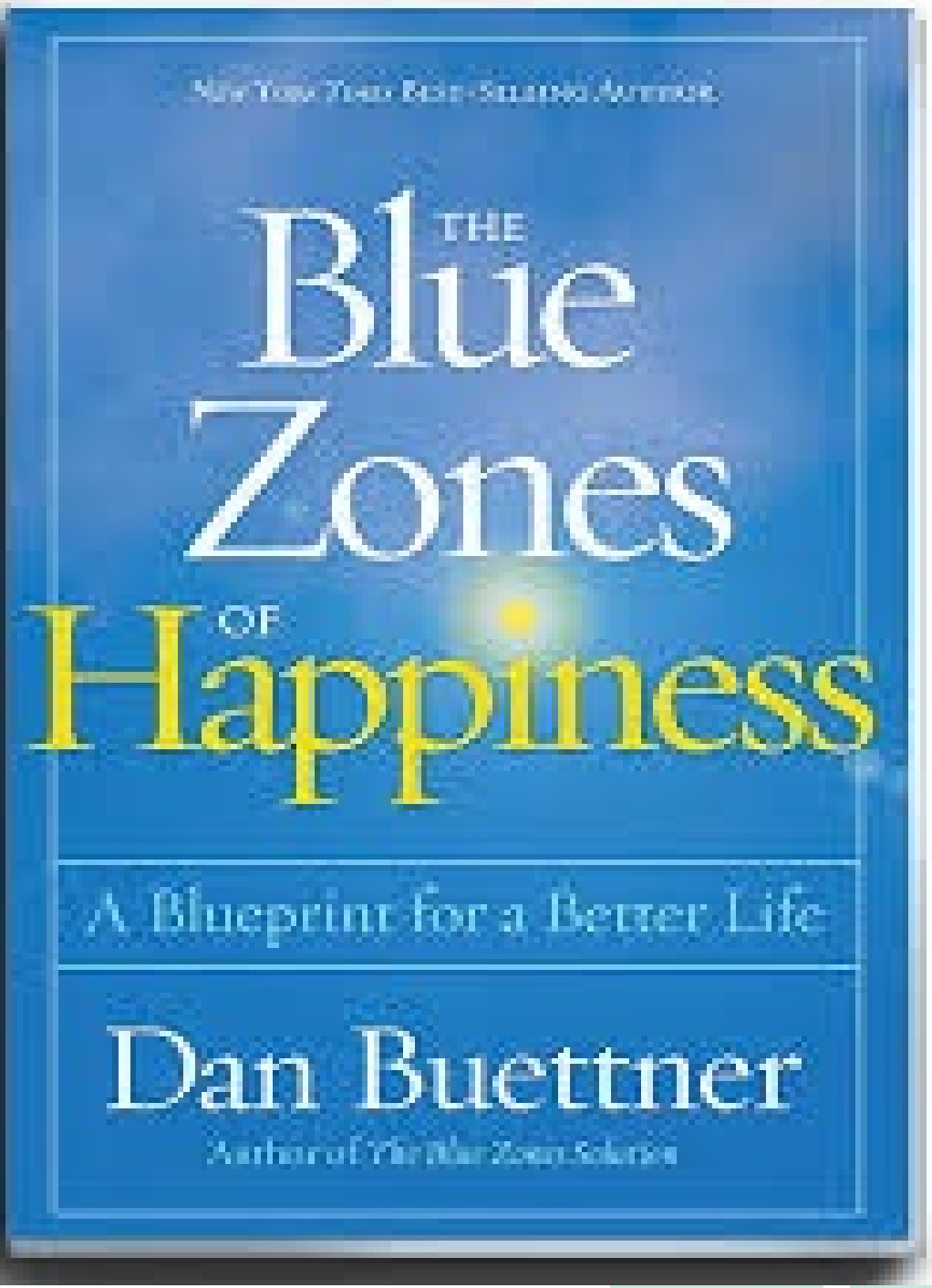
5. Alzheimer's Care: Reimagined for Populations

Cleveland Clinic


THE M[illegible] GEN TO MED SCIENCE D[illegible]
FOR HER VERY EXISTENCE
FOR ALL HER EXPERT LABOR
AND MUCH MORE
I WONDER IF CLINICAL TRUTH IS INCOMPATIBLE WITH MEDICAL SCIENCE? COULD MY CLINICAL PROFESSORS MAKE A LIVING WITHOUT HUMBUG?
BILL HEAD
THE COMMUNITY TO
MASS GEN'L HOSPITAL D[illegible]
DEMONSTRATION ANESTHESIA
PRACTICAL SOCIAL SERVICE
EMANCIPATION FROM HUMBUG
BY THE END RESULT SYSTEM
MEDICAL SCIENCE
DEATH BED TEAM
SURGICAL TEAM
MEDICAL TEAM
PRODUCTION DEPT
BACK BAY
IF I ONLY DARED LOOK AND SEE I MIGHT FIND A DOCTOR WHO COULD CURE MY OWN ILLS
CLINICAL TRUTH
BOARD OF TRUSTEES
IF WE LET HER KNOW THE TRUTH ABOUT OUR PATIENTS
DO YOU SUPPOSE SHE WOULD STILL BE WILLING TO LAY?
THE BACK BAY GOLDEN GOOSE OSTRICH




NATIONAL GEOGRAPHIC
Eat Like the World's Longest-Lived People
Discover Ways to Add Life to Your Years
Make the Healthy Choice the Easy Choice
Blue Zones
THE SCIENCE OF LIVING LONGER
Recipes and Advice From the New York Times Best-Selling Author DAN BUETTNER


New York Times Best-Selling Author
THE Blue Zones OF Happiness
A Blueprint for a Better Life
Dan Buettner
Author of The Blue Zones Solution


LOMA LINDA
CALIFORNIA
SARDINIA
ITALY
ICARIA
GREECE
OKINAWA
JAPAN
NICOYA
COSTA RICA
BLUE ZONES
LONGEVITY HOTSPOTS
BLUE ZONE LIFE LESSONS
MOVE NATURALLY
RIGHT TRIBE
RIGHT OUTLOOK
EAT WISELY

Characteristics Common to the Blue Zones

1. Move Naturally

Right Outlook

2. Know your purpose
3. Down shift

Eat Wisely

4. 80% rule
5. Plant slant
6. Wine@5

Belong

7. Family first
8. Belong
9. Right tribe

The FINGER Trial Ngandu et al. Lancet 2015

Finnish Geriatric Intervention Study to Prevent Cognitive Impairment & Disability

STUDY DESIGN	Proof of Concept Randomized Controlled Trial
Target Population	Population aged 60-77 with cognition at mean or slightly lower than expected for age at 6 centers across Finland over 2 years
Primary Outcome	Comprehensive Neuropsychological Battery (NBT) Z Score (Composite of 14 cognitive tests)
Analysis	Modified Intention to Treat
Intervention	Multi-Domain: I. Nutritional II. Physical Exercise III. Cognitive Training IV. Monitoring & Management of .vascular risk factors
Results	Between group difference change in NBT score per year 0.022 (CI 0.002-0.42)p=0.03

The FINGER Trial II - Ngandu et al. Lancet 2015

Finnish Geriatric Intervention Study to Prevent Cognitive Impairment & Disability

Highlights
72 % adherence to all 4 domains
Improvement on NTB Total score after 24 months 25% higher intervention vs. control (p=0.03)
Executive function 83 % higher intervention vs. control (p=0.039)
Processing speed 150% greater intervention vs. control (p=0.029)

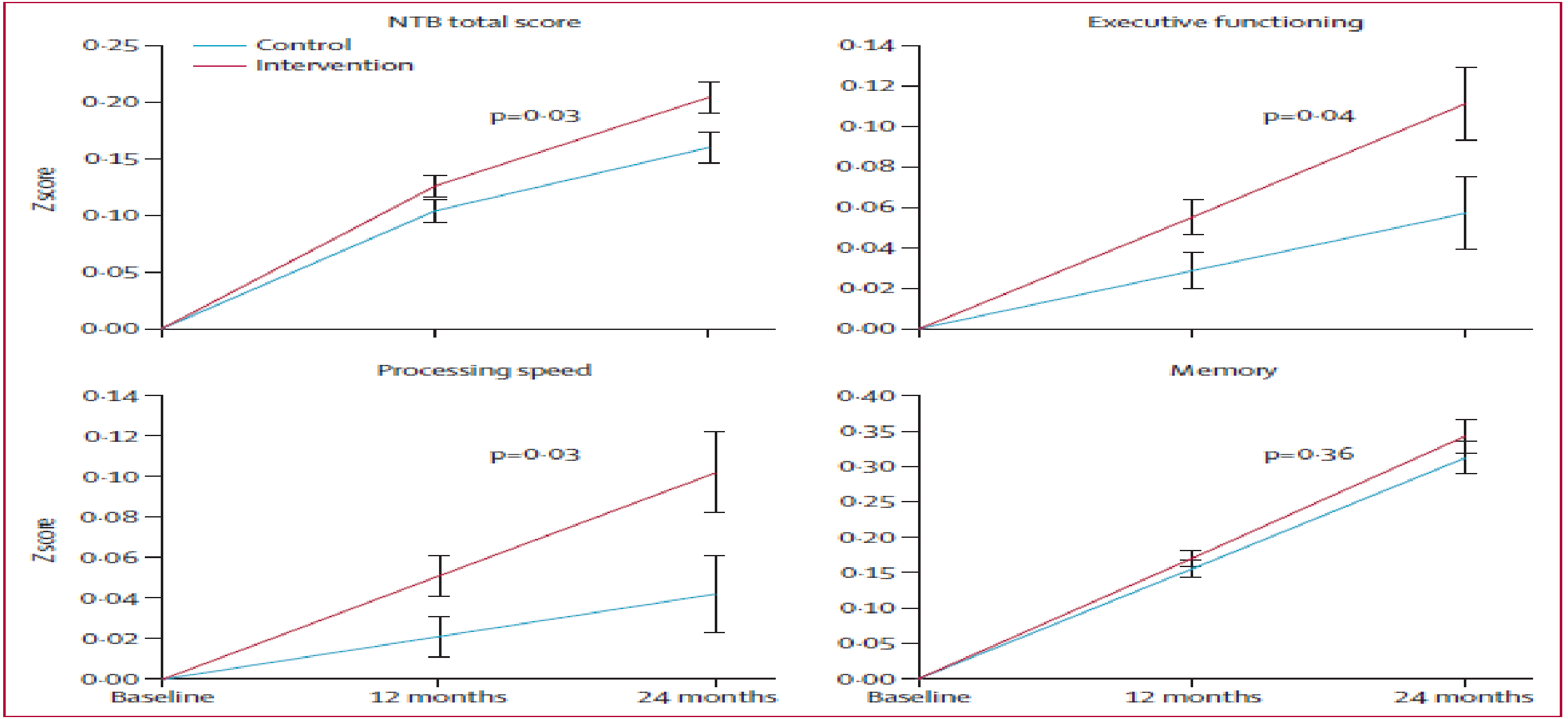


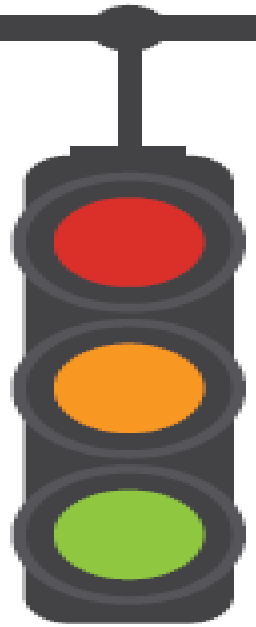
***Figure 2:* Change in cognitive performance during the 2 year intervention**
Figure shows estimated mean change in cognitive performance from baseline until 12 and 24 months (higher scores suggest better performance) in the modified intention-to-treat population. Error bars are SEs. Mixed-model repeated-measures analyses were used to assess between-group differences (group x time interaction) in changes from baseline to 24 months based on data from all participants with at least one post-baseline measurement. NTB=neuropsychiatric test battery.

Table 1. Initiating Advance Financial Planning and Referral Discussions[a]

Intervention for Patients and Their Families/Caregivers	What Clinicians Can Say
	Before diagnosis of cognitive impairment
Recommend a durable power of attorney for finances	"Because of serious illness, memory problems, or being in the hospital, everyone, at least for a short while, may need help with their money and paying bills." "Have you thought about who you would entrust to help with your money and property in case you could not manage on your own?" "A special form called a durable power of attorney for financial matters allows you (your loved one) to name someone to help you (him/her) with your (his/her) money now or when you are (he/she is) unable to manage on your (his/her) own."
	After diagnosis of cognitive impairment
Educate about future financial impairments	"It is common for patients with memory problems and dementia to have problems managing money. Many times, patients do not realize they have a problem. But, it is important to think about what you (he/she) can do now to protect your (his/her) money and property. Have you thought about this?" "Signs that you (your loved one) may need help with your (his/her) money or property include having difficulty balancing your (his/her) checkbook, paying bills, or making correct change."
Recommend practical interventions to support patients with financial impairment	"There are some things you can put in place now to help manage your (your loved one's) money. These include automatic bill pay and direct deposits through your (his/her) bank. There are also services that help manage your (his/her) money. You can call the Alzheimer's Association ([800] 272-3900) for referrals or suggestions. It may also be a good idea to talk with a social worker or someone at your (his/her) bank."
Refer for formal financial capacity assessment	"I am worried that your (your loved one's) memory loss is causing you (him/her) to have problems managing your (his/her) money. I would like to order some special tests. If you do (he/she does) have problems managing your (his/her) money, the tests will tell us what kinds of things you and your family can do to keep your (his/her) money safe."

Widera E et al JAMA 2011

Figure 1. Checklist of considerations in driving safety



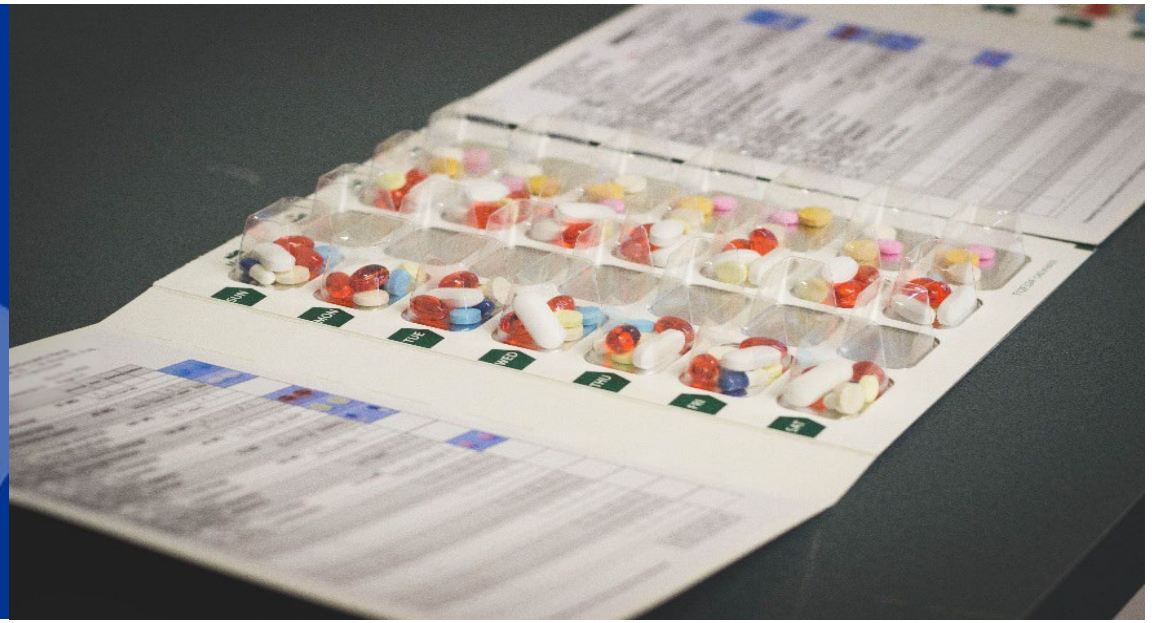
- ☐ History of driving accidents or near accidents*
- ☐ Family member concerns*
- ☐ Trail Making A and B tests—for processing speed, "task switching," and visuospatial and executive function
- ☐ Clock-drawing test—for visuospatial and executive function
- ☐ Copying intersecting pentagons or cube—for visuospatial function
- ☐ Cognitive test scores—possibly helpful
- ☐ Dementia severity according to the Canadian Medical Association guidelines[26]—inability to independently perform 2 instrumental activities of daily living or 1 basic activity of daily living

Lee L and Molnar F Canadian Fam Phys 2017

Managing IADL Impairment III: Medication Management
"Deprescribing"

deprescribing.org

Reducing medications safely to meet life's changes | Moins de médicaments, sécuritairement – pour mieux répondre aux défis de la vie



Deprescribing

Pharmacogenomics

Medication Adherence Packaging

Non Invasive
Continuous
Glucose
Monitoring

One Hundred Fifteenth Congress of the United States of America

AT THE SECOND SESSION

Begun and held at the City of Washington on Wednesday, the third day of January, two thousand and eighteen

An Act

To provide for the establishment and maintenance of a Family Caregiving Strategy, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

- Assisting Caregivers Today (ACT) Congressional Caucus created March 2015
- CMS introduced coverage for "Chronic Care Codes": - Non face to face care management activities for pts with > 2 chronic conditions
- Support federal Lifespan Respite Care Act

Modified Caregiver Strain Index

Directions: Here is a list of things that other caregivers have found to be difficult. Please put a checkmark in the columns that apply to you. We have included some examples that are common caregiver experiences to help you think about each item. Your situation may be slightly different, but the item could still apply.

	Yes, On a Regular Basis=2	Yes, Sometimes =1	No=0
My sleep is disturbed (For example: the person I care for is in and out of bed or wanders around at night)	_____	_____	_____
Caregiving is inconvenient (For example: helping takes so much time or it's a long drive over to help)	_____	_____	_____
Caregiving is a physical strain (For example: lifting in or out of a chair; effort or concentration is required)	_____	_____	_____
Caregiving is confining (For example: helping restricts free time or I cannot go visiting)	_____	_____	_____
There have been family adjustments (For example: helping has disrupted my routine; there is no privacy)	_____	_____	_____
There have been changes in personal plans (For example: I had to turn down a job; I could not go on vacation)	_____	_____	_____
There have been other demands on my time (For example: other family members need me)	_____	_____	_____
There have been emotional adjustments (For example: severe arguments about caregiving)	_____	_____	_____
Some behavior is upsetting (For example: incontinence; the person cared for has trouble remembering things; or the person I care for accuses people of taking things)	_____	_____	_____
It is upsetting to find the person I care for has changed so much from his/her former self (For example: he/she is a different person than he/she used to be)	_____	_____	_____
There have been work adjustments (For example: I have to take time off for caregiving duties)	_____	_____	_____
Caregiving is a financial strain	_____	_____	_____
I feel completely overwhelmed (For example: I worry about the person I care for; I have concerns about how I will manage)	_____	_____	_____

[Sum responses for "Yes, on a regular basis" (2 pts each) and "yes, sometimes" (1 pt each)]

Total Score =

Centers for Medicare & Medicaid Innovation (CMMI) GUIDE MODEL

Care Delivery Requirements

Participants must provide specified services across the domains outlined below. Participants will tailor the exact mix of services based on each beneficiary's individual care plan.

COMPREHENSIVE ASSESSMENT

Beneficiaries and caregivers receive separate assessments to identify their needs and a home visit to assess the beneficiary's safety.

CARE PLAN

Beneficiaries receive care plans that address their goals, preferences, and needs, which helps them feel certain about next steps.

24/7 ACCESS

Beneficiaries and caregivers can call a member of their care team or a third-party representative using a 24/7 helpline.

ONGOING MONITORING & SUPPORT

Care navigators provide long-term help to beneficiaries and caregivers so they can revisit their goals and needs at any time and are not left alone in the process.

REFERRAL & SUPPORT COORDINATION

Beneficiaries' care navigator connects them and their caregivers to community-based services and supports, such as home-delivered meals and transportation.

CAREGIVER SUPPORT

Caregivers take educational classes and beneficiaries receive respite services, which helps relieve the burden of caregiving duties.

MEDICATION MANAGEMENT

Clinician reviews and reconciles medication as needed; care navigators provide tips for beneficiaries to maintain the correct medication schedule.

CARE COORDINATION & TRANSITION

Beneficiaries receive timely referrals to specialists to address other health issues, such as diabetes, and the care navigators coordinate care with the specialist.

Guiding an Improved Dementia Experience (GUIDE) Model Overview Factsheet

MODEL PURPOSE

Dementia takes a toll on not just the people living with the disease but also on their loved ones and caregivers in a way that almost no other illness does. About 6.7 million Americans currently live with Alzheimer's disease or another form of dementia, a number that is projected to grow by nearly 14 million by 2060. To help address the unique needs of this population, the GUIDE Model aims to:

Improve quality of life for people living with dementia by addressing their behavioral health and functional needs, coordinating their care for dementia and co-occurring conditions, and improving transitions between community, hospital, and post-acute settings.

Reduce burden and strain on unpaid caregivers of people living with dementia by providing caregiver skills training, referrals to community-based social services and supports, 24/7 access to a support line, and respite services.

Prevent or delay long-term nursing home care for as long as appropriate by supporting caregivers and enabling people living with dementia to remain safely in their homes for as long as possible.

CARE DELIVERY APPROACH

The model will promote improved dementia care by defining and requiring a comprehensive, standardized care delivery approach that will include the following:

Standardized set of services for beneficiaries and their unpaid caregivers.

An interdisciplinary care team to deliver these services.

A training requirement for care navigators who are part of the care team.

The interdisciplinary care team will deliver services by creating and maintaining a **person-centered care plan**, which will include details on the beneficiary's goals, strengths, and needs; comprehensive assessment results; and recommendations for service providers and community-based social services and supports.

CARE COORDINATION

The care plan will identify the beneficiary's primary care provider and specialists and outline the care coordination services needed to help manage the beneficiary's dementia and co-occurring conditions.

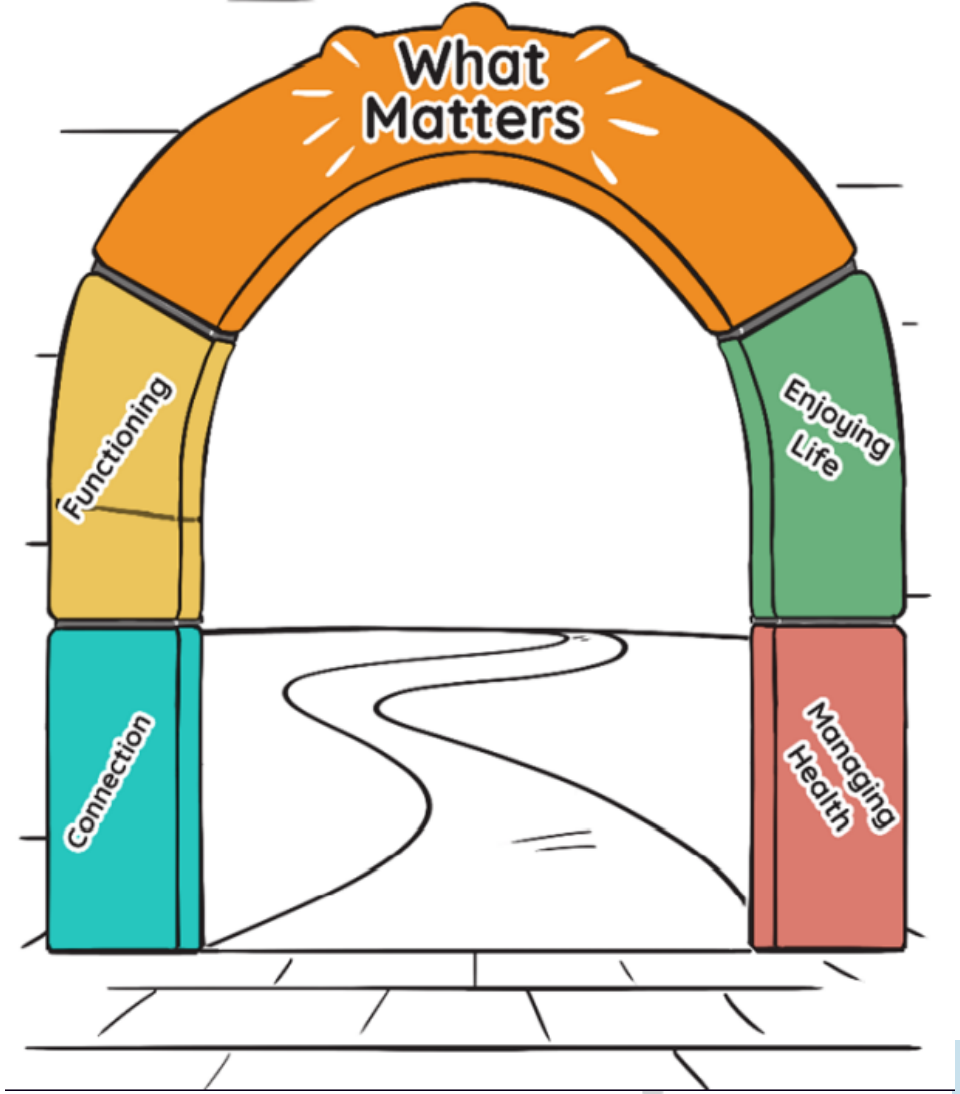
CAREGIVER SERVICES

Participants will assess and address caregiver needs and include the caregiver as part of the care team as appropriate. Caregiver services will include ongoing monitoring and support via 24/7 access to a support line.

Matters Most

arison of Traditional Disease-Specific and Goal-Oriented Outcomes.*

Measurement Domain	Examples of Diseases	Traditional Outcomes	Goal-Oriented Outcomes
Survival	Cancer, heart failure	Overall, disease-specific, and disease-free survival	None if survival not a high-priority goal; survival until personal milestones are met (e.g., grandchild's wedding)
Biomarkers	Diabetes, COPD	Change in indicators of disease activity (e.g., glycated hemoglobin level, CRP level, and pulmonary-function tests)	None (not a meaningful outcome observed or felt by patient)
Signs and symptoms	Heart failure, COPD, arthritis	Inventory of disease-specific signs and symptoms (e.g., dyspnea, edema, and back pain)	Symptoms that have been identified as important by the patient (e.g., control of dyspnea or pain sufficient to perform an activity such as bowling or walking grandchild to school)
Functional status, including mobility	Cancer, heart failure, COPD	Usually none or disease-specific (e.g., Karnofsky score, NYHA functional classification, and 6-minute walk test)	Ability to complete or compensate for inability to complete specific tasks identified as important by the patient (e.g., ability to get dressed without help)



N ENGL J MED 366;9 NEJM.ORG MARCH 1, 2012

Perspective

MARCH 1, 2012

Goal-Oriented Patient Care — An Alternative Health Outcomes Paradigm

David B. Reuben, M.D., and Mary E. Tinetti, M.D.

Patient Priorities Care (PPC) Current Care Planning vs. Advanced Care Planning (ACP)

Received: 9 February 2022 | Accepted: 18 February 2022

DOI: 10.1111/jgs.17727

EDITORIAL

Journal of the American Geriatrics Society

Should we still believe in advance care planning?

Viewpoint

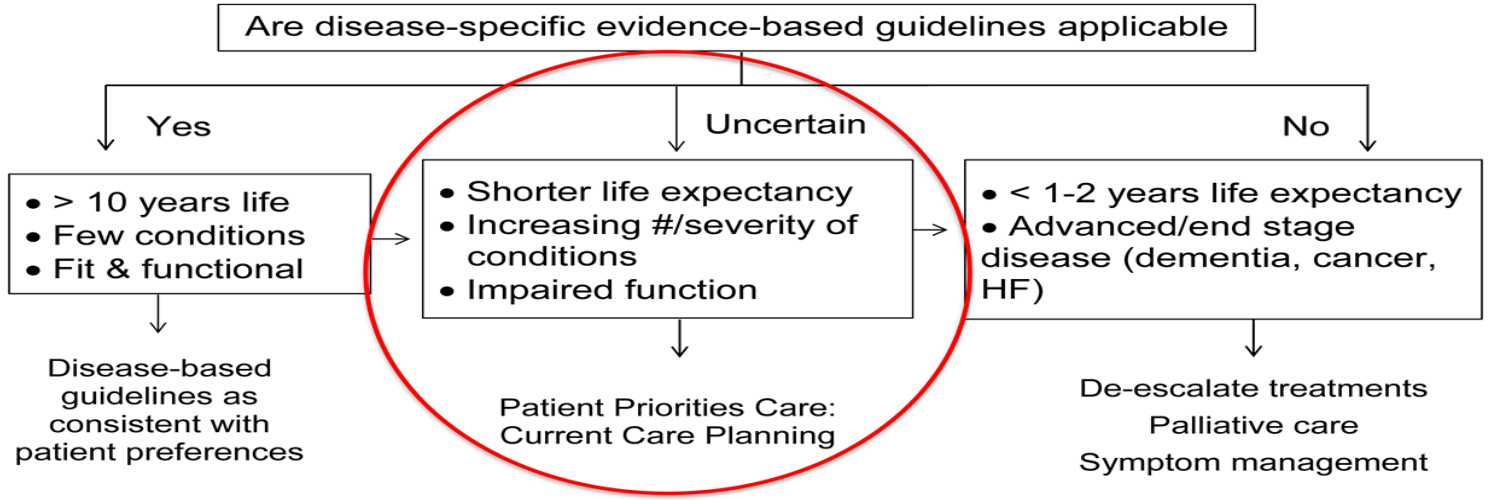
October 8, 2021

JAMA Network

What's Wrong With Advance Care Planning?

R. Sean Morrison, MD[1,2]; Diane E. Meier, MD[1]; Robert M. Arnold, MD[3]

Decision-making and care of older adults with multiple chronic conditions



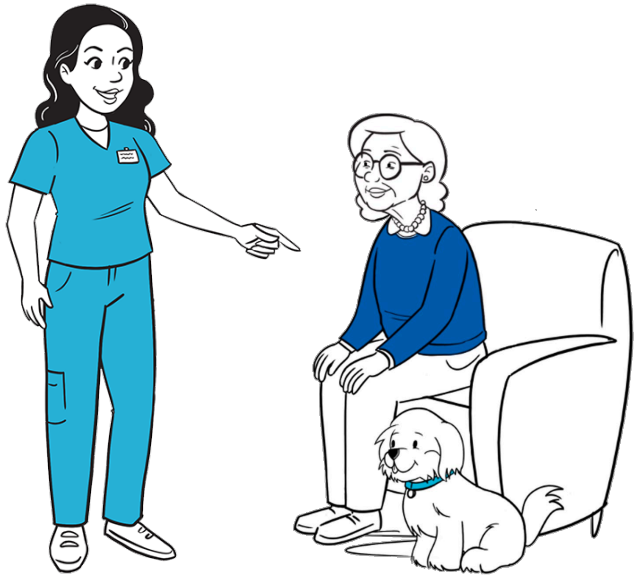
Balancing
Multiple Chronic Comorbidities

Balancing MCC

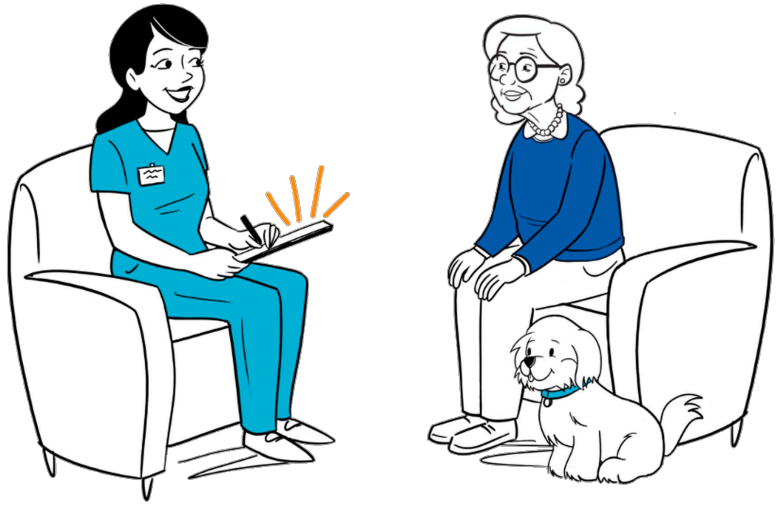
MCC Older Adult Exclusion

Patient Priorities Care

moves decision-making and conversation…



"**You need (fill in treatment) for your** (fill in disease)."



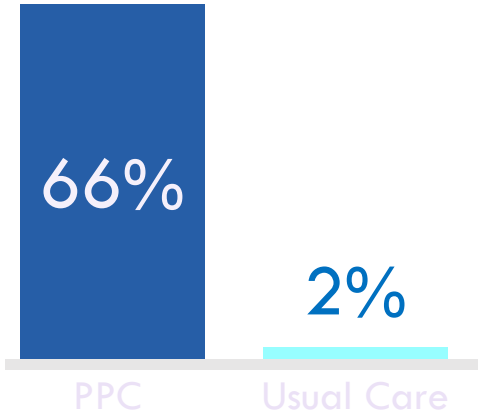
"**Knowing your health conditions, your overall health, and what matters most to you, I suggest we try** (fill in care option)."

what we know so far…

Patient priorities aligned care is effective

Compared with usual care, PPC is associated with…

Focus on patient's goals



↓ Unwanted care

- ✓ Medications stopped (2-3x less)
- ✓ Tests ordered (~30% fewer)
- ✓ Self-management added (30% fewer)

↓ Treatment burden
(TBQ; p=0.04)

Tinetti, et al. JAMA Int Med, 2019

SP: A Personal Journey

- Social Prescribing without knowing it!


Gardening at a community center can help otherwise lonely people connect

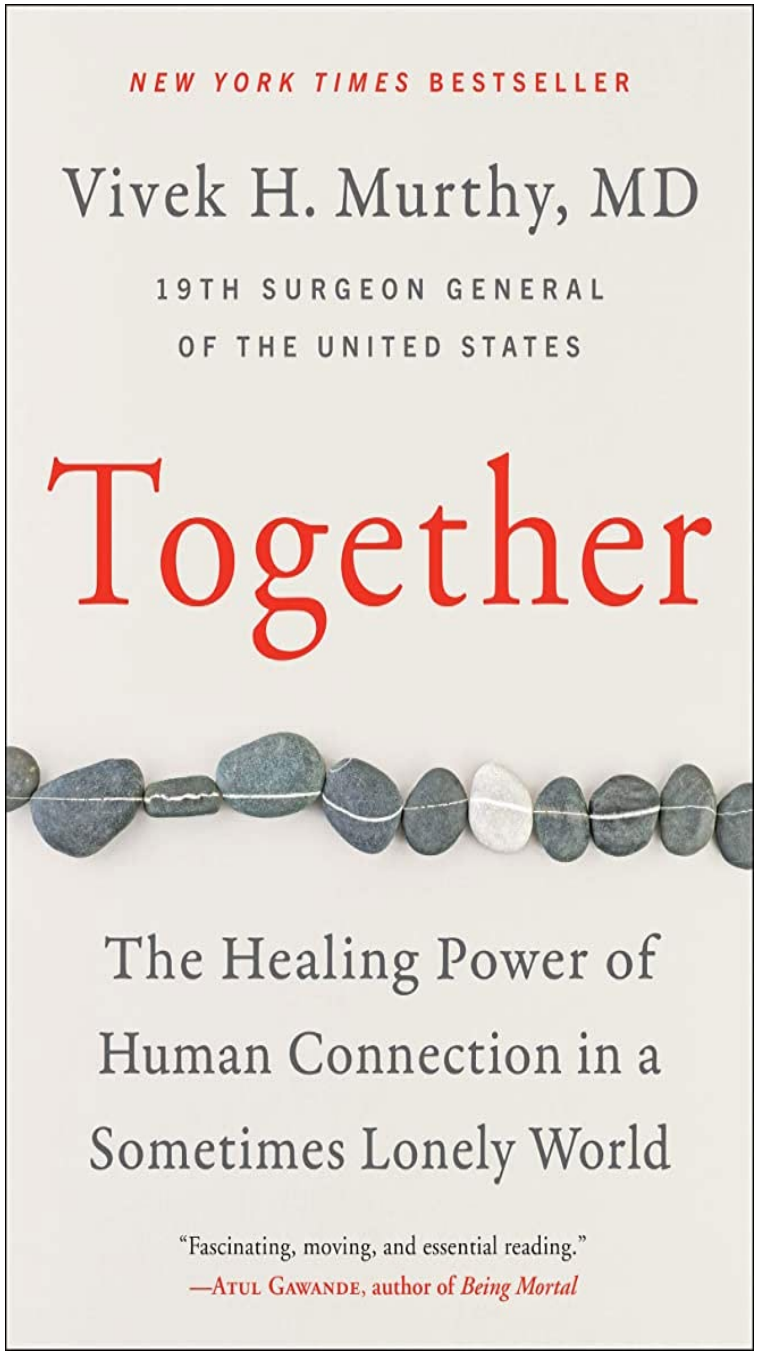
Prescribing Culture, Community, and Connection

SOCIAL PRESCRIBING CAN BOLSTER MENTAL AND PHYSICAL HEALTH

BY RACHEL CHEN


Seniors might be "prescribed" a painting class

It took two years and nearly 50 emergency-room visits for Dr. Ardeshir Hashmi to realize he didn't need to prescribe pills for his 93-year-old patient's excruciating chest pains. He needed to prescribe ballroom dance.



Loneliness can present as great a mortality risk as smoking 15 cigarettes a day

Key Takeaways

- Alzheimer's Dementia (AD) is a global pandemic for which Amyloid cascade based therapeutics have failed to date

- Current research re-focus perhaps towards non amyloid pathways

- Geriatric care for AD is a key cornerstone of Population Health management

- Future of AD care: A "practical dementia pathway" focused on 4 pillars of:

  (i) Addressing IADL impairments

  (ii) Non pharmacotherapeutic multi-component lifestyle modifications

  (iii) Caregiver well being

  (iv) Patient Priorities Care (PPC) & Social Prescribing

Cleveland Clinic

100 YEARS

EST. 1921

THE FUTURE OF HEALTHCARE SINCE 1921

THANK YOU

EVMS Eastern Virginia Medical School | Community focus. World impact.

Additional Follow-Ups

1) **Recording of the Event**
   - The Brock Institute team will edit today's recording and prepare for posting via EVMS YouTube. This will be made available to all attendees after the event, as well as posted on the Brock Institute website.

   - You can see past Brock Institute – Glennan Center Community Lecture and Grand Round Presentations here: https://www.evms.edu/community/brock_institute/events_and_activities_/brock_institute_glennan_lecture/

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