Dementia Update 2024

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Disclosures

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Objectives

At the conclusion of the presentation participants will be able to:

- Define and evaluate dementia
- Explore the amyloid hypothesis and treatments
- Learn the potentially modifiable risk factors

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Patient case

HPI: 85 year old African American woman with atrial fibrillation on apixaban who lives alone, was recently hospitalized for confusion, workup showed UTI, HbA1c 10. Adult son recalled some decline in memory for a year, low appetite, weight loss since a few months ago last holiday. He started caring for the patient since hospitalization, found that she was not taking her diabetic medications, not cleaning her home, getting angry when asked to shower. When asked she is incontinent of urine and wearing a diaper. Son saw the news about lecanemab, wondering if patient needs it.

Hospital treated her for UTI which is resolved, confusion improved, but still unable to manage ADLs

Medication management – son started managing since hospitalization

Finances – there were unpaid bills at home, so son started managing

Driving – son took away patient's keys, wondering if patient can drive

Meds: apixaban, insulin, aspirin 81 mg daily, atorvastatin 40 mg daily

PMH: afib, diabetes, hearing loss but does not like to wear hearing aids

SH: Widowed, 2 adult children, lived alone until recently moved in with son. Has 4th grade education.

FH: Mom had dementia

Definitions

Mild cognitive impairment – heterogeneous syndrome in which cognitive impairment leads to no or minimal impairment of activities of daily living and does not meet criteria of dementia.

Dementia – significant cognitive decline from a previous level of performance in **1 or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition)** that interferes with independence in everyday activities.

Early onset <age 65; late onset >age 65

-memory loss

-challenges with planning or with problem solving

-difficulty completing familiar tasks

-confusion about time or place

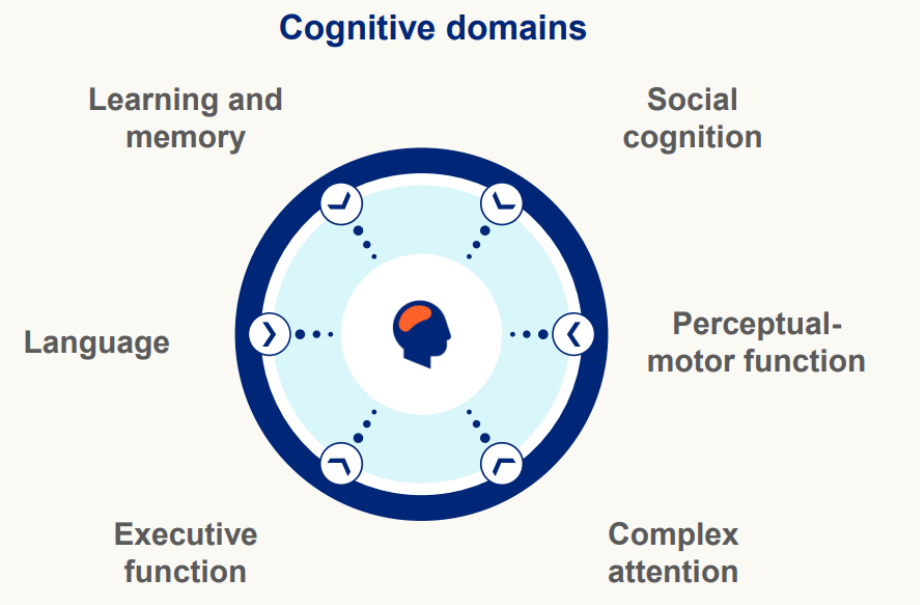
-trouble interpreting visual images or spatial relationships

-difficulty speaking or writing

-poor judgement

-mood or personality changes

-social withdrawal



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Initial Evaluation for AD and dementia

Optum Forum for Evidence-Based Medicine 9/2023.

1. Thorough History
   - daily functioning and independence
   - review of medications
   - screening for depression, psychiatric disorders
   - alcohol and illicit drug use
   - progressive decline over time

2. Cognitive screening tool

3. Workup - CMP, TSH, B12, (HIV, RPR)

4. CT or MRI - hippocampal atrophy, structural

5. Genetic testing NOT recommended
   - limited clinical utility
   - poor predictive value

Table 1. Examples of Brief Cognitive Screening Tools

Screening tool	Scoring ranges	Download instructions and copyright information
Saint Louis University Mental Status exam© (SLUMS)	Normal: 27-30 (25-30 with less than high school education) Mild disorder: 21-26 (20-24 with less than high school education) Dementia: 1-20 (1-19 with less than high school education)	Free to use clinically with training: https://www.slu.edu/medicine/internalmedicine/geriatric-medicine/agingsuccessfully/assessment-tools/mental-status-exam.php
Montreal Cognitive Assessment© (MoCA)	MoCA scoring details are provided with training and certification (see download instructions)	Training and certification are required to use the MoCA. Although the screening test can be used freely, there is a fee for training: http://mocacognition. com/
Mini-Cog©	Scoring detailed in website. Total scores of 0, 1 or 2 indicate higher likelihood of cognitive impairment. When greater screening sensitivity is desired, a score of 3 may indicate cognitive impairment.	Free to use clinically with training: https://minicog.com
Mini-Mental Status Examination© (MMSE)	MMSE scoring details are provided purchase (see download instructions)	The MMSE requires purchases for use: https://www.parinc.com/Products/Pkey/237

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FAST Dementia Staging

CMS.gov

Normal	Stage #1: No difficulty, either subjectively or objectively
Normal	Stage #2: Complains of forgetting location of objects; subjective work difficulties
Early	Stage #3: Decreased job functioning evident to coworkers; difficulty in traveling to new locations
Mild	Stage #4: Decreased ability to perform complex tasks (e.g., planning dinner for guests; handling finances)
Moderate	Stage #5: Requires assistance in choosing proper clothing
Mod-Severe	Stage #6: Decreased ability to dress, bathe, and toilet independently: Sub-stage 6a: Difficulty putting clothing on properly Sub-stage 6b: Unable to bathe properly; may develop fear of bathing Sub-stage 6c: Inability to handle mechanics of toileting (i.e., forgets to flush, does not wipe properly) Sub-stage 6d: Urinary incontinence Sub-stage 6e: Fecal incontinence
Severe	Stage #7: Loss of speech, locomotion, and consciousness: Sub-stage 7a: Ability to speak limited (1 to 5 words a day) Sub-stage 7b: All intelligible vocabulary lost Sub-stage 7c: Non-ambulatory Sub-stage 7d: Unable to sit up independently Sub-stage 7e: Unable to smile Sub-stage 7f: Unable to hold head up

Patient Case

History:

- Unable to live independently (was not taking meds or insulin; HbA1c 10, unpaid bills at home, losing weight/not eating properly)
- Review of medications – apixaban (anticoagulation causes risk of bleeding using antiamyloid therapy)
- Alcohol and illicit drug use - none
- Progressive decline over time – son noted over last 1 year when seeing her during the holidays

Exam:

- PHQ9 – 1 (no depression)
- FAST 6d (moderately severe; urinary incontinence)
- FMMSE 12 (<27 mild; <21 moderate, <10 severe)
- Work up:
- CBC, CMP, TSH, B12 normal except for CKD 3a, CT head done at hospital shows atrophy

- Diagnosis: Alzheimer dementia, late onset, severe, with behavioral disturbance (anger/agitation when asked to shower)

Dementia Management

Carlsson, Cynthia. Continuum, 2022.

- Treat comorbid medical problems: depression/anxiety disorders, hearing loss, pain, alcohol misuse
- Obstructive sleep apnea most common primary sleep disturbance in older adults – CPAP helpful
- Treat depression with medication and non-pharmacologic therapy
- Deprescribe meds with cognitive side effects if possible (polypharmacy)
- Acetylcholinesterase inhibitors and N-methyl-D-aspartate antagonist (NMDA) have been mainstay for dementia – GI side effects and bradycardia with donepezil, dizziness with memantine
- Assess safety concerns and develop plans with care partners - driving, medication management, falls, kitchen safety, wandering, and firearm use
- Engage patients early about advanced care planning
- Identification of educational, supportive, and resource needs of the patient and caregivers - PT/OT/ST, social workers, meal delivery, driving assessment, local transportation, day care, SNF, Alzheimer Association[1], local Area Agency on Aging[2]

1. https://www.alz.org/alzheimers-dementia/what-is-dementia
2. https://eldercare.acl.gov/Public/About/Aging_Network/AAA.aspx

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Patient Case

Management:

- Due to weight loss will not start donepezil.
- Start memantine 5 mg daily for 1 week, then bid for 1 week, then 5/10 for 1 week, then 10 bid.
- Do not need to medicate anger/mood unless interfere with patient/caregiver quality of life/safety.
- Son added his name to patient bank account.
- Letter for son to manage financial and medical decisions on behalf of patient.
- Recommend no driving.
- Alzheimer websites given to son, discuss advanced care planning.
- Social work consult for caregiver assistance or placement, reassess in 3 months.

Why Serum Biomarkers are not Widely Used

Hansson et al, Alzheimer's and Dementia, 2022.

- Need to be validated in diverse ethnic, socioeconomic population in real world clinics
- Need accurate reference standards
- Need tools for interpretation of results
- Confounders – race, ethnicity, high BMI, peripheral neuropathies, other diseases, kidney disease – need large cohort
- Biological variation – intra-day, between day variations in individuals with various conditions
- Need prospective longitudinal study of serum biomarkers in real world memory clinics
- Need prospective studies in the PCP clinic with representative and diverse populations (heterogeneous causes: renal, cardiovascular, diabetes, depression)
- Controversial use in patients with subjective complaints and normal objective exam
- Should only be used in specialist clinics and confirmed with CSF or PET

Expert opinion Dr. Clifford Jack. *Neurology Today* 9/2024: "We are specifically recommending to NOT test cognitively unimpaired individuals… do not do it, because there are no approved treatments for people without clinical symptoms."

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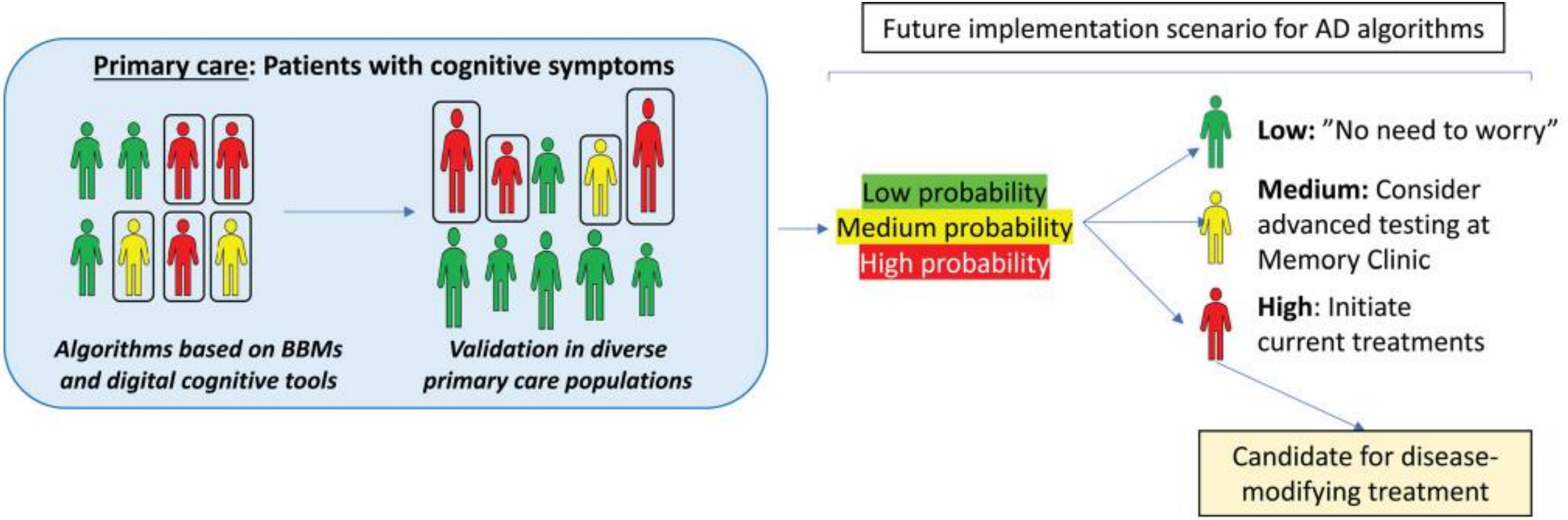
Future Model for Using Blood Based Biomarkers

Hasson et al, Alzheimer's and Dementia, 2022.



Amyloid Hypothesis

Optum Forum for Evidence-Based Medicine 9/2023.

Hypothesis that amyloid-ß aggregation is primary cause of Alzheimer disease

Problems:

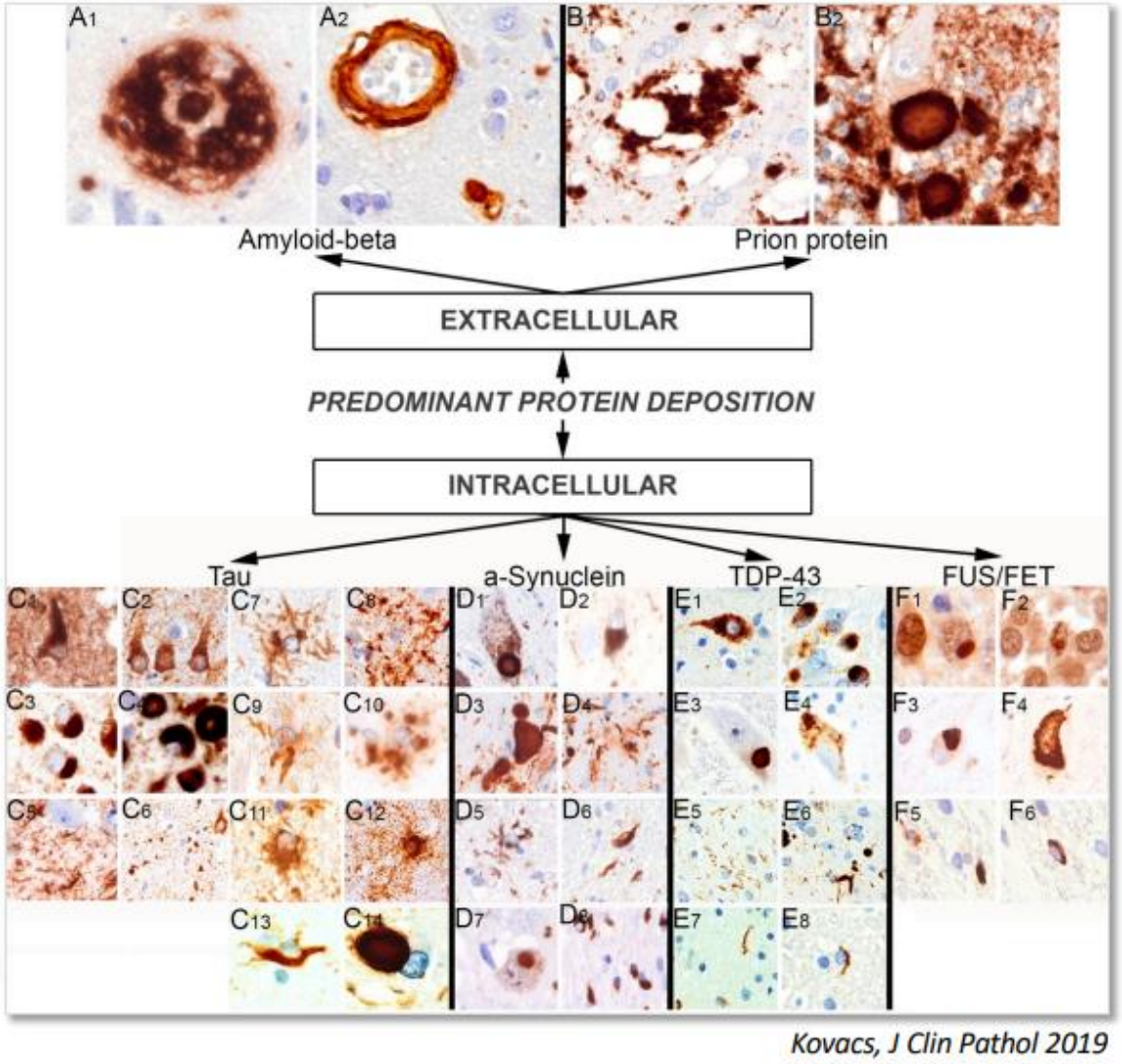
Genome-wide association studies have implicated risk genes that are not involved in amyloid-ß processing.

Many older adults have brain amyloid-ß that fulfills Alzheimer’s disease criteria but have no symptoms.

Lowering amyloid burden does not clearly correlate with improved clinical outcomes.

Amyloid beta versus Tau

Iadecola, Costantino, AAN Plenary Lecture 2023



Amyloid beta – deposit in extracellular plaques (anti-amyloid therapy)

Tau – deposit in intracellular neurofibrillary tangles

Monoclonal Antibody Therapies

- Aducanumab 2021 (not FDA approved) – unclear clinical efficacy with high adverse reactions
- Lecanemab 2022 – FDA approved but not widely available (can access in clinical trials)
- Donenamab – not yet fully FDA approved - Clinically meaningful change on the iADRS has been estimated at 5 points for MCI, but 9 points for mild dementia (Optum Forum for Evidence-Based Medicine 9/2023).
- Gantenerumab – 2022 did not achieve statistical clinical efficacy

Lecanemab

Clarity – NEJM 11/2022

Age 50-90 MCI due to AD or mild AD, positive amyloid in PET or spinal tap

Less worsening in cognitive scores (CDR-SB) at 1.5 years, edema/effusions

Infusion 10 mg/kg every 2 weeks

**2 deaths after trial open label (stroke, cerebral hemorrhage – both on anticoagulation)

4.5 percent Black and 22.5 percent Hispanic participants, comorbidities including hypertension, diabetes, heart disease, obesity, and renal disease

ICER 3/2023 – promising but inconclusive if lecanemab provides net health benefit to supportive care with risk of ARIA 21% with effusion, hemorrhage, or both

JAMA letter 5/2023 – lecanemab high cost can possibly lead to beneficiary premium increases; Medicare spending may increase by $2 billion to $5 billion

Neurology letter 8/2023 – donepezil outperformed lecanemab in CDR-SB (0.53 vs 0.45) and in ADAS-Cog (2.37 slowing vs 1.44 slowing) therefore symptomatic benefits are very small; amyloid present in patients who are asymptomatic; multi-focal hemorrhage in patient given tPA for stroke who was on lecanemab; elderly patients may develop a fib, stroke requiring thrombolysis in future; giving lecanemab to all MCI, mild Alzheimer patients would cost $120 billion per year

Candidates for Monoclonal Antibody Therapies

Medicine for Early Dementia Treatment Optum 2024

- Only 1 or 2 out of every 10 people with MCI due to Alzheimer or mild Alzheimer
- Low genetic risk for side effects
- Have not had a recent stroke
- Not on blood thinners
- Not taking immunosuppressants or immunomodulating drugs
- No other life-limiting conditions (like cancer spread throughout the body)

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Lecanemab Considerations

Lecanemab Appropriate Use Considerations. Alzheimer Association, 2023.

Inclusion:

- Mild Alzheimer Disease
- BMI >17, <35
- Have partner/family

ARIA rates reported for the CLARITY AD trial of lecanemab

	APOE4 Noncarrier Lecanemab (N=278)	*APOE4* Heterozygote Lecanemab (N=479)	*APOE4* Homozygote Lecanemab (N=141)
ARIA-E	5.4%	10.9%	32.6%
Symptomatic ARIA-E	1.4%	1.7%	9.2%
Serious event with ARIA-E	0.7%	0.4%	2.1%
Total ARIA-H (Concurrent & Isolated)	11.9%	14.0%	39.0%

Exclusion:

- Microhemorrhages on MRI
- Stroke, TIA, seizure last 1 year
- Psychiatric illness, hallucinations that can interfere with participation
- GDS>8
- Immunologic disease requiring immunosuppressants, IVIG, monoclonal antibodies
- Bleeding disorders, anticoagulants, tPA/TNK (patients cannot get tPA/TNK in future for stroke or atrial fibrillation when on therapy)
- Unstable medical conditions (cardiac, respiratory, renal, GI disease), life limiting conditions (metastatic cancer)

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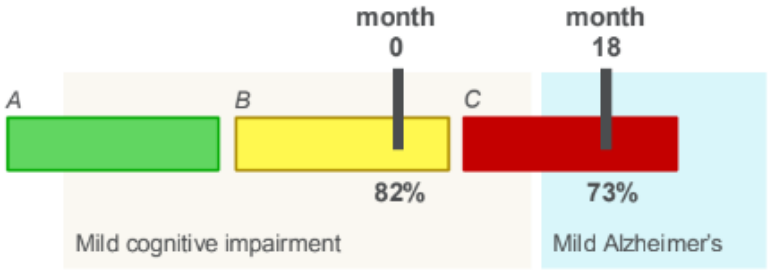
Positive effects after 18 months

Usual care
± exercise and brain training

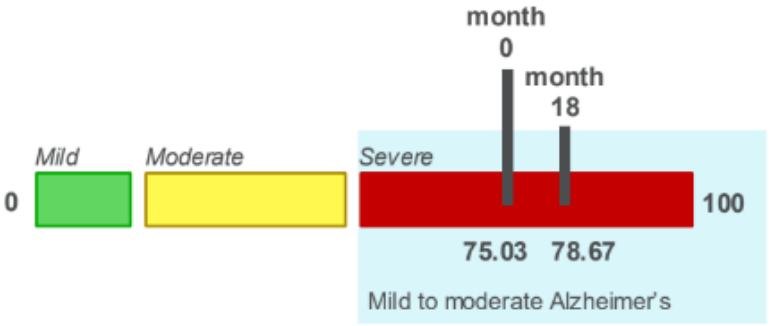
Trouble with thinking

With usual care, your thinking "grade" may drop 9% to a C.



Protein buildup in the brain

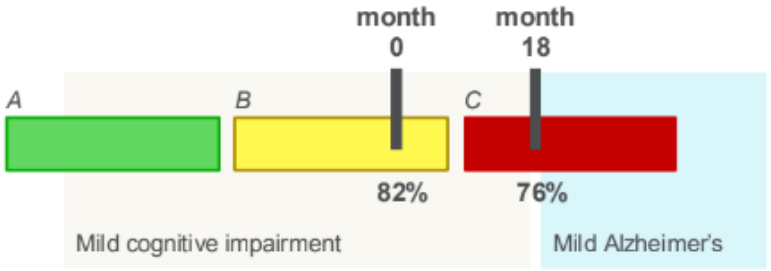
On usual care, protein buildup may not change much.



Monoclonal antibodies
+ usual care

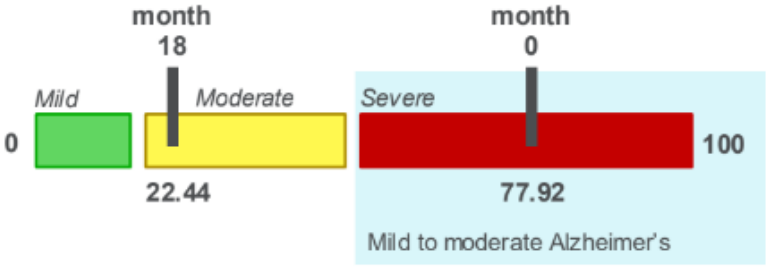
Trouble with thinking

Your thinking "grade" may drop 6% to a C on lecanemab and usual care.



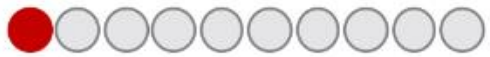
Protein buildup in the brain

Protein buildup may be lowered with lecanemab and usual care.



Side effects

Brain bleeding or swelling



Of these 11, less than 1 may have symptoms. No matter the care, brain bleeding or swelling is more common with a certain gene.

Infusion-related reactions

Without infusions, there's no chance of reactions. Instead, 7 to 13 in 100 people may have diarrhea, nausea, vomiting or dizziness.

Costs

Total costs for cholinesterase inhibitors

less than $100 to **several thousand dollars**
per year

Total costs vary by medicine. Generic forms of cholinesterase inhibitors are inexpensive.

There are no testing requirements for safety. There are no infusion costs.

Side effects

Brain bleeding or swelling

Of these 30, 3 or 4 may have symptoms like dizziness, headaches, visual disturbances, confusion. It's more common with a certain gene. Medicine may be stopped.

Infusion-related reactions

Reactions may include fever, chills, nausea, flushing, low blood pressure. People are usually able to continue the infusion. Or reactions stop once the infusion stops.

Costs

Total costs for lecanemab

tens of thousands of dollars
per year

Total costs include:

- Advanced imaging. This includes a PET scan and several MRIs.
- Genetic testing
- Infusion fees every 2 or 4 weeks
- Drug costs

Monoclonal Antibodies – Unknowns

Medicine for Early Dementia Treatment Optum 2024

- If patients will notice a 3% change in thinking “grade” by adding monoclonal antibodies to usual care. Meaningful change to clinicians is about 6-11%.
- If lessening this protein buildup in the brain is enough to slow the illness down.
- If people taking monoclonal antibodies are able live at home safely for longer.
- If you need to keep taking monoclonal antibodies past 18 months.
- How Black/African American people may respond to lecanemab. (under-represented in data.)

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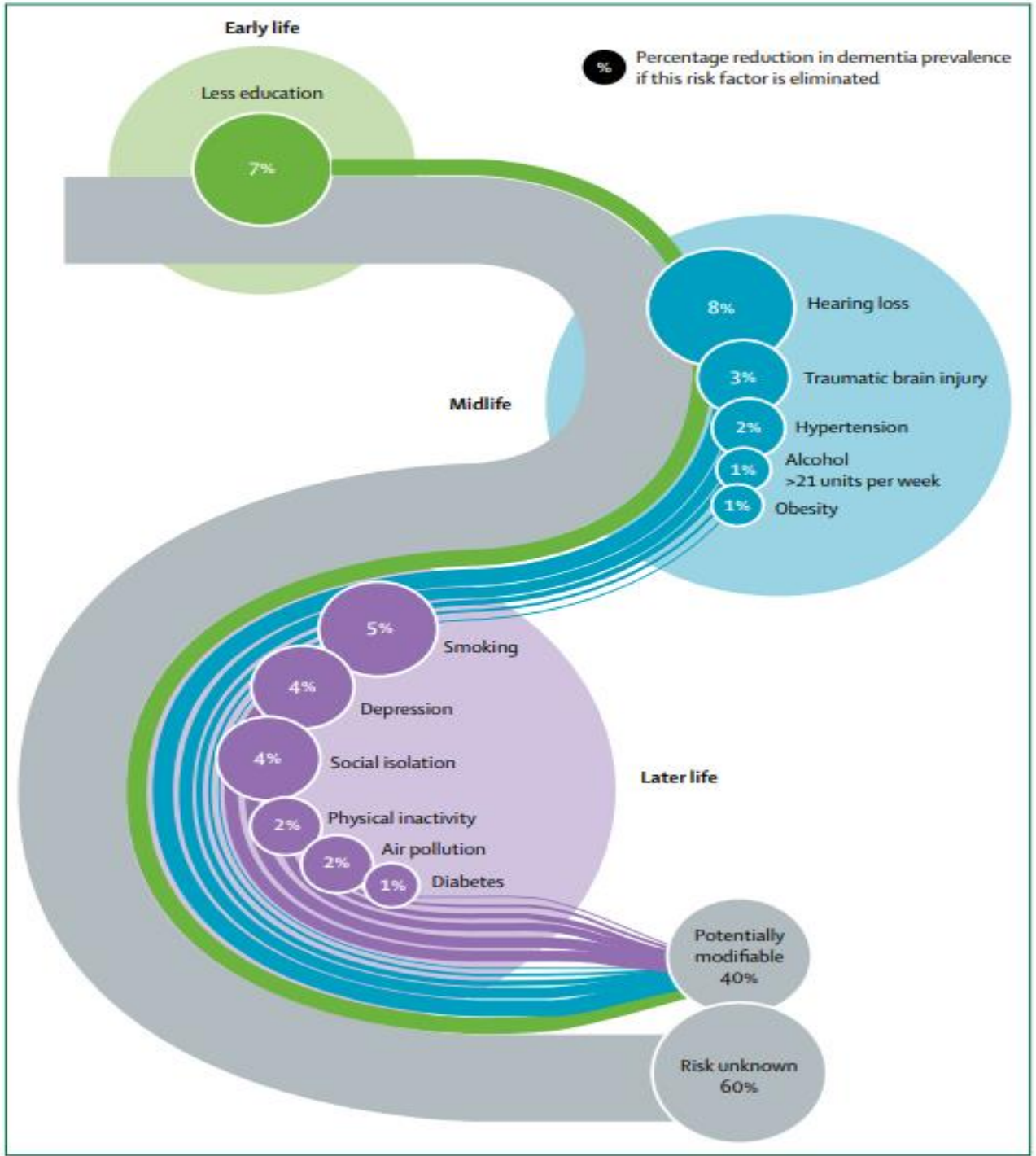
Potentially Modifiable Risk Factors Dementia –
Livingston et al., Lancet 2020



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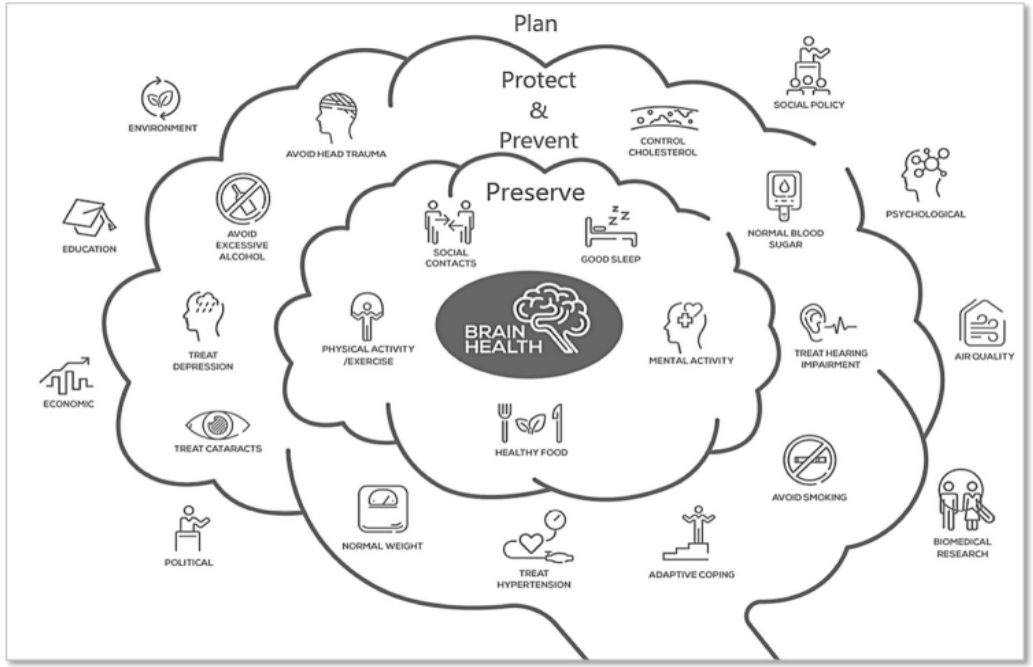
Brain Health

Iadecola, Costantino, AAN Plenary Lecture 2023

- Neurodegeneration and neurovascular conditions have pathogenic overlap
- Systemic conditions cause subclinical brain disease
  - Liver-heart-brain axis (gray matter atrophy, white matter degeneration, small vessel disease)
  - Kidney-brain axis (decreased eGFR and dementia)
  - Gut-brain axis (gut microbiome)
  - Lung-brain axis (lung microbiome and neuroinflammation)
  - COVID (long-COVID)

Maintenance of brain health



Plan:
- Social policy
- Environment
- Education
- Medical research

Protect and Prevent:
- Risk factors
- High-risk behaviors
- Adverse events
- Vision and hearing

Preserve:
- Healthy lifestyle

European Academy of Neurology (Bassetti et al., Eur J Neurol, 2022)

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Patient Case

Potentially modifiable risk factors:

- 4th grade education
- hearing loss
- diabetes
- widowed, living alone

Systemic effects:

- diabetes
- CKD 3a

Not a candidate for anti-amyloid therapy: advanced/severe dementia, on anticoagulation

African Americans less represented in clinical trials on antiamyloid therapy
African Americans have higher incidence of Alzheimer disease than Caucasians
Bias in screening tools against people with less education and less verbal skills

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Summary

Dementia is a significant cognitive decline from a previous level of performance that interferes with living independently.

Amyloid hypothesis assumes that amyloid-ß aggregation is the primary cause of Alzheimer disease and that lowering the amyloid burden would decrease cognitive decline.

Antiamyloid therapies are being developed which may improve cognitive decline but the clinical significance is unclear.

Antiamyloid may be used in mild Alzheimer disease in a small number of individuals, but have significant side effects, costs, burden of time (frequency of infusions, scans) that need to be discussed.

It is important to promote healthy living during youth and adult life to modify risk factors to decrease the risk of dementia in late life.

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Appendix

Serum Biomarker Candidates:

Hansson et al, Alzheimer's and Dementia, 2022.

Currently used in clinical trials only:

--Amyloid beta 42/40 – small change between positive and negative individuals due to peripheral production

--Serum phosphorylated tau - related to density of amyloid beta plaques and tau tangles - screening in clinical trials

--Neurofilament light chains - axonal damage (nonspecific)

--Glial fibrillary acidic protein – astrocyte activation to clear amyloid beta - higher in brain astrocytes than peripheral macrophages – need additional study to validate

Validated Testing for Alzheimer Disease Pathology

Hasson et al, Alzheimer's and Dementia, 2022.

Beta Amyloid PET scan – deposition of beta amyloid in plaques

CSF amyloid beta 42/40 ratio – low ratio reflects depletion of Amyloid beta 42 due to growing plaques

-Can be used in symptomatic patients to determine AD vs non-AD

Plasma phosphorylated Tau 217

Ashton et al, JAMA Neurology 2024

Certain plasma p-tau – associated with neurofibrillary tangle pathology

pTau- 217 (phosphorylated tau at threonine 217) - high performance in differentiating AD from other neurodegenerative disorders, and in detecting AD pathology in patients with MCI

- Associated with longitudinal trajectory associated with brain atrophy and declining cognitive performance in people with amyloid beta pathology
- Preclinical population with lower prevalence of amyloid beta abnormalities – plasma p-tau can help with diagnosis and prognosis longitudinal change (increase with amyloid beta only, and with amyloid beta and pTau)
- Anti amyloid therapies may be less effective in patient with advanced tau pathology
- Related to density of amyloid beta plaques and tau tangles

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Aducanumab (no traditional FDA approval)

AAN Guidelines 2022, FDA Update 2021, Optum Forum for Evidence-Based Medicine 9/2023.

Class II studies:

ENGAGE – no clinical efficacy; EMERGE – unclear efficacy

-Decreased amyloid deposition in the brain on amyloid-PET scan at 1 year vs placebo

-Efficacy varied on dose and outcome but had no effect versus less worsening (vs placebo) of unclear clinical significance

-Adverse reactions

ARIA-E 35% of the treatment versus 3% placebo

ARIA-H, microhemorhage 19% versus 7%

ARIA-H, siderosis 15% versus 2%

. -Monthly infusion dose titrated to 10 mg/kg over 6 months

-Study duration 1.5 years but unknown duration of therapy in real world

-Studies excluded: dementia due to other causes, younger patients, underrepresented minority groups, prior stroke, brain bleed, antiplatelet therapy, psychiatric conditions that might contribute to cognitive impairment, cardiovascular disease, CKD, age>85

- Analysis of 2.87 million Medicare beneficiaries with symptomatic AD in 2021 - 91% of patients diagnosed with AD dementia and 86% of patients with MCI met at least 1 exclusion criterion

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Other anti-amyloid therapy

Optum Forum for Evidence-Based Medicine 9/2023.

Donanemab (clinical trials):

-Phase 2 clinical trial enrolled 257 patients with MCI or mild dementia attributed to early Alzheimer's disease.

-Primary outcome was change in the Integrated Alzheimer's Disease Rating Scale (iADRS) at 76 weeks.

-Positive significant change in iADRS (-6.86 with treatment and -10.06 with placebo, p=0.004).

-Clinically meaningful change on the iADRS has been estimated at 5 points for MCI, but 9 points for mild dementia.

-Phase 3 trial - low, medium, high tau pathology based on PET

-Positive significant change iADRS (-3.25 in the low/medium tau cohorts; -2.92 in the combined population) and the CDR-SB (-0.67 in the low/medium tau cohorts; -0.7 in the combined population). - -Brain amyloid decreased significantly.

-ARIA-E 24% in treatment versus 1.9% placebo group

-ARIA-H in 19.7% versus 7.4%

Gantenerumab (November 2022 press release):

-2 phase 3 trials: lowing of clinical progression of -0.31 and -0.19 points on the CDR-SB compared to placebo.

-Not statistically significant