THE ALZHEIMER'S PROJECT CLINICAL ROUNDTABLE

Dementia Update
Disease Modifying Medications for Alzheimer's Disease: Risks and Benefits

Live Stream & Recorded October 19, 2023

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Speaker Disclosures

Gabriel Leger, MD, Neurologist, UC San Diego

Michael Lobatz, MD, Neurologist, Chair, Alzheimer's Project Clinical Roundtable

Ian Neel, MD, Geriatrician, UC San Diego

Educational Outcome

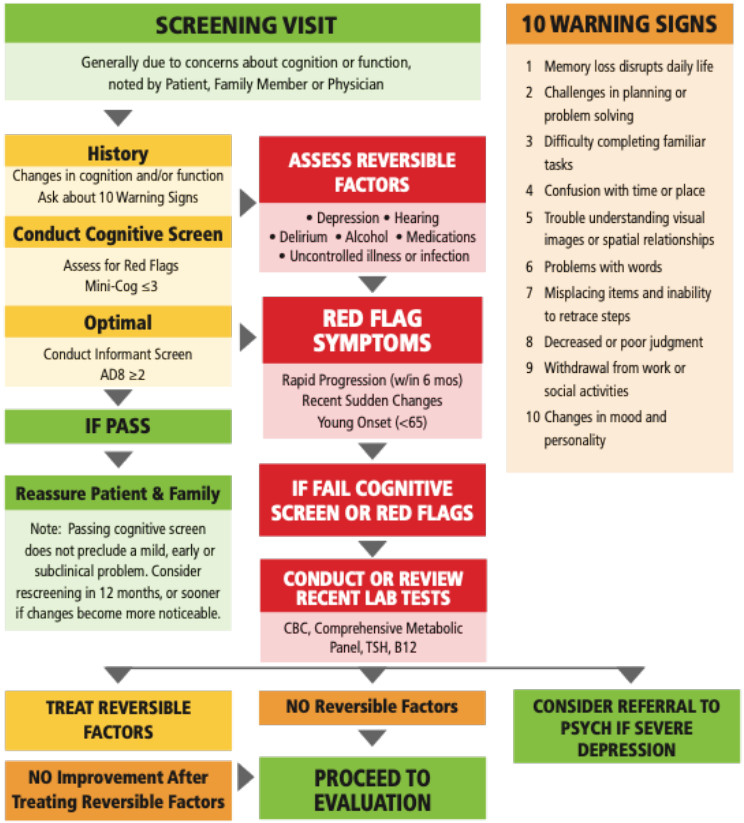
At the conclusion of this program, learners will demonstrate:

- *enhanced knowledge of new disease-modifying medications work, indications of use & FDA guidelines,*
- *effective communication of risks and benefits of the medications,*
- *and indications and timing for appropriate referrals to specialists*

by scoring 80% or better on a posttest/interactive questions.

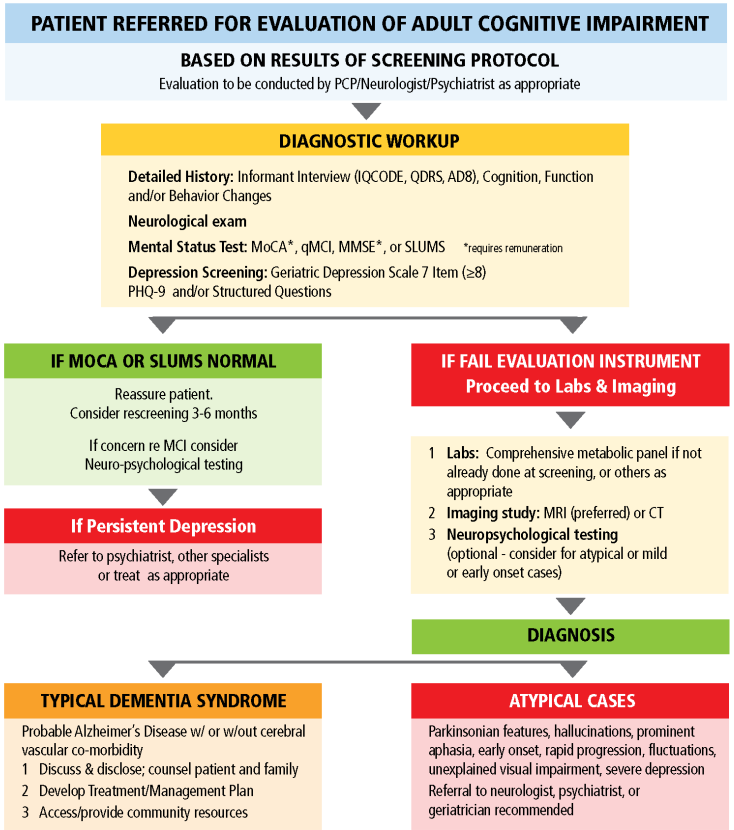
Alzheimer's Clinical Roundtable
Recommended Screening Algorithm for Adult Cognitive Impairment

NOTE: Cognitive screening may be a part of a regular annual physical exam.

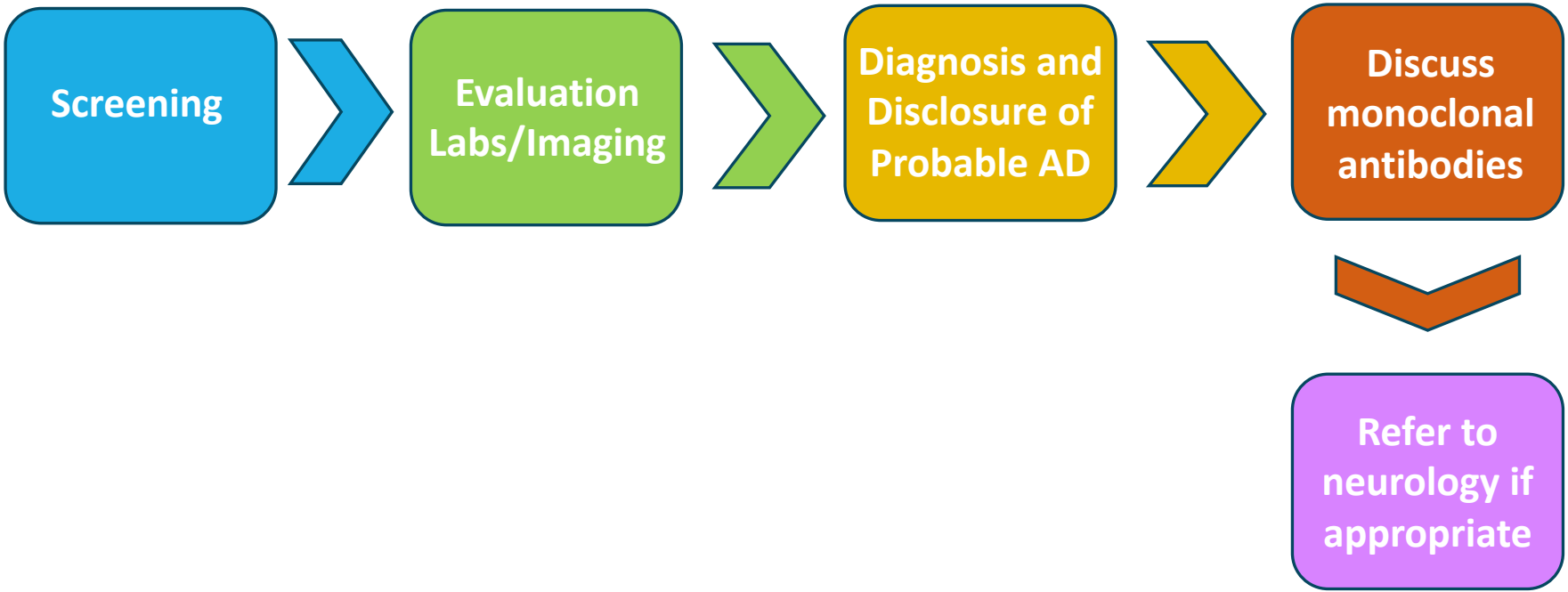


10 WARNING SIGNS

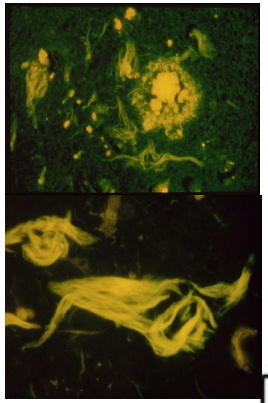
1. Memory loss disrupts daily life
2. Challenges in planning or problem solving
3. Difficulty completing familiar tasks
4. Confusion with time or place
5. Trouble understanding visual images or spatial relationships
6. Problems with words
7. Misplacing items and inability to retrace steps
8. Decreased or poor judgment
9. Withdrawal from work or social activities
10. Changes in mood and personality

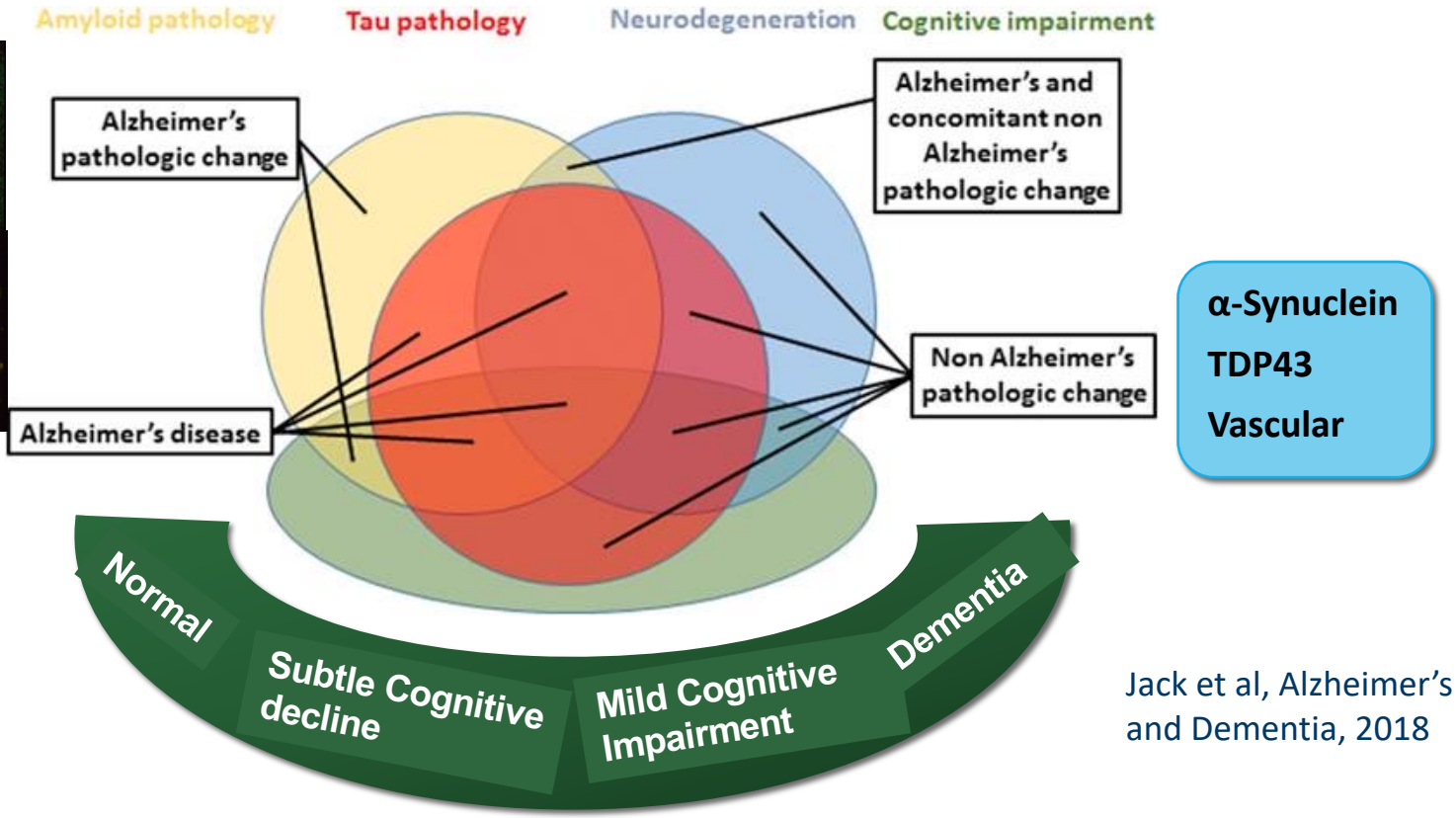

PATIENT REFERRED FOR EVALUATION OF ADULT COGNITIVE IMPAIRMENT
BASED ON RESULTS OF SCREENING PROTOCOL
Evaluation to be conducted by PCP/Neurologist/Psychiatrist as appropriate
DIAGNOSTIC WORKUP
Detailed History: Informant Interview (IQCODE, QDRS, AD8), Cognition, Function and/or Behavior Changes
Neurological exam
Mental Status Test: MoCA*, qMCI, MMSE*, or SLUMS *requires remuneration
Depression Screening: Geriatric Depression Scale 7 Item (≥8)
PHQ-9 and/or Structured Questions
IF MOCA OR SLUMS NORMAL
Reassure patient.
Consider rescreening 3-6 months
If concern re MCI consider
Neuro-psychological testing
If Persistent Depression
Refer to psychiatrist, other specialists or treat as appropriate
IF FAIL EVALUATION INSTRUMENT
Proceed to Labs & Imaging
1 Labs: Comprehensive metabolic panel if not already done at screening, or others as appropriate
2 Imaging study: MRI (preferred) or CT
3 Neuropsychological testing (optional - consider for atypical or mild or early onset cases)
DIAGNOSIS
TYPICAL DEMENTIA SYNDROME
Probable Alzheimer's Disease w/ or w/out cerebral vascular co-morbidity
1 Discuss & disclose; counsel patient and family
2 Develop Treatment/Management Plan
3 Access/provide community resources
ATYPICAL CASES
Parkinsonian features, hallucinations, prominent aphasia, early onset, rapid progression, fluctuations, unexplained visual impairment, severe depression
Referral to neurologist, psychiatrist, or geriatrician recommended

Role of the PCP: Cognitive Screening to Potential Referral

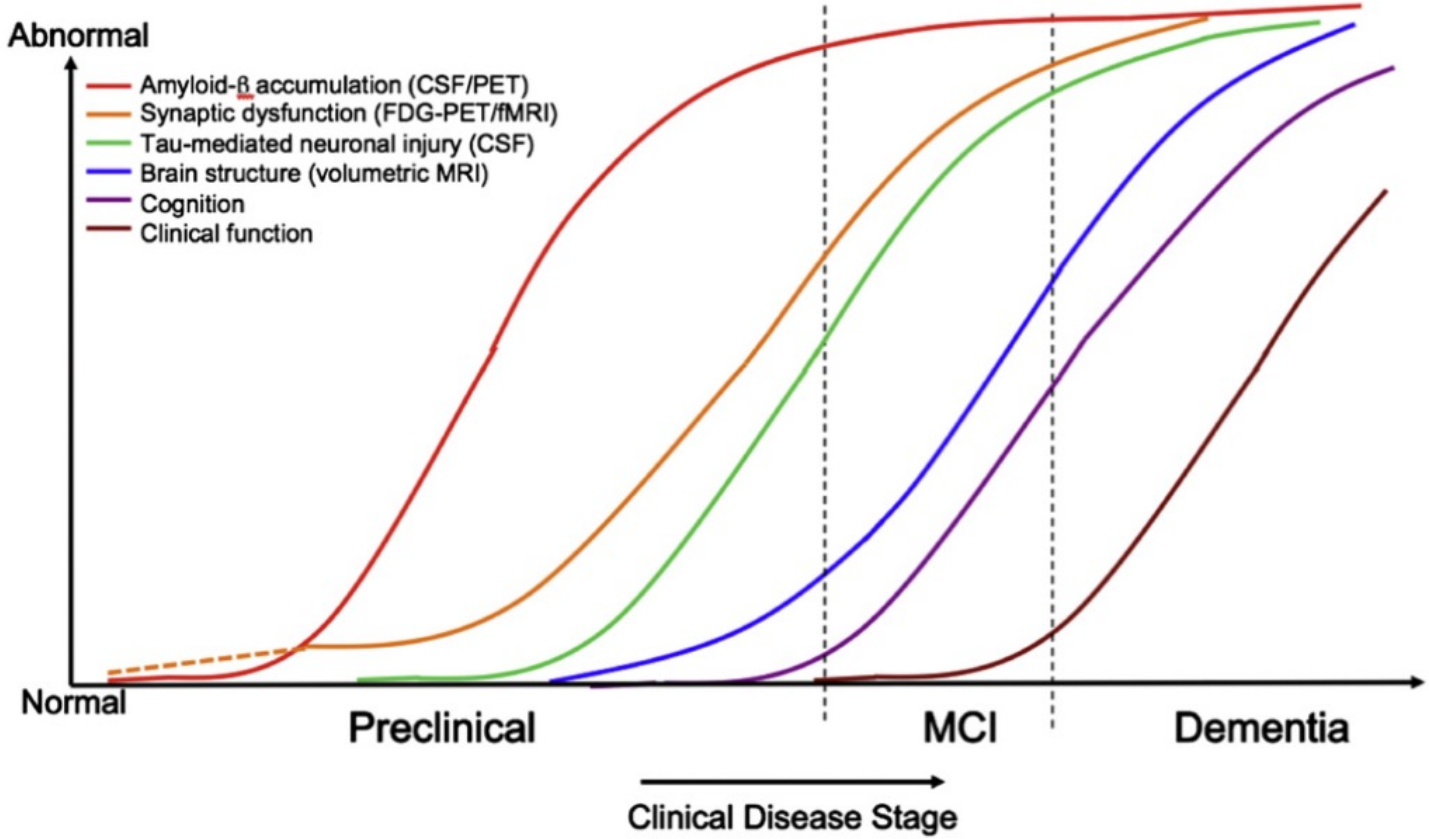


NIA-AA Research Framework: Towards a biological definition of Alzheimer's disease – Amyloid, Tau, Neurodegeneration



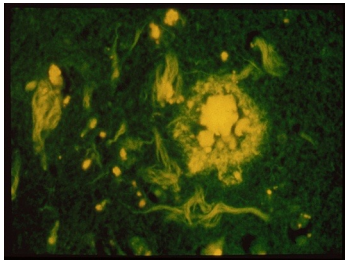


Jack et al, Alzheimer's and Dementia, 2018

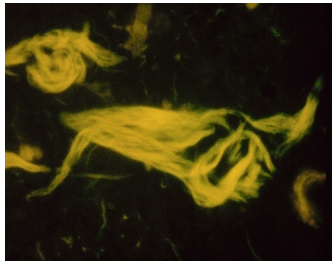


Sperling, R.A. et al., 2011. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer‘s Association workgroups on diagnostic guidelines for Alzheimer’s disease. *Alzheimer“s & dementia : the journal of the Alzheimer”s Association*, 7(3), pp.280–292.

Biomarkers can detect and map A,T and N



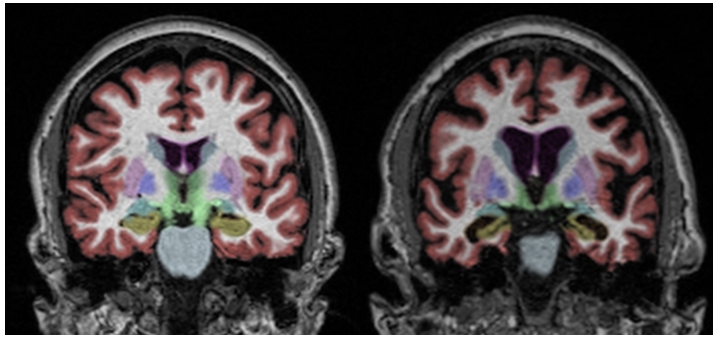
Amyloid plaques



Neurofibrillary tangles

A Amyloid PET, CSF or plasma Aβ42/40

T Tau PET, CSF or plasma P-tau



Brain atrophy and neuron loss

N Neurodegeneration

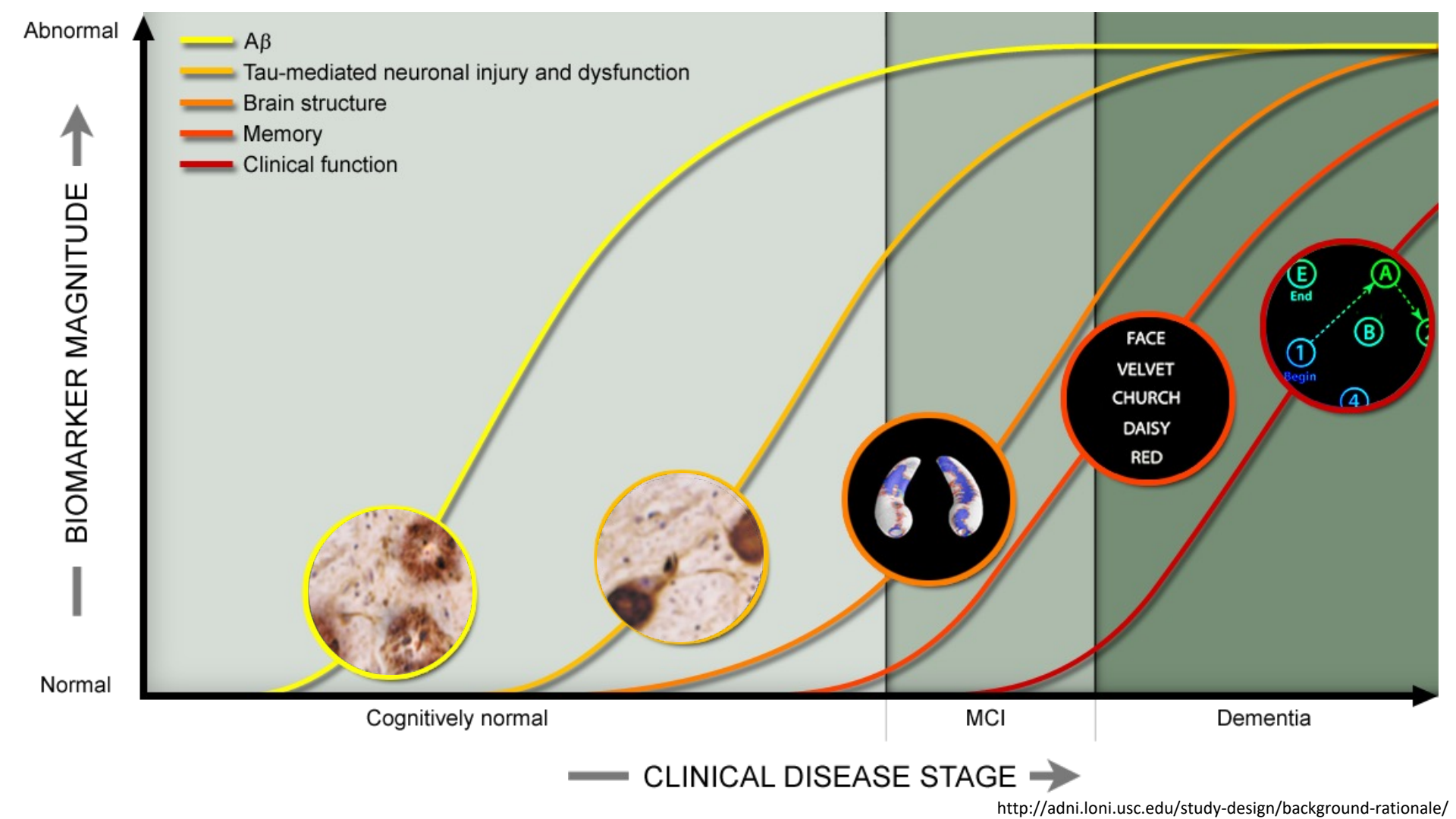
Anatomy:

MRI - atrophy, pathways

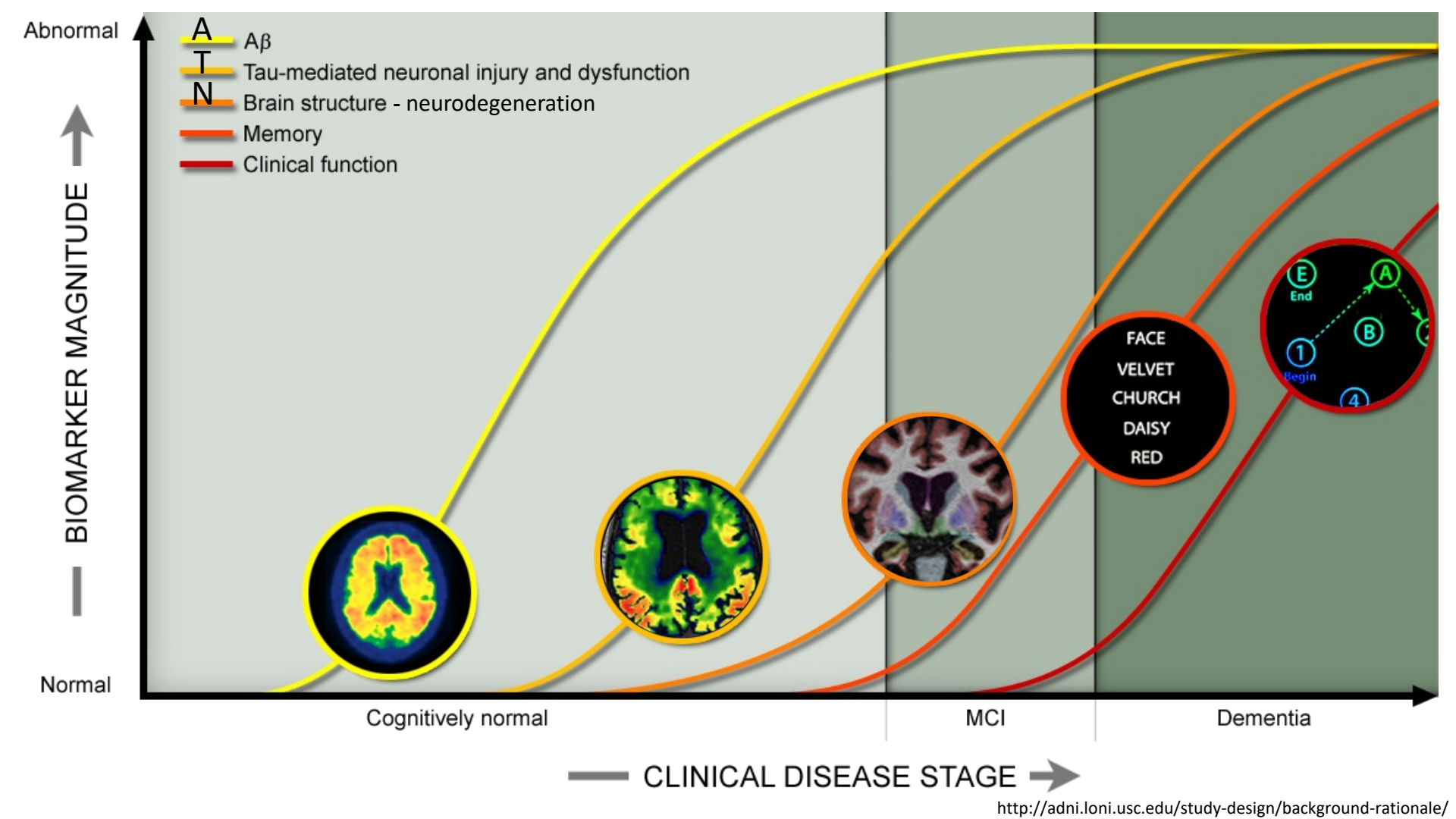
PET - glucose use

Biochemistry:

CSF or plasma - tau, NfL, others



http://adni.loni.usc.edu/study-design/background-rationale/



http://adni.loni.usc.edu/study-design/background-rationale/

Anti-amyloid immunotherapy

Lecanemab: binds to soluble protofibrils of amyloid and clears amyloid from plaques.

Positive phase 2 and phase 3 trials.

FDA approval in July 2023; covered by CMS

Donanemab: binds to insoluble amyloid and clears plaques

Positive phase 2 and phase 3 trials

Both antibodies *slowed clinical progression*

Both were associated with an adverse event called ARIA.

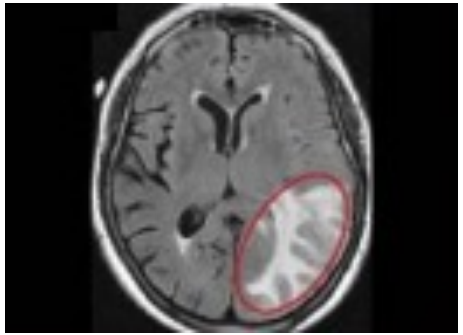
This resulted in a boxed warning from the FDA

ARIA – Amyloid Related Imaging Abnormality

Most ARIA episodes are asymptomatic and can be seen on MRI

However, symptoms may occur:

- headache, nausea, confusion, dizziness
- rarely stroke or seizures



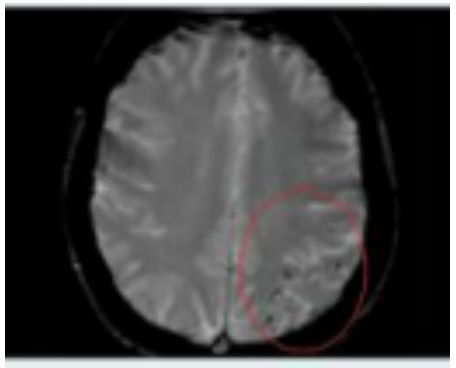
ARIA-E

Mitigate

Baseline MRI: exclude people with >4 microhemorrhages

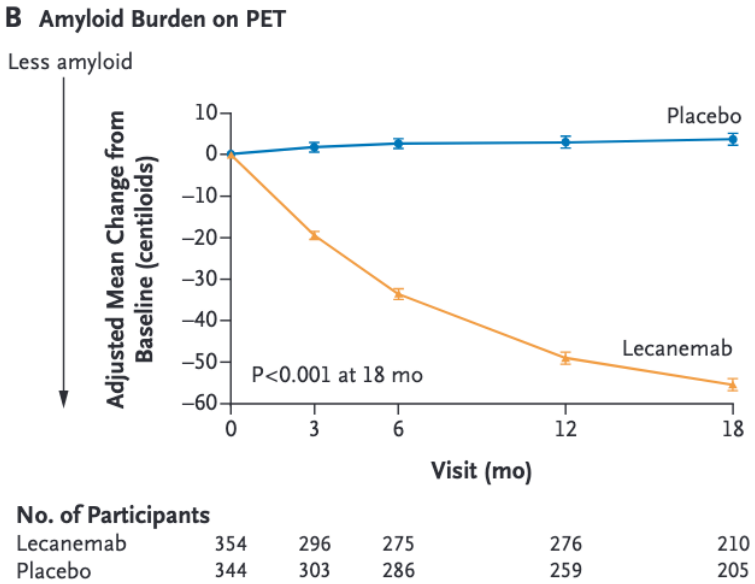
Monitor

Safety MRI at 2, 3 and 6 months and if symptoms emerge esp. early in treatment



ARIA-H

Lecanemab lowers amyloid and results in clinical slowing



- Phase 3 RCT, 18 month
- Lecanemab 10 mg/kg vs placebo
- IV q2 weeks
- N =1795 (898 Lecanemab & 897 placebo)
- Slowed progression on global, cognitive and IADL ratings

ARIA-E

12.6% of Lecanemab, 2.8% symptomatic

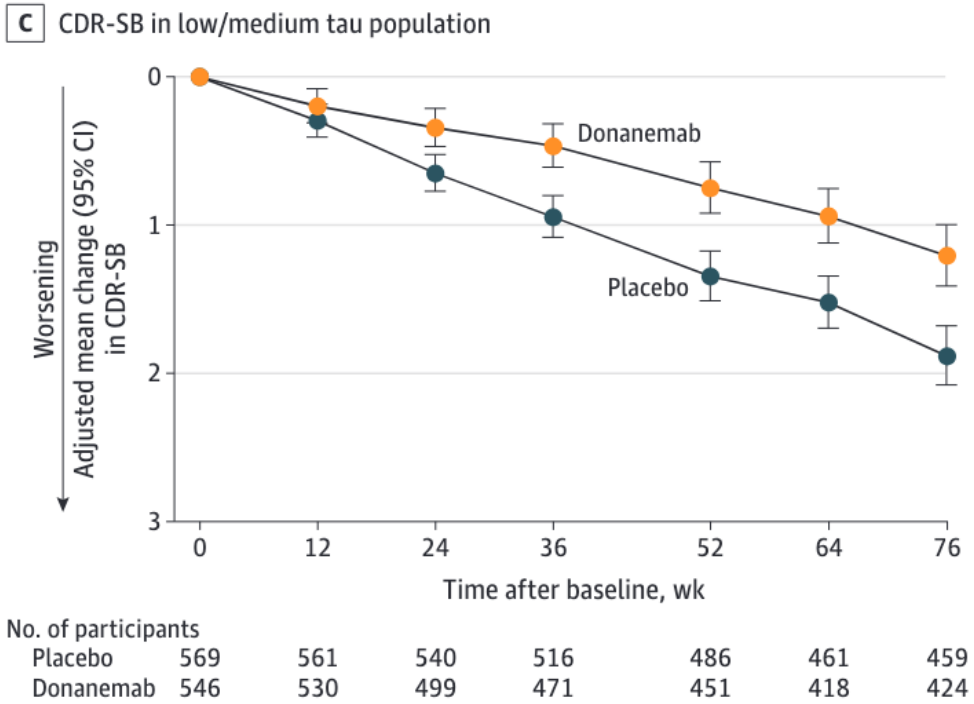
ARIA-H

8.9% of Lecanemab, 7.8% of placebo

ARIA higher in APOE ε4 carriers
(ε2-3/2-3 5.4%, ε2-3/4 10.9% ε4/4 32.6%)

Dyck, C. H. van *et al.* Lecanemab in Early Alzheimer's Disease. *New Engl J Med* **388**, 9–21 (2022).

Donanemab clears amyloid and has clinical benefit



- Phase 3 trial x 18 months
- Donanemab I-V every 4 weeks x 76 weeks
- MCI/mild AD
- slowing of a composite scale (ADRI-AD) by 37%
- slowing of ADCS-ADL by 37%
- Cleared amyloid in 80% by 76 weeks
- Clinical benefits were stronger in people with low tau PET burden

1.6% rate of serious ARIA

Sims, J. R. *et al.* Donanemab in Early Symptomatic Alzheimer Disease. *JAMA* **330**, 512–527 (2023).

Implications for practice

Now that anti-amyloid therapies are available, we need to:

- detect MCI or mild dementia
- determine if Alzheimer's is the cause of cognitive decline

  (awareness that biomarker tests must beused to confirm diagnosis)
- explain risks and benefits of anti-amyloid immunotherapy
- refer appropriate patients for consideration of therapy

Primary or referring practitioner: workup

Screen for MCI or Mild Alzheimer's

- History: mild memory loss, most complex ADL intact or needs only a little assistance

- Cognitive testing: could consider anti-amyloid therapy if
  - MoCA: usually > 18
  - Mini-Mental State Exam: > 21
  - Rule out other causes of dementia
- General good health. **Not on anticoagulants**.
- **Able to have safety MRIs**.

If an MRI is ordered for diagnosis, please include GRE or SWI sequences (to assess ARIA risk), and obtain volumetric MRI analysis if possible

Primary or referring practitioner: discussion with patient

Diagnosis of MCI or Mild AD

Alzheimer's will need to be confirmed with a biomarker

e.g., CSF or amyloid PET

- blood tests are emerging but are not yet FDA approved

Best if the neurologist carries out this testing

Treatment will require IV infusions every 2 weeks

Likely costs: Lecanemab costs $26,000 per year. While covered by Medicare, there may be significant copayments for drug, infusions, diagnostic tests, PET scan and the 3 safety MRIs.

What will Memory Clinic/Neurologist do?

Review the workup

Repeat components as needed

Review inclusion/exclusion criteria

Obtain Alzheimer biomarker (CSF or amyloid PET or plasma)

Obtain MRI with GRE or SWI sequences to assess microbleeds

Obtain APOE genotyping to evaluate ARIA risk

Discuss treatment plan with patient and family

Monitoring while on Lecanemab/Donanemab

General health and cognition

Infusion Center manages infusion reactions (up to 26% of patients

Symptoms that might be ARIA -> may need to go to ED

Safety MRIs: weeks 8, 12 and 26

- if significant or symptomatic ARIA –> hold or d/c treatment

New ***anticoagulation or IV tPA*** treatment carries **major risk of intracranial hemorrhage** –

if these are necessary, probably should stop the MAB

Caution advised when interpreting the news reporting of this data

The TRAILBLAZER-ALZ2 trial met all of its primary and secondary endpoints. Most encouragingly, the company reports that nearly half (47%) of the study participants taking donanemab had no decline of cognition and function for one year (compared to 29% on placebo). Donanemab slowed clinical decline by 35% compared to placebo on the primary outcome measure and resulted in 40% less decline in the ability to perform activities of daily living.

For people in the earliest stages of Alzheimer's, these results suggest donanemab will significantly change the course of the disease. Like the other treatments in its class already approved by the FDA, Aduhelm™ and Leqembi™, these results indicate donanemab gives people more time at or near their full abilities to participate in daily life, remain independent and make future health care decisions. Treatments that deliver these benefits are just as valuable as treatments that extend the lives of those with other diseases.

Source: Alzheimer's Association Statement on Donanemab Phase 3 Data | alz.org

Principles of Prescribing for Older Adults

- Start with a low dosage
- Titrate dose upward slowly as tolerated
- Avoid starting multiple medications simultaneously
- When prescribing a new medication ask yourself:
  - Is this necessary?
  - What is the goal of this medication?
  - What are the benefits and what are the risks?
  - Can I address this issue by stopping another medication instead of starting a new one?
  - What are the drug-drug interactions?
  - Can the patient afford it?
  - Can I treat two conditions with one agent?

The Alzheimer's Project Clinical Roundtable facilitated by

ChampionsforHealth.org/alzheimers

Website includes patient/caregiver resources, AVS attachments.
Website updated regularly with most current information

The Alzheimer's Project Clinical Roundtable funded by

www.Dementiacareaware.org

www.sandiegoimperialgwep.com

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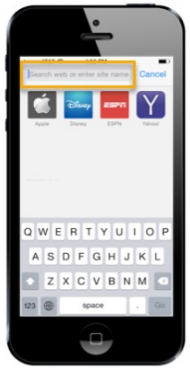
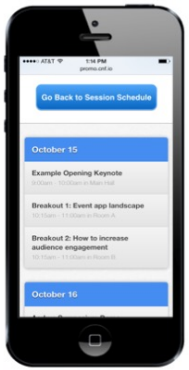


3. Find and Click/Tap on Dementia Update: Disease Modifying Medications for Alzheimer's Disease – Risks & Benefits



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