Major Update in Diagnosis a n d Treatment of A l z h e i m e r D i s e a s e

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Disclosures

- I serve on the Speaker's Bureau for Eisai, Inc, and for Eli Lilly, Inc.
- I have no financial interest in any pharmaceutical company.
- I will mention investigational tests and treatments but will point out their regulatory status.

Agenda

- Discuss recent changes in diagnostic criteria for Alzheimer Disease
- Discuss management of Alzheimer Disease, with a focus on pharmacological management
- Special focus on the new, disease-modifying treatments for Alzheimer Disease

Diagnostic Criteria for Alzheimer Disease

McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer’s disease: Recommendations from the National Institute on Aging and the Alzheimer's Assocation Workgroup. *Alzheimers Dement.* 2011;7:263-269.

Jack CR, Jr., Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement.* 2018;14:535-562.

Jack CR, Jr., Andrews JS, Beach TG. Revised criteria for diagnosis and staging of Alzheimer’s disease: Alzheimer’s Association Workgroup. *Alzheimers Dement.* 2024;20:5143-5169.

“Probable” Alzheimer Disease: 2011 NIA/AA Criteria

- Meets criteria for dementia
- Insidious onset
- Evidence of progression
- Neurological exam is usually normal except for cognition
- Not due to another condition
- Should not be diagnosed when medications are being used which cause cognitive impairment or may contribute to the presence of dementia

Presentations of AD

- Amnestic presentation (usual)
  - Memory loss early and predominant
- Non-amnestic presentations
  - Language presentation
    - “Logopenic aphasia” - extreme difficulty finding words or repeating long sentences, but object knowledge and single-word repetition intact
  - Visuospatial presentation
    - Cortical visual loss - visual exam is normal, but patient can’t seem to see things
  - Executive presentation

Fundamental Principles

- It is necessary to separate syndrome from biology
- AD is defined by its biology with the following implications:
  - The disease is first evident with β-amyloid plaques, and later neocortical tau tangles, while people are asymptomatic
  - In living people the disease is diagnosed by disease specific core biomarkers
  - Unimpaired individuals with abnormal biomarkers are at risk for symptoms due to AD—they are not “at risk” for a disease they already have

Diagnosis of Alzheimer Disease

- AD can be established by abnormality on a single Core 1 biomarker
- At present, the following CSF, plasma, or imaging biomarkers can be diagnostic of AD: amyloid PET, CSF Aβ42/40, CSF p-tau181/Aβ42, CSF t-tau/Aβ42, p-tau 217
- Core 2 biomarkers are not considered standalone tests for diagnosis of AD, but may be combined with Core 1 to stage biological severity and inform on likely rate of progression

Qualifiers on Biological Diagnosis

- Only biomarkers proven accurate should be used (≥90%)
- Clinical judgement is always required
- In the absence of approved interventions for asymptomatic individuals, AD biomarker testing should not be used in asymptomatic individuals
- Treatments targeting core AD pathology in symptomatic persons with biologically confirmed AD should not be initiated without regard to clinical context assessing risk/benefit on an individual level

Core Biomarkers

Biomarker Category	CSF or Plasma	Imaging
Core 1		
A (Aβ proteinopathy)	Aβ42	Amyloid PET
T1 (phosphorylated and secreted AD tau)	P-tau 217, p-tau 181, p-tau 231	
Core 2		
T2 (AD tau proteinopathy)	pT205, MTBR-243, non-phosphorylated tau fragements	Tau PET

Additional Biomarkers

Biomarker Category	CSF or Plasma	Imaging
Biomarkers of non-specific processes involved in AD		
N (injury, dysfunction, or degeneration of neuropil)	NfL	Anatomic MR or CT, FDG PET
I (inflammation) - Astrocytic activation	GFAP	

Additional Biomarkers

Biomarker Category	CSF or Plasma	Imaging
Biomarkers of non-AD co-pathology		
V (vascular brain injury)		Anatomic infarction, WMH
S (α-synuclein)	αSyn-SAA	

Biological Staging of AD

	Initial Stage	Early Stage	Intermediate Stage	Advanced Stage
	(A)	(B)	(C)	(D)
PET	amyloid PET	tau PET medial temporal region	tau PET moderate neocortical uptake	tau PET high neocortical uptake
	A+T-	$A+T_{MTL+}$	$A+T_{MOD+}$	$A+T_{HIGH+}$
Core 1 fluid	CSF Aβ42/40, p-tau181/Aβ42, t-tau/Aβ42 cam establish that an individual is in biological stage A or higher but cannot discriminate among PET stages A-D at present			

Clinical Staging of the AD Continuum

- Stage 0 - Asymptomatic, deterministic gene
- Stage 1 - Asymptomatic, biomarker evidence only
- Stage 2 - Transitional decline: mild detectable change, but minimal impact on daily function
- Stage 3 - Cognitive impairment with early functional impact (MCI)
- Stage 4 - Dementia with mild functional impairment (IADLs only)
- Stage 5 - Dementia with moderate functional impairment (IADLs + ADLs)
- Stage 6 - Dementia with severe functional impairment (fully dependent)

Integrated Biological and Clinical Staging

	Stage 0	Clinical Stage 1	Clinical Stage 2	Clinical Stage 3	Clinical Stages 4-6
Initial biological stage (A)	X	1A	2A	3A	4-6A
Early biological stage (B)	X	1B	2B	3B	4-6B
Intermediate biological stage (C)	X	1C	2C	3C	4-6C
Advanced biological stage (D)	X	1D	2D	3D	4-6D

Do We Always Need Biomarkers?

- Diagnosis can still be made under the 2011 criteria for those people not candidates for treatment with a monoclonal antibody against amyloid (ie, those with moderate-severe dementia)
- At this point, biomarkers should not be used in asymptomatic individuals (ie to predict likelihood of developing dementia in the future)
- Presence of Alzheimer biomarkers does not guarantee the absence of other relevant pathologies, and it’s not possible to gauge the degree to which symptoms are due to Alzheimer Disease vs other pathologies with biomarkers
- Biomarkers define the biological disease, not the clinical syndrome of dementia - dementia remains, and always will remain, a clinical diagnosis

Pharmacological Treatment of Alzheimer Disease

Drug Treatments as of 2022

- Cholinesterase inhibitors (CEIs)
  - Donepezil (Aricept®) - start at 5 mg daily, increase to 10 mg daily
  - Rivastigmine (Exelon®) - start at 1.5 mg BID, increase monthly to 6 mg BID; or 4.6 mg/24 hr patch daily and increase monthly to 13.3 mg/24 hr daily skin patch
  - Galantamine (Razadyne®) - start at 4 mg BID, increase monthly to 12 mg BID
- NMDA Antagonists
  - Memantine (Namenda®) - start 5 mg daily and increase to 10 mg BID
- Combination Drugs
  - Namzaric® (donepezil + memantine)

Brexpiprazole (Rexulti®): An Answer to Managing Agitation?

- Results similar to other antipsychotics, but sponsoring company artfully managed results for presentation to FDA
- Drug has minimal effect on agitation compared to placebo
- Brexpiprazole costs over $1000 per month, compared to $10/month for risperidone
- Brexpiprazole increases risk of death four-fold compared to 1.5 x higher death risk with risperidone
- Read this report from the British Medical Journal: https://www.bmj.com/content/382/bmj.p1801

New Treatments Aimed at AD Biology

- Monoclonal antibodies against Aβ-42 protein
  - Aducanumab (Aduhelm®) - now withdrawn from the market
  - Lecanemab (Leqembi®) - fully approved by FDA
  - Donanemab (Kisunla®) - fully approved by FDA

Monoclonal Antibodies Against Amyloid (MABs)

- Humanized monoclonal IgG1 antibody directed against aggregated soluble forms of Aβ-42 and insoluble forms (lecanemab) or directed against insoluble, “plaque” form of Aβ-42 (donanemab)
- First fully-approved treatments aimed at the unique pathology of AD
- Likely to represent disease-modifying treatments for early AD
- Indicated for treatment of Mild Cognitive Impairment or mild dementia due to Alzheimer Disease

Amyloid Related Imaging Abnormalities (ARIA)

- The “peculiar” side effect of MABs
- ARIA-E (“edema”) - fluid leaking into brain tissue (“swelling”)
- ARIA-H (“hemosiderin”) - blood leaking into brain tissue
  - Micro-hemorrhage, Superficial siderosis

Amyloid Related Imaging Abnormalities (ARIA)

- Can occur spontaneously in Alzheimer Disease, more common in those treated with MABs
- ARIA typically occurs early in course of infusions, is usually asymptomatic, and usually resolves; recurrent ARIA is rare
- Symptoms may include headache, dizziness, increased confusion, difficulty walking, difficulty seeing
- Can be severe or even fatal (uncommon)

Lecanemab

- CLARITY was a Phase 3, randomized, double-blind, parallel-group study of lecanemab vs placebo
- 1795 patients aged 50-90 diagnosed with MCI (2/3) or mild dementia (1/3), defined by MMSE ≥22, randomized to drug or placebo
- Treated with lecanemab 10 mg/kg infusion q2 weeks, for 18 months
- Primary endpoint: CDR-SB

CLARITY Trial

- Inclusion: diagnosis of MCI or mild dementia due to Alzheimer Disease; age 50-90; MMSE ≥ 22; positive amyloid PET or CSF biomarkers
- Exclusion: baseline MRI with pre-existing ARIA, > 4 micro hemorrhages, any area of superficial siderosis, ICH > 1 cm, severe White Matter Hyperintensities

CLARITY Trial

	Lecan	Placebo
Number	898	897
Age	71.4	71.0
Female	51.6	53.0
Amyloid (CL)	77.92	75.03
MMSE	25.5	25.6
CDR-SB	3.17	3.22
ΔCDR-SB	1.21	1.66

CLARITY Trial

- Overall 27% less progression in treated group over 18 months
- All endpoints met statistical significance
- Pre-specified analysis by severity of AD shows greater efficacy in earlier stages of disease

ARIA in CLARITY

	Lecanemab	Placebo
Any ARIA	21.5	9.5
ARIA E	12.6	1.7
Symptomatic ARIA E	2.8	0
ARIA H	17.3	9.0
Symptomatic ARIA H	0.7	0.2

ARIA in CLARITY by ApoE Status

	E4 non carrier	E4 heterozygote	E4 homozygote
ARIA-E	5.4	10.9	32.6
ARIA-H	11.9	14.0	39.0

Donanemab

- TRAILBLAZER-ALZ 2 was a Phase 3, randomized, double-blind, parallel-group study of donanemab vs placebo
- 1736 patients aged 60-85 diagnosed with MCI (1/5) or mild dementia (4/5), defined by MMSE 20-28, randomized to drug or placebo
- Treated with donanemab infusion q4 weeks, for 18 months; initial 3 infusions 700 mg each, subsequent infusions 1400 each
- Amyloid PET done at start of study and every 6 months during study—if amyloid PET became normal, subject was switched to placebo
- Tau PET done at start of study, subjects divided into low-medium tau group, and combined group for data analysis
- Primary endpoint: iADRS

TRAILBLAZER Trial

- Inclusion: diagnosis of MCI (defined as MMSE ≥ 27) or mild dementia due to Alzheimer Disease; age 60-85; MMSE 20-28; positive amyloid PET, positive tau PET
- Exclusion: baseline MRI with pre-existing ARIA, > 4 micro hemorrhages, > 1 area of superficial siderosis, ICH > 1 cm, severe White Matter Hyperintensities

TRAILBLAZER Trial

	Donan	Placebo
Number	860	876
Age	73.0	73.0
Female	57.3	57.4
Amyloid (CL)	103.5	101.6
MMSE	22.4	22.2
CDR-SB	4.0	3.9
ΔCDR-SB	1.72	2.42

TRAILBLAZER Trial

- Overall 35% less progression on iADRS in low-medium tau group over 18 months; 22% less progression in combined group
- All but one endpoint met statistical significance for combined group
- In all measures, low-medium tau group had better efficacy than combined group; “MCI” group had even better efficacy (60% less progression)
- Patients who switched to placebo mid-study: 17% at 6 months, 47% at 12 months - this group had 27% less progression at 18 months

ARIA in TRAILBLAZER

	Donanemab	Placebo
Any ARIA	36.8	14.9
ARIA E	24.0	2.1
Symptomatic ARIA E	6.1	0.1
ARIA H	31.4	13.6

ARIA in TRAILBLAZER by ApoE Status

	E4 non carrier	E4 heterozygote	E4 homozygote
ARIA-E	15.7	27.1	40.6
ARIA-H	18.8	32.3	50.3

TRAILBLAZER-ALZ 6 Trial

- This study explores alternative dosing regimens for donanemab
- 6-month data presented at CTAD: modified dosing using 350 mg - 700 mg - 1050 mg - 1400 mg found almost 50% reduction in ARIA rates

TRAILBLAZER-ALZ 6 Trial

	Standard Dosing	Modified Dosing
Any ARIA	32.4	23.6
ARIA-E	23.7	13.7
ARIA-H	25.1	20.3

Process of Selecting and Treating Patients Using MABs

- Diagnose MCI or mild dementia, MMSE ≥22, aged 50-90 for lecanemab; MMSE 20-28, aged 60-85 for donanemab
- Do not treat if on anticoagulant; if history of stroke within past 12 months; history of immunologic disease (eg lupus, rheumatoid arthritis, Crohn's disease) or systemic treatment with immunosuppressants; treatment with another monoclonal antibody
- Screening MRI to rule out amyloid angiopathy/ARIA
  - Do not treat if >4 micro hemorrhages not related to hypertension, a single macro hemorrhage > 1 cm, severe white matter hyper intensities (Fazekas 3), more than 2 lacunar infarcts, or a single stroke involving major vascular territory

Process of Selecting and Treating Patients Using MABs

- Must prove amyloid is present in brain, using one of three biomarkers:
  - CSF Aβ42/Aβ40 or p-tau 181/Aβ42
  - Amyloid PET
  - Phospho-tau 217 (p-tau 217)
- Recommended to test ApoE genotype, strictly for estimating risk of ARIA

Monitoring for ARIA

- Repeat MRI for any symptoms possibly due to ARIA (dizziness, headache, increased confusion, vision changes)
- If asymptomatic and on lecanemab, surveillance MRI after infusions 4, 6, and 13;
- If asymptomatic and on donanemab, surveillance MRI after infusions 1, 2, 3, and 6;
- Appropriate Use Criteria adds a surveillance MRI at one year (prior to infusion #26), and we plan to do MRI q6 months while on drug

Monitoring for ARIA

Aria-E on MRI	No symptoms	Mild symptoms	Moderate symptoms	Severe symptoms
Mild	Continue dosing	Suspend dosing	Suspend dosing	Discontinue dosing
Moderate	Suspend dosing	Suspend dosing	Suspend dosing	Discontinue dosing
Severe	Discontinue dosing	Discontinue dosing	Discontinue dosing	Discontinue dosing
Aria-H on MRI				
Mild	Continue dosing	Suspend dosing	Suspend dosing	Discontinue dosing
Moderate	Suspend dosing	Suspend dosing	Suspend dosing	Discontinue dosing
Severe	Discontinue dosing	Discontinue dosing	Discontinue dosing	Discontinue dosing

Insurance Coverage for MABs

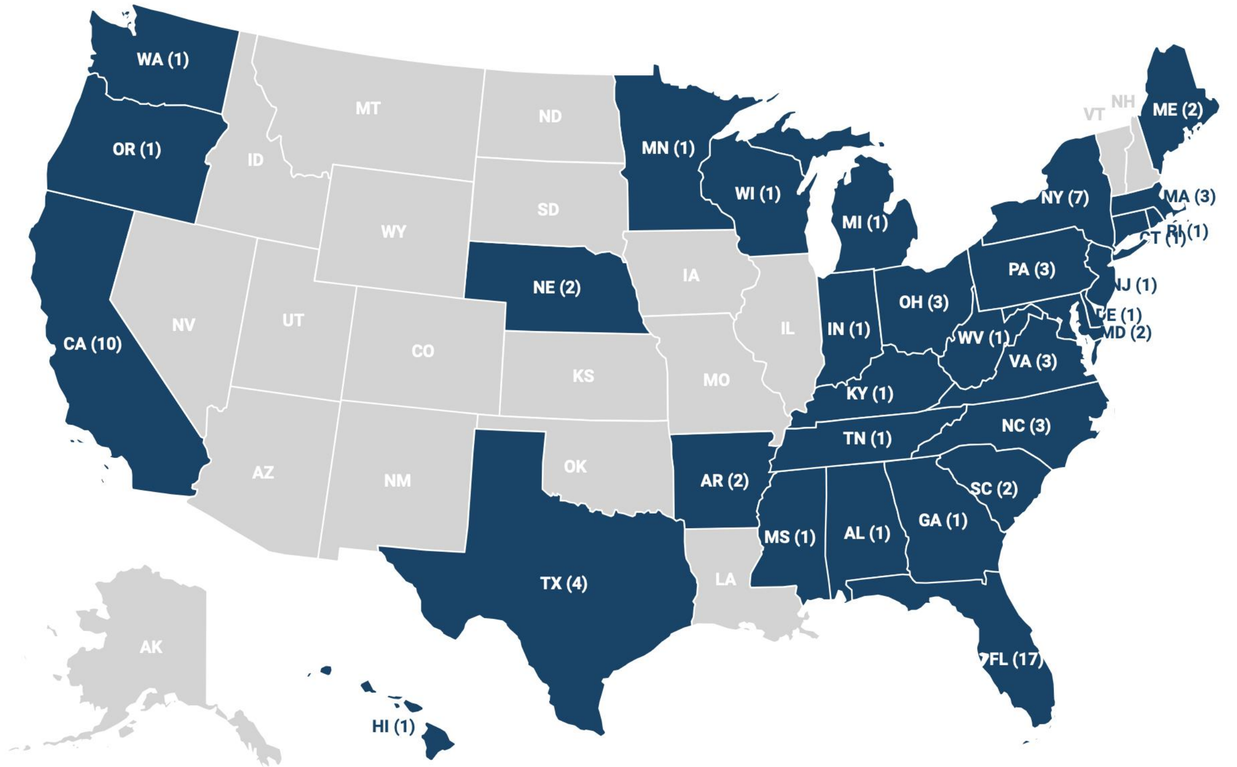
To receive Medicare coverage, people will need to:

1) be enrolled in Medicare,

2) be diagnosed with mild cognitive impairment or mild Alzheimer's disease dementia, with documented evidence of beta-amyloid plaque on the brain, and

3) have a physician who participates in a qualifying registry ("Coverage with Evidence Development" or CED) with an appropriate clinical team and follow-up care.

ALZHEIMER'S NETWORK



Partnering Organizations

ALZHEIMER'S ASSOCIATION

American College of Radiology™

ASNR
American Society of Neuroradiology

School of Public Health
BROWN UNIVERSITY

Do the Monoclonal Antibodies Make the Cholinesterase Inhibitors Obsolete?

Cholinesterase Inhibitors (eg donepezil) remain important treatments for dementia due to Alzheimer Disease, and also for treatment of Dementia with Lewy bodies

Lifestyle modifications (physical exercise, eating “heart healthy,” and staying mentally active) remain crucial for prevention of dementia and to slow or stop progression of Mild Cognitive Impairment

Questions?