Clinical Care Considerations for Disease-modifying Therapies for Alzheimer's Disease

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Disease-modifying Therapies for AD

- **June 2021** – Food and Drug Administration (FDA) grants accelerated approval of aducanumab
- **January 2022** –Centers for Medicare & Medicaid Services (CMS) releases a proposed National Coverage Determination (NCD) decision memorandum
- **April 2022** – CMS releases a national policy for coverage of aducanumab and any future monoclonal antibodies directed against amyloid approved by the FDA with an indication for use in treating AD through coverage with evidence development (CED)
- **January 2023** FDA approves lecanemab via the Accelerated Approval pathway and CMS affirms existing national coverage determination

https://www.fda.gov; https://www.cms.gov

Outline: *Clinical Care Considerations for Disease-modifying Therapies for AD*

1. Current vs. emerging clinical landscape
2. Diagnostic challenges
3. Access, use and interpretation of biomarkers
4. Screening for appropriate patients
5. Therapeutic delivery
6. Safety monitoring
7. Health equity

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Current Clinical Care Landscape

Patient assessment and diagnosis

- Patient presents to clinician with memory concern
- Detailed medical, psychosocial, and functional history obtained
- Physical exam
- Basic labs to rule out other causes of cognitive decline
- Neuroimaging (MRI or CT head) completed
- Contributing factors addressed (e.g., depression, sleep apnea, etc.)
- Assess goals of care, provide caregiver support, identify lifestyle and behavioral interventions

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Current Clinical Care Landscape

Medical therapy

- Medications started: cholinesterase inhibitors and/or NMDA antagonist
- General medication monitoring:
  - Cholinesterase inhibitors: gastrointestinal side effects, slow heart rate, vivid dreams
  - NMDA antagonist: kidney function

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Emerging Clinical Care Landscape

- Assess contraindications to anti-amyloid therapy
- Provide education on disease-modifying therapy
- Order amyloid PET scan or lumbar puncture for cerebrospinal fluid collection to evaluate for elevated amyloid
- Schedule intravenous infusions every 2 weeks
- Schedule monitoring MRIs
- Triage and manage adverse effects from IV disease-modifying therapies (allergic reactions, headaches, abnormal MRI results, dose/rate adjustments)
- Manage rescheduling of infusions, MRIs, etc.

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Emerging Clinical Care Landscape

Development of Appropriate Use Guidelines

- Appropriate patient
- Appropriate treatment and monitoring
- Appropriate patient discussions
- Aducanumab treatment in non-AD amyloid-bearing conditions and atypical AD

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Cummings J et al. J Prev Alzheimers Dis. 2022; 9(2): 221–230.

Appropriate Use Guidelines

Resources needed for the appropriate use of aducanumab (Expert Panel Recommendations)

- Clinicians skilled in the detection and recognition of early AD
- Amyloid PET access or access to individuals with lumbar puncture expertise
- Experts in amyloid PET interpretation or CLIA-certified laboratory available for CSF measurements
- Infusion resources (office/clinic; general infusion center; AD-specific infusion center; home infusion with visiting nurse)
- MRI access
- Experts proficient in recognition of ARIA on MRI
- Experts proficient in clinical recognition and management of ARIA
- Family and patient education and support resources
- Clinicians and staff who deliver culturally competent care
- Genetic counseling available for patients with questions regarding implications of APOE genotyping and interpretation of genetic testing

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Cummings J et al. J Prev Alzheimers Dis. 2021; 8(4): 398–410.

Appropriate Use Guidelines

Participant Feature	Appropriate Use in Clinical Practice
Age	50-85; younger or older patients meeting all other criteria for treatment may be considered candidates for aducanumab
Diagnosis	MCI due to AD or mild AD dementia
Cognitive states	Mild decline of cognition with no or limited impairment of activities of daily living
Amyloid status	Amyloid positive PET (visual read) or CSF findings consistent with AD
Genetic testing	APOE genotype determined
Neurological examination	Non-AD neurological disorders excluded
Cardiovascular history	Stable cardiovascular conditions required
Medical history	Stable medical conditions required; autoimmune disorders or seizures excluded
Psychiatric history	Stable psychiatrically
Clotting status	Patients with bleeding disorders or on anticoagulants excluded
Concomitant medications	Patients can be on standard of care with cholinesterase inhibitors and memantine
Laboratory studies	Normal vitamin B12 level, thyroid, metabolic panel, liver function tests, complete blood count, clotting studies, platelet count, erythrocyte sedimentaton rate, C-reactive protein
Baseline MRI	None of the following: Acute or subacute hemorrhage or macrohemorrhage, cortical infarction larger than 1.5 cm, one lacunar infarction larger than 1.5 cm, more than four microhemorrhages, more than one area of superficial siderosis, extensive white matter disease indicative of ischemic injury
Informed consent	Patient and care partner must understand the nature and requirements of therapy & expected outcoms

Cummings J et al. J Prev Alzheimers Dis. 2022; 9(2): 221–230.

Diagnostic Challenges

- Significant shortage of physicians in the US with expertise in diagnosing and managing persons with ADRD (geriatricians, neurologists, and psychiatrists)
- PCPs are frequently called on to diagnose and treat individuals with ADRD despite 40% reporting being somewhat uncomfortable making a diagnosis

- Alzheimer's Association. 2020 Alzheimer's disease facts and figures. Alzheimers & Dementia;16:391-460
- U.S. Department of Health and Human Services HRSA, National Center for Health Workforce Analysis. . Health Workforce Projections: Neurology Physicians and Physician Assistants. 2017.
- U.S. Department of Health and Human Services HRSA, National Center for Health Workforce Analysis. National and Regional Projections of Supply and Demand for Geriatricians: 2013-2025. Rockville, Maryland. 2017.

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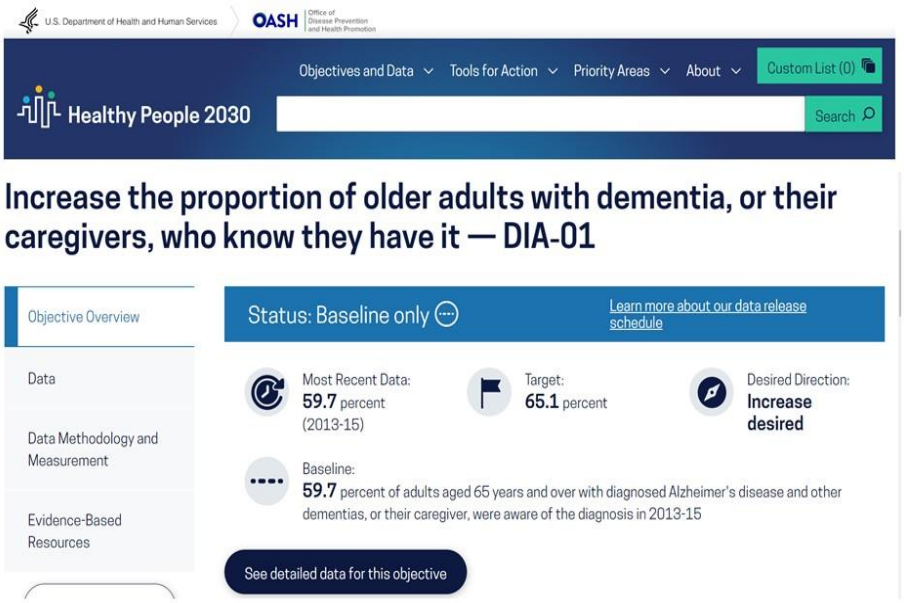
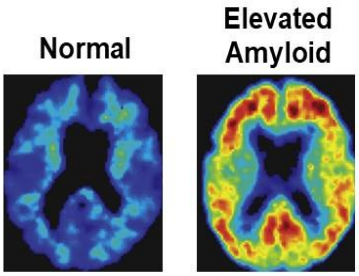
Diagnostic Challenges



https://health.gov/healthypeople/objectives-and-data/browse-objectives/dementias

Access, Use and Interpretation of Biomarkers

- Up to 40% of patients diagnosed with early AD may not have amyloid pathology when studied with amyloid imaging
- Access to amyloid PET imaging or lumbar puncture for cerebrospinal fluid collection
- Plasma biomarkers will increase access to amyloid testing
- Clinicians will need to learn how to interpret biomarkers
- Questions about how to interpret mixed pathology



Sevigny J, et al. *Alzheimer Dis Assoc Disord*. 2016;30:1–7
Vitali et al. *Semin Neurol*. 2008;28(4):467-483.

Screening for Appropriate Patients

- **Prescribing information:** LEQEMBI should be initiated in patients with mild cognitive impairment (MCI) or mild dementia stage of disease, ***the population in which treatment was initiated in clinical trials.***
- Participants were 50 to 90 years of age (few individuals were <65 or >80 years old)
- Amyloid positivity determined by PET or cerebrospinal fluid Aβ1–42
- Mini mental state examination (MMSE) score >=22 at Screening and Baseline and <=30 at Screening and Baseline
- Body mass index (BMI) >17 and less than <35 at Screening
- Able to have an MRI scan

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Leqembi Prescribing Information. 1/2023

van Dyck CH et al. N Engl J Med 2023;388:9-21. DOI: 10.1056/NEJMoa2212948

Screening for Appropriate Patients

Clarity AD Study had numerous exclusion criteria:

- Any neurological condition that may be contributing to cognitive impairment
- History of transient ischemic attacks (TIA), stroke, or seizures within 12 months
- Any psychiatric diagnosis or symptoms (example, hallucinations, major depression, or delusions) that could interfere with study procedures
- Geriatric Depression Scale (GDS) score >=8 at Screening
- Contraindications to MRI scanning
- Evidence of other clinically significant lesions on brain MRI that could indicate a dementia diagnosis other than Alzheimer's disease
- Other significant disease findings on brain MRI at screening
- Any immunological disease which is not adequately controlled, or which requires treatment
- Participants with a bleeding disorder or who are on anticoagulant therapy

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https://clinicaltrials.gov/ct2/show/NCT03887455

Screening for Appropriate Patients

- Translating clinical trial results (risks/benefits) into tangible examples that are clinically meaningful to persons living with Alzheimer's disease and their caregivers
- Developing goals of care
- Mobilizing interdisciplinary teams to help with education

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Rentz DM, et al. Alzheimers Dement (N Y). 2021 Jun 26;7(1):e12181.
Cohen S et al. J Prev Alzheimers Dis. 2022;9(3):507-522.
van Dyck CH et al. N Engl J Med 2023;388:9-21. DOI: 10.1056/NEJMoa2212948

Therapeutic Delivery

- Currently given IV every 2 weeks, weight-based dosing
- Subcutaneous therapies under investigation, but not yet proven effective
- Challenges of scheduling through infusion clinics
- Staffing needs in infusion clinics
- Will home-based infusions be available? Currently being studied in clinical trials
- Home-based infusions could increase access, but may be limited by staffing availability

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Safety Monitoring

- Need for increased MRI access – instead of just one diagnostic MRI, individual may have 4 or more MRIs for monitoring
- Need neuroradiologists with expertise in interpreting Amyloid Related Imaging Abnormalities (ARIA) edema and microbleeds
- Will need training of physicians, nurses, emergency medicine providers, home health aids, caregivers on when to seek medical attention for symptoms of headache, confusion, visual changes, dizziness, nausea, and gait difficulty
- Physicians and infusion clinics will need training on managing infusion reactions (dose adjustment, pre-medications, etc.)

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Safety Monitoring

- Development of clinical radiology guidelines to standardize monitoring approaches: *Amyloid-Related Imaging Abnormalities with Emerging Alzheimer Disease Therapeutics: Detection and Reporting Recommendations for Clinical Practice*
- The Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) - a voluntary provider-enrolled patient registry that collects information on treatments for Alzheimer's disease (www.alz-net.org)

ALZHEIMER'S NETWORK

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Cogswell PM. AJNR AmJNeuroradiol 43:E19–E35 Sep 2022

Health Equity

- Continued low rates of racial and ethnic diversity in AD clinical trials
- Barriers to diagnostic and other healthcare services for dementia care
- Difficulty with access to PET scans, lumbar punctures, infusion centers in rural areas
- Transportation difficulties
- Health literacy challenges

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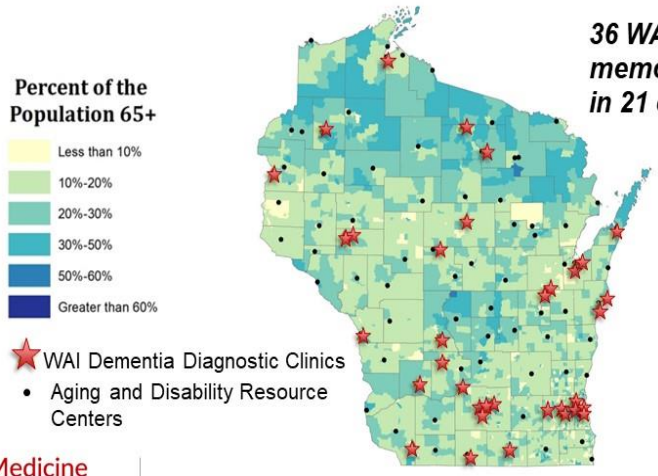
Wisconsin Alzheimer's Institute's (WAI) Dementia Diagnostic Clinic Network



36 WAI-affiliated memory clinics in 21 counties

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Maria Mora Pinzon, MD, MS, FACPM

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Maps courtesy of William Buckingham, PhD

Future Directions

- Expansion of initiatives to improve diagnosis of MCI and dementia in primary care
- Training of PCPs in use and interpretation of AD biomarkers (PET and cerebrospinal fluid)
- Research to optimize accuracy of blood-based biomarkers in the diagnosis amyloid pathology
- Continued revisions of appropriate use guidelines based on continued safety data collection
- Continued research on subcutaneous formulations and/or home infusions to improve access
- Continued study on translating clinical trial outcomes into “clinically meaningful” information to inform patient decision-making

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