University of Maryland Medical System

Alzheimer's Disease Pharmacotherapy:
Anti-amyloid therapy and treatment updates

Millad J. Sobhanian, PharmD, BCPS
Clinical Pharmacy Specialist, Neurology
University of Maryland Medical System
Millad.Sobhanian@umm.edu

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Objectives

- Review pharmacology of Alzheimer's disease with focus on anti-amyloid therapies
- Identify notable risks, screening, and monitoring requirements for anti-amyloid therapies
- Design a framework for integrating anti-amyloid therapies into practice and highlight new and emerging areas of interest for AD treatment

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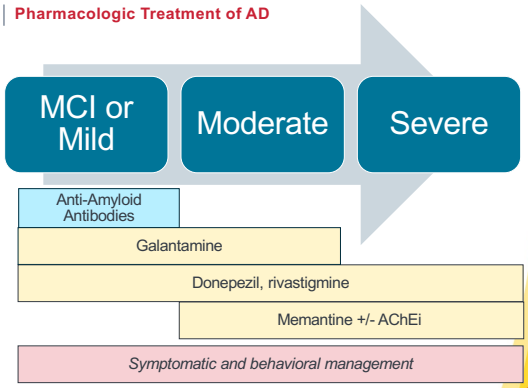
Pharmacologic Treatment of AD



AD = Alzheimer's Disease; MCI = mild cognitive impairment; AChEi = acetylcholinesterase ezyme inhibitor
J Control Release. 2024 Mar:367:402-424

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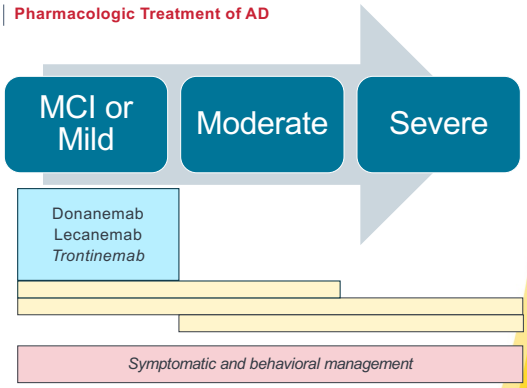
Pharmacologic Treatment of AD



AD = Alzheimer's Disease; MCI = mild cognitive impairment; AChEi = acetylcholinesterase ezyme inhibitor
J Control Release. 2024 Mar:367:402-424

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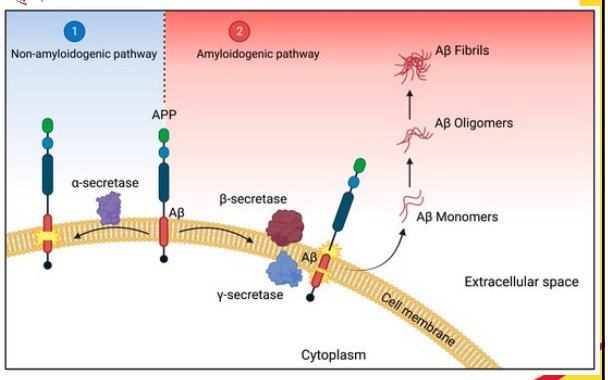
Amyloid physiology and pathology in Alzheimer's Disease



APP = amyloid precursor protein; AD = Alzheimer's Disease; Aβ = amyloid beta
Int J Mol Sci. 2023 Feb 15;24(4):3895.

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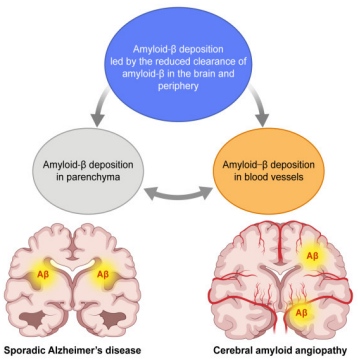
Amyloid physiology and pathology in AD



AD = Alzheimer's Disease; Aβ = amyloid beta
Biol Psychiatry. 2018 Feb 15;83(4):311-319.

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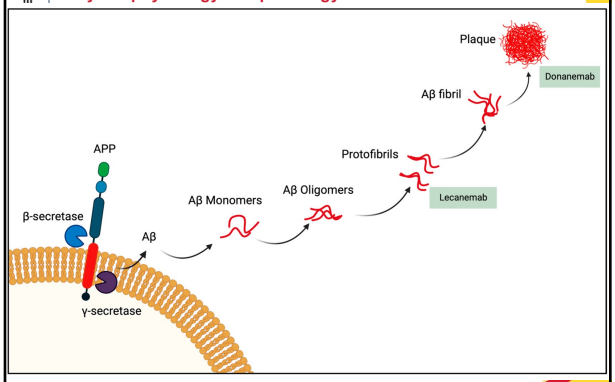
Amyloid physiology and pathology in Alzheimer's Disease



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Int J Mol Sci. 2023 Feb 15;24(4):3895.

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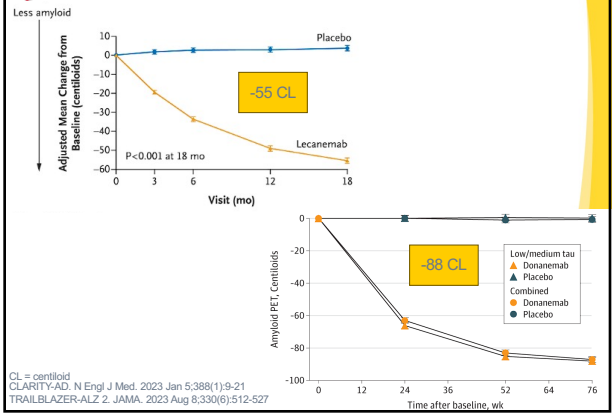
Anti-Amyloid antibodies - Change in Amyloid Burden



CL = centiloid
CLARITY-AD. N Engl J Med. 2023 Jan 5;388(1):9-21
TRAILBLAZER-ALZ 2. JAMA. 2023 Aug 8;330(6):512-527

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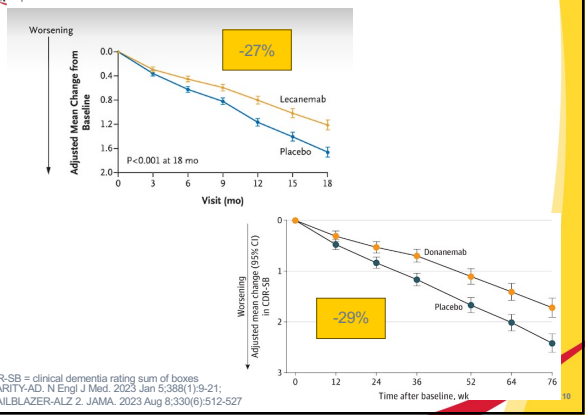
Anti-Amyloid antibodies - Change in Rate of Decline



CDR-SB = clinical dementia rating sum of boxes
CLARITY-AD. N Engl J Med. 2023 Jan 5;388(1):9-21;
TRAILBLAZER-ALZ 2. JAMA. 2023 Aug 8;330(6):512-527

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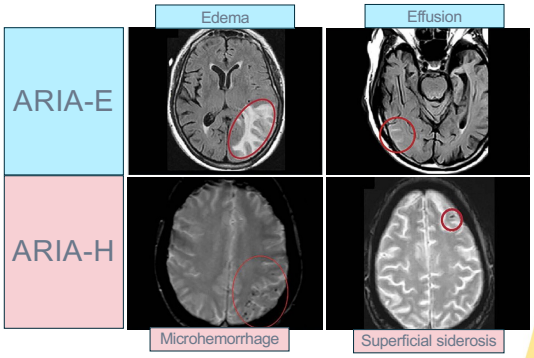
Amyloid-related Imaging Abnormalities (ARIA)



ARIA = amyloid-related imaging abnormalities;
ARIA-E = ARIA with edema; ARIA-H = ARIA with hemosiderin deposits
Brain. 2023 Nov 2;146(11):4414-4424.

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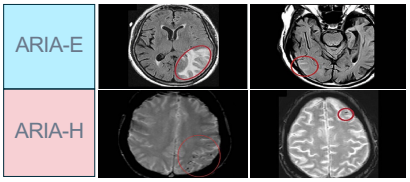
Anti-amyloid therapies – Rate of ARIA in Pivotal Trials



	Lecanemab	Donanemab
ARIA	21.5%	36.8%
ARIA-E	12.6%	24%
ARIA-H	17.3%	31.4%
Symptomatic ARIA-E	2.8%	6.1%

ARIA = amyloid-related imaging abnormalities;
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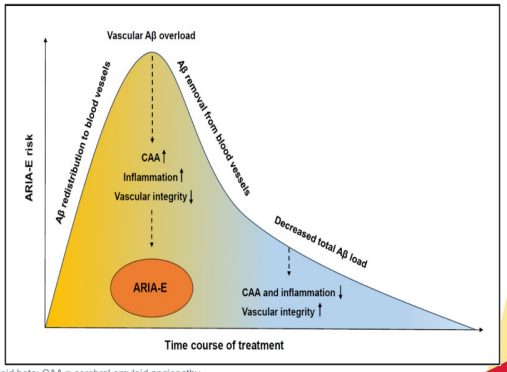

AB = amyloid beta; CAA = cerebral amyloid angiopathy
ARIA = amyloid-related imaging abnormalities; ARIA-E = ARIA with edema
Alzheimers Res Ther. 2026 Mar 28;18:79.

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ARIA Risk Factors

- Apolipoprotein E4 genotype
- Dose-dependence
- Baseline Amyloid Burden
- Antithrombotic use
- Cerebrovascular disease
- Hypertension

ARIA = amyloid-related imaging abnormalities
J Prev Alzheimers Dis.. 2022;9(2):211-220

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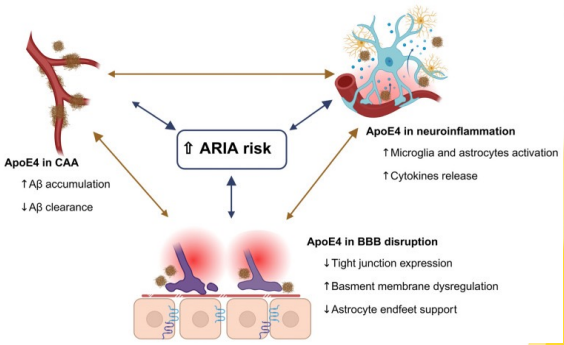
Apolipoprotein E4 Genotype – AD and ARIA Severity



ARIA = amyloid-related imaging abnormalities; CAA = cerebral amyloid angiopathy; BBB = blood brain barrier
ApoE4 = apolipoprotein E4; AD = Alzheimer's disease
Lancet Neurol. 2021 Jan;20(1):68-80.

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Apolipoprotein E4 Genotype – Risk Magnitude

AD Risk Relative to non-carrier:

- 1 allele (heterozygous, ε3/ε4) increase by ~1-2 fold
- 2 alleles (homozygous, ε4/ε4) increase by ~3-4 fold

	Genotype	Donanemab	Lecanemab
Any ARIA	ε3/ε3	22%	13%
	ε3/ε4	35%	19%
	ε4/ε4	58%	45%

	Genotype	Donanemab	Lecanemab
Symptomatic ARIA	ε3/ε3	3%	1.4%
	ε3/ε4	5%	1.7%
	ε4/ε4	12%	9.2%

ARIA = amyloid-related imaging abnormalities
Lancet Neurol. 2021 Jan;20(1):68-80.

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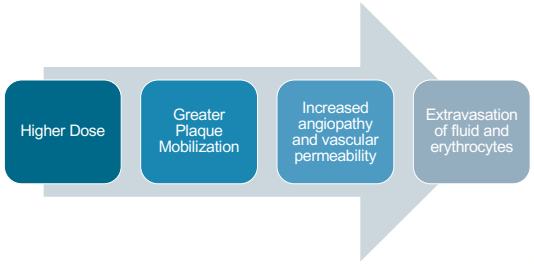
ARIA Risk Factors – Dose-Dependence



Lecanemab Dose	2.5 mg/kg	5 mg/kg	10 mg/kg
ARIA-E	1.9%	3.3%	9.9%

ARIA-E = amyloid-related imaging abnormalities with edema
J Prev Alzheimers Dis.. 2022;9(2):211-220; Alzheimers Dement (N Y). 2023 Mar 20;9(1):e12377

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ARIA Risk Factors – Dose-Dependence - Donanemab

1:1:1:1 Randomization stratified by APOE and by baseline amyloid — Primary Outcome

Visit number	1	2	3	4	5	6	7	8	9	10	11	12
Study week	Screening	0	2	4	6	8	10	12	14	16	20	24
Standard		700	PBO	700	PBO	700	PBO	1400	PBO	1400	1400	1400
Modified titration		350	PBO	700	PBO	1050	PBO	1400	PBO	1400	1400	1400
Dose skipping		700	PBO	PBO	PBO	1400	PBO	1400	PBO	1400	1400	1400
Cmax		350	350	350	350	350	350	700	700	1400	1400	1400
Amyloid PET scan	√											√
MRI	√			√				√				√

350 = 1 x 350 mg vial
700 = 2 x 350 mg vials
1050 = 3 x 350 mg vials
1400 = 4 x 350 mg vials

	Standard	Modified
N	208	**212**
Any ARIA	32.4%	**23.6%**
ARIA-E	23.7%	**13.7%**
ARIA-H	25.1%	**20.3%**

TRAILBLAZER-ALZ 6.J Prev Alzheimers Dis. 2025 Sep;12(8):100266

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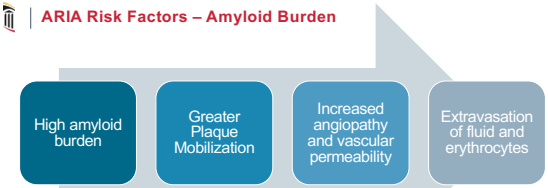
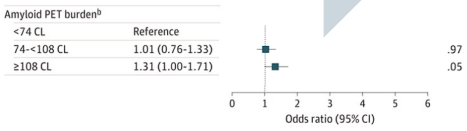
ARIA Risk Factors – Amyloid Burden





- Favors mild disease and early initiation

CL = centiloids; ARIA = amyloid related imaging abnormalities
J Prev Alzheimers Dis. 2022;9(2):211-220; JAMA Neurol. 2025 May 1;82(5):461-469.

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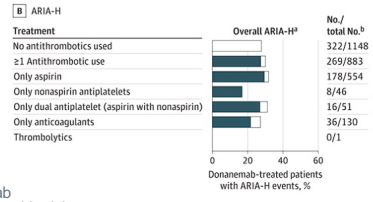
ARIA Risk Factors – Antithrombotic use



- Donanemab
  - Comparable risk
  - No deaths involving antithrombotic use
- Lecanemab
  - Higher risk of macrohemorrhage with anticoagulation
    - 2.7% vs 0.6% incidence
    - At least 1 death involving exposure
- Majority aspirin monotherapy
- Anticoagulant exposure limited – *not currently recommended*

ARIA = amyloid related imaging abnormalities with hemosiderin deposit
J Prev Alzheimers Dis.. 2022;9(2):211-220; JAMA Neurol. 2025 May 1;82(5):461-469.; Alzheimers Res Ther. 2026 Mar 28;18(1):79

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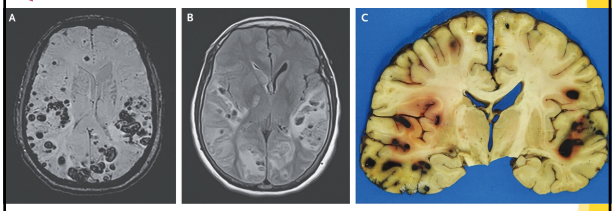
ARIA Risk Factors – Antithrombotic use – Thrombolytics



- 65-year-old, homozygous early AD
- 3 doses of lecanemab
- Acute onset - aphasia and L gaze preference; ischemic stroke
- Received alteplase > developed extensive multi-focal IPH
- Donanemab – fatality after thrombolytic with severe ARIA-E
- **Thrombolytics relative contraindication**

IPH = intraparenchymal hemorrhage; ARIA-E = amyloid related imaging abnormalities with edema
N Engl J Med. 2023;388(5):478-479.; Alzheimers Res Ther. 2026 Mar 28;18(1):79

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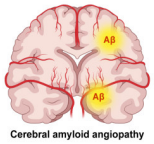
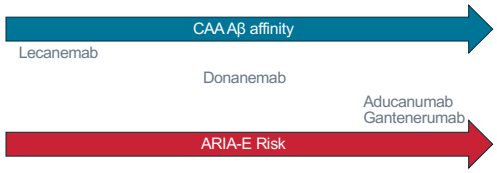
ARIA Risk Factors – Cerebrovascular Disease



Cerebral amyloid angiopathy

- Higher vascular amyloid burden
  - Vessel wall weakening
  - Increased permeability
- Transient CAA exacerbation



CAA = cerebral amyloid angiopathy; Aβ = amyloid beta; ARIA = ARIA with edema
Neurology. 2019;92(24):1146-1156.; Sci Rep. 2024;14(1):10868.

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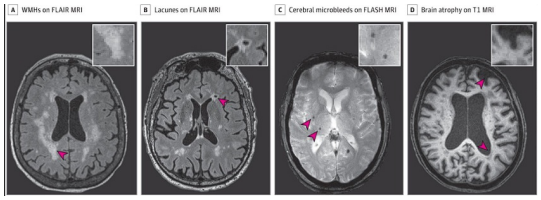
ARIA Risk Factors – Cerebrovascular Disease



- White Matter Hyperintensities (WMH)
  - WMH Burden and ARIA(+) = OR 2.813, CI 1.8-8.44
  - Severe WMH excluded from trials
- Recent stroke/TIA excluded
  - Cytotoxic edema + vascular injury = ARIA risk ↑
- Cerebral microbleeds and superficial siderosis – excluded from trials
  - Markers of CAA
  - Pre-existing vascular damage

WMH = white matter hyperintensities; CAA = cerebral amyloid angiopathy; ARIA = amyloid related imaging abnormalities
Neurology. 2019;92(24):1146-1156.; Sci Rep. 2024;14(1):10868.

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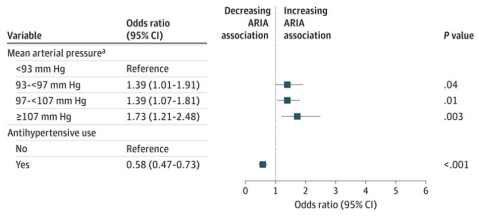
ARIA Risk Factors – Hypertension – Modifiable Risk Factor



- Hypertension may compromise vessel integrity
- Only identified risk factor for donanemab, not lecanemab

J Prev Alzheimers Dis.. 2022;9(2):211-220; JAMA Neurol. 2025 May 1;82(5):461-469.
Alzheimers Res Ther. 2026 Mar 28;18(1):79

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Anti-amyloid therapies

	Lecanemab	Donanemab
Dosing	Every 2 weeks	Every 4 weeks
MRI frequency	4 within 6 months of initiation	
Efficacy (18 months)		
Rate of Decline	27% on CDR-SB	29% on CDR-SB
Amyloid Reduction	55.5 centiloids	88.0 centiloids
ARIA	21.5%	36.8% (23.6%)
ARIA-E	12.6%	24% (13.7%)
ARIA-H	17.3%	31.4% (20.3%)
Symptomatic ARIA-E	2.8%	6.1%

ARIA = amyloid related imaging abnormalities with (E)dema or (H)emosiderin deposits
CDR-SB = clinical dementia rating sum of boxes

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Identifying Candidates - Baseline Assessment and Screening

☑ MCI or Mild AD	Clinical Stage 3-4	MMSE 20-30	Primary AD
Amyloid (+)	Absence of MRI contraindications	Reliable Care Partner	

APOE Homozygosity	Anti-platelet Agents	Seizure Disorder
Immunologic Disorders	Hematologic Disorders	Unstable medical Conditions

Mod-Severe AD	Clinical Stage 5+	>4 Cerebral Microbleeds
☒ Superficial Siderosis	Major cerebrovascular burden	CAA-ri
Other Structural Abnormality	Concomitant Anticoagulation	Mixed AD

AD = Alzheimer's dementia; MMSE = mini-mental status exam;
CAA-ri = cerebral amyloid angiopathy related inflammation
J Prev Alzheimers Dis. 2023;10(3):362-377.; *J Prev Alzheimers Dis.* 2025;12(5):100150.

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Identifying Candidates - Confirm AD

- Cognitive screening – MMSE, MoCA
  - Functional testing (iADL, FAQ)
- Rule out reversible causes of cognitive impairment
  - Thyroid function
  - Metabolic imbalance
  - Infection
  - Medication
- Brain imaging
- Biomarker confirmation
  - Amyloid PET ("Gold-standard")
  - CSF
  - Blood based biomarkers

AD = Alzheimer's disease; MMSE = mini-mental status exam; MoCA = Montreal cognitive assessment
iADL = activities of daily living; FAQ = functional activities questionnaire
J Prev Alzheimers Dis. 2023;10(3):362-377.; *J Prev Alzheimers Dis.* 2025;12(5):100150.

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Blood Based Biomarkers

- Aβ42/40 (MS, IA)
- P-tau217 (MS, IA)
- P-tau217/Aβ42ratio (IA)
- *P-tau231 (IA)*
- *P-tau181 (IA)*

Note: several brands available for each assay

MS = mass spec; IA = immunoassay
Alz Dement. 2025; 21(7):e70535.

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Blood Based Biomarkers – Alzheimer's Association Guideline

- **Triaging test** (high-sensitivity):
  - Negative rules out AD pathology, high probability
  - Positive requires confirmatory test
  - **90% sensitivity and 75% specificity**
- **Diagnostic test** (high sensitivity and high specificity)
  - Negative rules out AD, high probability
  - Positive confirms pathology, high probability
  - **90% sensitivity, 90% specificity**

Note: reference standard of Amyloid PET, CSF, AD neuropathology

AD = Alzheimer's disease
Alz Dement. 2025; 21(7):e70535.

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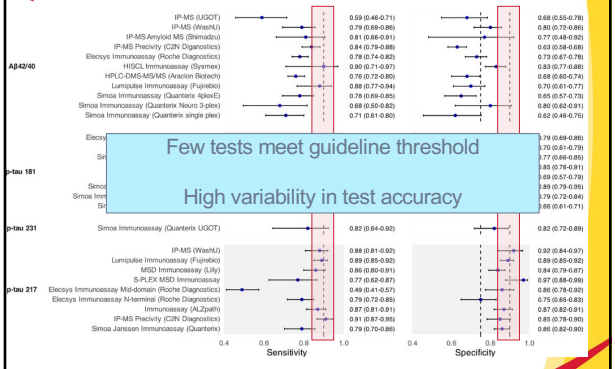
Blood Based Biomarkers – Meta-analysis



Alz Dement. 2025; 21(11):e70828.

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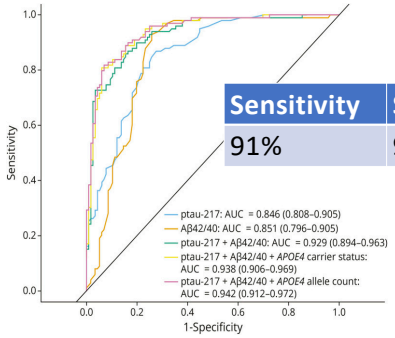
Blood Based Biomarkers – Multi-marker Prediction Tool



Sensitivity	Specificity
91%	91%

AB = amyloid beta
Neurol Clin Pract. 2025;15(6):e200546.

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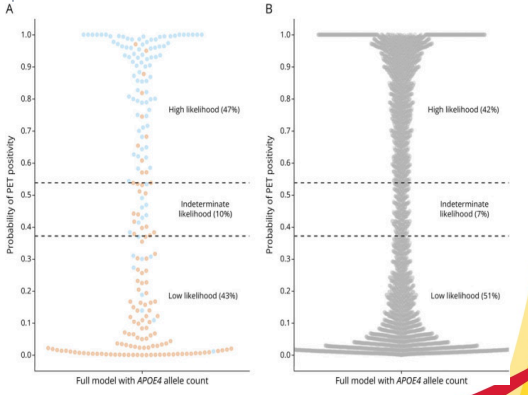
Blood Based Biomarkers – Multi-marker Prediction Tool



Neurol Clin Pract. 2025;15(6):e200546.

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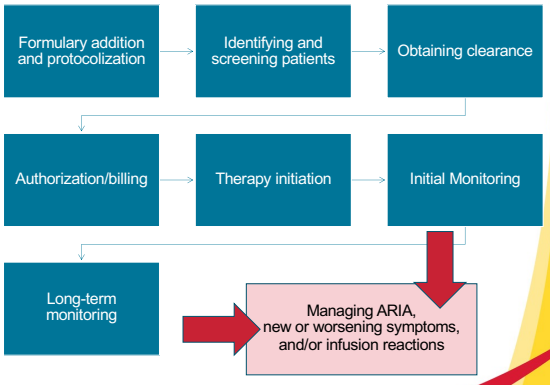
Implementation of Anti-amyloid Therapy: Roadmap



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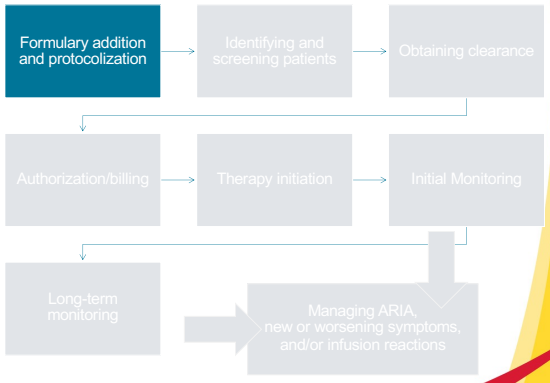
Implementation of Anti-amyloid Therapy: Roadmap



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Formulary addition and protocolization

Considerations for formulary addition
- Efficacy and safety – risks vs benefit
- Cost-consideration
- Site of administration
- Availability of chair space

Establishing clear guidelines for use
- Screening requirements
- Documentation of clearance and consent

Documentation for billing
- CMS registry information
- Prior authorization checklist

Workflow and protocols
- Scheduling infusion/imaging
- Communicating urgent/emergent findings on imaging
- Screening questions prior to infusion

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Example: Documentation

The following pre-LECANEMAB screening has been reviewed:

☐ Cognitive testing completed and confirmed MCI associated with AD***OR Mild dementia stage of AD***OR moderate to severe dementia stage of AD
- Test utilized: ***(e.g. MMSE, MoCA)
- Score:***
- Date of testing:***

☐ Disability testing (e.g. FAQ, Global CDR, ADL/iADL)
- Test utilized: ***
- Score:***
- Date of testing:***

☐ Confirmed amyloid pathology
- Amyloid PET: *** ; OR
- CSF: ***
- Date of testing:***

☐ Completed APOE genotyping and is NOT homozygous for APOE
- Test result:***
- Date of testing:***

☐ Ruled out contraindications by clinical history and drug interactions
- Patient does NOT have recent history of stroke/TIA or ICH in the past 12 months or any history of seizures
- Patient is NOT taking concomitant anticoagulation
- Patient does NOT have documented history of bleeding disorder or coagulopathy
- Patient does NOT have evidence of additional contraindication as described in UMHS formulary restriction criteria

☐ Patient has MRI completed within 1 year of starting therapy
- There is NO evidence of imaging abnormality suggesting non-AD dementia
- There is NO evidence of microhemorrhages, macrohemorrhage, vasogenic edema, ARIA, CAA-ri, or other major intracranial pathology that would otherwise preclude treatment with lecanemab

☐ Patient has been enrolled in CMS registry for ***
- ☐ Date enrolled:***
- ☐ CED study registry submission number:***

☐ Patient has a care partner or family member who can ensure that the patient has the support needed to be treated with lecanemab
- Name of supporting care partner(s) or family member(s):***

☐ Patient, care partners, and family member have been provided with a copy of medication guide for reference

☐ Patient, care partners, and family members have been counseled and understand the requirements for lecanemab therapy as well as the potential benefit and harm of treatment

Patient has been counseled on the risks/benefits of the medication. Patient verbalized understanding and provided ***(VERBAL or WRITTEN) consent to lecanemab treatment.

Patient has completed all the required screening and is cleared to start LECANEMAB infusions.

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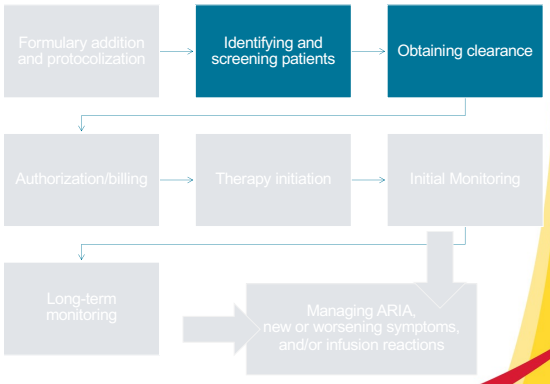
Implementation of Anti-amyloid Therapy: Roadmap



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Identifying, Screening, and Clearing Patients

Initial Screening
- Not required to be completed by specialist
- Smart-set development
- Workflow for screening and patient identification
- Identify and address barriers to access

Initial counseling and eligibility determination
- Thorough counseling on process/expectation and costs
- Provide written education
- Establish care partner
- Assess ability for treatment/monitoring adherence
- Obtain and document consent

Additional testing and counseling
- Genetic counseling for ApoE homozygotes
- Repercussions of gene testing
- Neuropsychiatric testing

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Pre-screening Considerations

Confirmatory testing
- MoCA 18+
- MMSE 22+
- Neuropsychological testing

APoE Gene Testing

Baseline MRI (<1 yr)

Absolute/Relative Contraindications
- History of stroke/TIA 12 months
- Concomitant AC or DAPT
- History of bleeding disorder/coagulopathy
- CAA or ABRA
- Imaging abnormality
- APoE carrier
- Other medical conditions likely to cause cognitive impairment

Amyloid screening
- CSF
- Amyloid PET
- *Blood based biomarkers*

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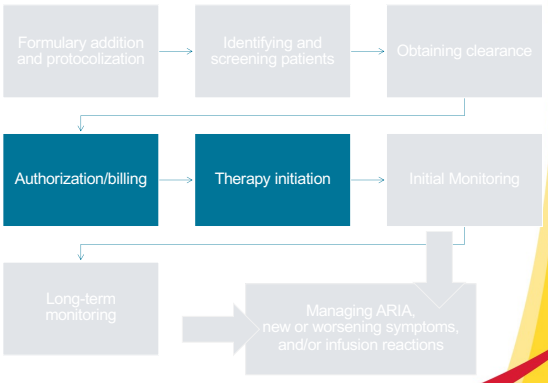
Implementation of Anti-amyloid Therapy: Roadmap



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Obtaining authorization and therapy initiation

Documentation for billing
- Prior authorization checklist
- CMS registry enrollment – REQUIRED
- Clearance note placement

Infusion initiation
- Provider to place orders (e.g. therapy plan) - discoverable
- Infusion center to obtain authorization
- Consider 'screening' external centers
- Provide patient 'drug card'

Advanced scheduling
- Consider scheduling infusion to 2nd MRI
- Provide patient copy of schedule (template/tracker)
- Build into therapy plans or smartest
- Include 'hard-stops' on orders

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CMS Registry – Required information

- Provider's NPI
- Patient's Medicare Beneficiary Identification Number
- Provider's contact information
- Clinical diagnosis and date
  - Mild cognitive impairment or mild-Alzheimer's dementia
- Confirmatory amyloid testing and date
  - Amyloid PET
  - CSF testing
- Cognitive testing and date
  - MoCA (Montreal Cognitive Assessment)
  - MMSE (Mini-mental Status Exam)
- Functional testing and date
  - FAQ (Functional Activities Questionnaire)
- Anticoagulant and/or antiplatelet use
- Monoclonal antibody used
- Presence or absence of ARIA and date of confirmatory imaging

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Example: Care Team mAb tracker

mAb / MRI Patient Tracker:

*Infusions are every X weeks for 18 months. MRIs are to be completed prior to specific infusion numbers.

Consent Form (date): _____

	Date/time:
1st infusion	
2nd infusion	
3rd infusion	
4th infusion	
MRI	Location:
5th infusion	
6th infusion	
MRI	Location:
7th infusion	
8th infusion	

Helpful phone numbers:
XYZ Clinic: 804-555-0000
Radiology Scheduling: 804-555-0001
NOW infusion: 804-555-0002
SPP Infusion: 804-555-0003
ABC Infusion Scheudling: 804-555-0004
ABC infusion Pharmacy:804-555-0005

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Example: Patient Wallet Card and Appointment tracker

I AM TAKING (Anti-Amyloid mAb)

Prescribed by: _____

Infusion 1	Infusion 2
Date:	Date:
Time:	Time:
Location:	Location:
Contact Details:	Contact Details:
MRI #1	**Infusion 5**
Date:	Date:
Time:	Time:
Location:	Location:
Contact Details:	Contact Details:

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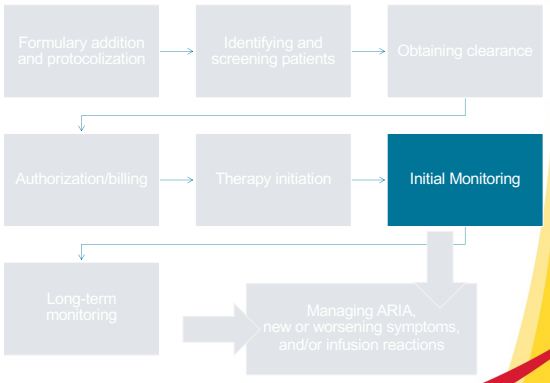
Implementation of Anti-amyloid Therapy: Roadmap



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Initial Monitoring

Infusion monitoring and screening

- Pre-infusion questionnaire (e.g. ARIA, AC/AP, imaging)
- Document clearance for MRI
- Utilize and update appointment tracker
- Empower patient/caregiver to self-monitor/notify

Obtaining clearance

- Neuroradiologist to document imaging findings
- Clear path for communicating emergent findings
- Ordering provider to document clearance
- Nurse and/or pharmacists as final check point

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MRI Schedule Monitoring

ARIA MRI Schedule (Lecanemab)

Symptoms: headache, dizziness, confusion, visual changes, nausea, gait disturbances

Serious and severe ARIA: seizure, encephalopathy, stupor, focal neurological deficits

Monitor for ARIA symptoms with each MRI

Mild: discomfort not impacting daily activity
Moderate: discomfort impacting daily activity
Severe: Incapacitating pain and discomfort

ARIA = amyloid related imaging abnormalities
JAMA Intern Med. 2025;185(8):1029-1031.

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Example Infusion Note Template and Nurse Script

New or worsening symptoms concerning for ARIA:

- Difficulty walking: {YES /NO:21278}
- Loss of balance: {YES /NO:21278}
- Confusion: {YES /NO:21278}
- Dizziness: {YES /NO:21278}
- Weakness or sensory-loss: {YES /NO:21278}
- Speech, vision, and/or hearing problems: {YES /NO:21278}
- Fainting or passing out: {YES /NO:21278}
- Seizures: {YES /NO:21278}
- Headache: {YES /NO:21278}
- Nausea: {YES /NO:21278}

IF YES TO ANY OF THE ABOVE DO NOT INFUSE AND NOTIFY PROVIDER (delete after assessing)

Has the patient started or currently taking any anticoagulants or antiplatelets? {YES /NO:21278}

IF YES DO NOT INFUSE AND NOTIFY PROVIDER (delete after assessing), patients are okay to infuse if taking antiplatelet monotherapy (e.g. aspirin)

Prior to 5th, 7th, and 14th infusion, has patient completed MRI and cleared for infusion by provider? {YES /NO:21278}

IF NO DO NOT INFUSE AND NOTIFY PROVIDER (delete after assessing)

Patient has been enrolled in CMS registry for NCT06058234

- Date enrolled: ***
- CED study registry submission number: ***

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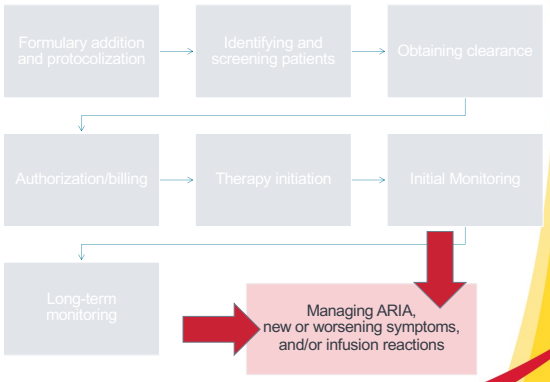
Implementation of Anti-amyloid Therapy: Roadmap



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Managing Infusion reactions and ARIA

Infusion or hypersensitivity reactions
- Non-specific reactions
- PRN administration
- Pretreat subsequent

ARIA or related symptoms
- Protocol for nurse identification and management
- Differentiate severity
- Continue vs suspend vs discontinue

Emergency management
- Identification of mAb utilization
- Stroke and emergency management
- Thrombolytic relative/absolute contraindication
- Lack of guidance on acute management – steroids(?), symptom mgmt

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ARIA Management

Continue treatment
- Mild ARIA
- Asymptomatic

Suspend treatment: Monthly MRI
- Mild-moderate ARIA
- Mild-moderate symptoms
- *Consider retrial if resolves*

Discontinue treatment
- Severe ARIA or symptoms

ARIA Type	Mild	Moderate	Severe
ARIA-E	Location and size of abnormality		
ARIA-H microhemorrhage	# of new incidents		
ARIA-H superficial siderosis	# of focal areas present		

Discontinue Treatment
- Macrohemorrhage
- > 1 ARIA superficial siderosis
- > 10 new onset microhemorrhages
- > 2 ARIA episodes
- Severe ARIA symptoms
- Initiates anticoagulant

ARIA = amyloid related imaging abnormalities
JAMA Intern Med. 2025;185(8):1029-1031.

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Implementation of Anti-amyloid Therapy: Roadmap

Formulary addition and protocolization → Identifying and screening patients → Obtaining clearance → Initial Monitoring → Therapy initiation → Authorization/billing → Long-term monitoring

Managing ARIA, new or worsening symptoms, and/or infusion reactions

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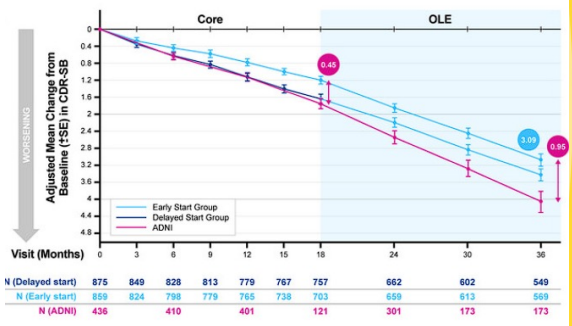
Long-term Monitoring – Lecanemab – Efficacy



ADNI = Alzheimer's disease Neuroimaging Initiative; OLE = open-labe extension
CDR-SB = clinical dementia rating sum of boxes
Alzheimers Dement. 2025;21(12):e70905.

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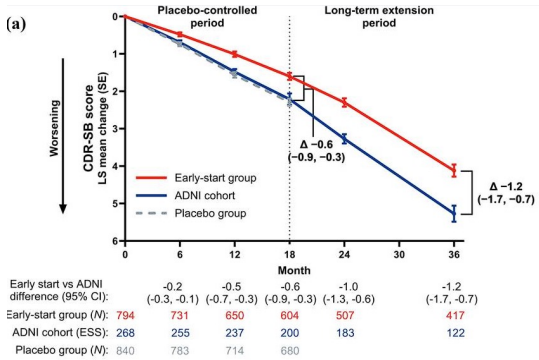
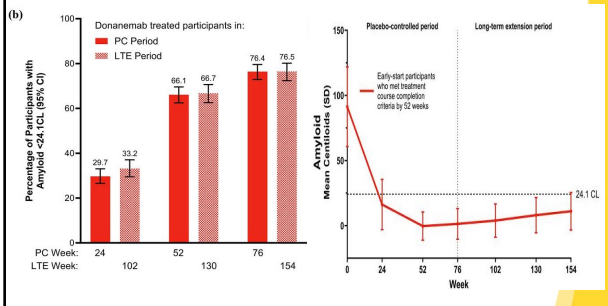
Long-term Monitoring – Donanemab – Efficacy



ADNI = Alzheimer's disease Neuroimaging Initiative;
J Prev Alzheimers Dis. 2026;13(2):100446.

55

Long-term Monitoring – Donanemab – Efficacy



PC = placebo controlled; LTE = long-term extension; CL = centiloid
J Prev Alzheimers Dis. 2026;13(2):100446.

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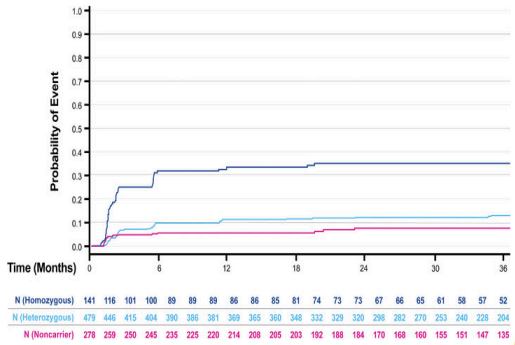
Long-term Monitoring – Lecanemab – ARIA



ARIA = amyloid related imaging abnormalities
Alzheimers Dement. 2025;21(12):e70905.

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Long-term Monitoring – Donanemab – ARIA

	Completed treatment	Continued treatment	Delayed start
N	393	157	657
ARIA-E	5 (1.3%)	13 (8.3%)	171 (26%)
ARIA-H	24 (6.1%)	30 (19.1%)	161 (24.5%)

Completed treatment – amyloid (-), stopped donanemab

Continued treatment – amyloid (+), continued donanemab

Delayed start – placebo to treatment

ARIA = amyloid related imaging abnormalities with (E)dema or (H)emosiderin deposits
J Prev Alzheimers Dis. 2026;13(2):100446.

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Long-term Monitoring

Continue standard monitoring
- Require updated clearance (e.g. 6 months)
- Ensure updated CMS registry

Clinical efficacy
- Assess clinically relevant benefit
- Advanced cognitive testing
- Criteria for continuation
- Repeat amyloid testing (e.g. donanemab)
- Shared decision making (consider burden)

Modifying Therapy
- Lecanemab – monthly infusion or subcutaneous
- Stop donanemab with negative PET

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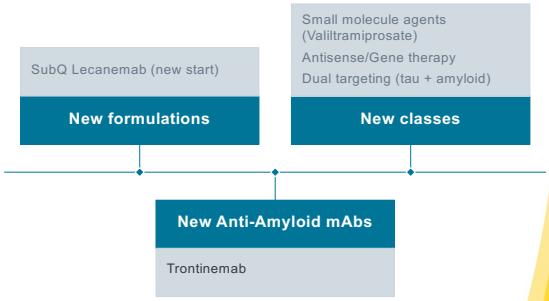
Future Directions



SubQ = subcutaneous
Brain Res. 2026;1870:150047.; *Neurotherapeutics.* 2025;22(3):e00570.; *Expert Opin Pharmacother.* 2024;25(7):791-799.; NCT07169578

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Alzheimer's Disease Pharmacotherapy:
Anti-amyloid therapy and treatment updates

Millad J. Sobhanian, PharmD, BCPS
Clinical Pharmacy Specialist, Neurology
University of Maryland Medical System
Millad.Sobhanian@umm.edu

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Barriers to Access: Cost & Social Determinants of Health

Direct financial burden
- Drug cost
- Testing costs

Unrealized Costs
- Transportation – scheduling rides
- Lost time for work
- Additional testing/hospitalization

Access to Resources
- Home vs infusion clinic
- Availability of lab testing and imaging
- Proximity to healthcare center

Social support
- Caregiver availability and persistence

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Estimated Cost

COMPONENT	COST	EST OOP COST
Amyloid PET Scan	$3,000	$600
Baseline + monitoring MRI	$4,000	$800
Office visits (1 year)	$350	$70
Neuropsych testing	$600	$120
Baseline labs	$300	$60
ApoE Gene Testing	$125	$125
Annual Drug Cost	$26,500	$5,300
Annual Infusion Cost	$3600	$720
Est Total cost (Year 1)	$38,475	$7,795

Does not include unrealized costs

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Barriers to Access: Cost & Social Determinants of Health

Utilize support programs
- Assist with navigating authorization processes
- Finding infusion centers
- Ensure appropriate billing

Copay support programs (excludes government programs)
- Drug costs through manufacturer
- Some support for PET testing available (limited)

Medicare
- 'Extra help' program through CMS
- Foundation support programs

Medicaid coverage
- Covered in all 50 states
- Variable coverage criteria
- Variable 'preferred' agent and health system formulary restrictions
- Accessibility

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Alzheimer's Disease (AD) Background and Epidemiology

- Progressive, debilitating neurodegenerative disease
  - Deficient memory acquisition and recall
  - Aphasia, apraxia, agnosia, dysexecutive syndrome
  - Other behavioral and neuropsychiatric symptoms
- Most common form of dementia (60-80%)
  - ~7 million affected in the US
  - Growing population – expected to double by 2060
- Highest incidence
  - African American population
  - Female gender
  - Advancing age

Loscher W & Klein P. *CNS Drugs*. 2021

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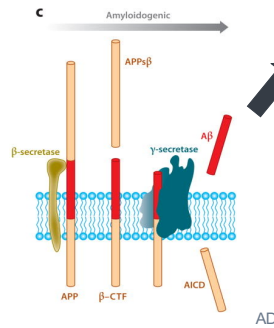
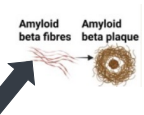
AD Pathophysiology – Pathogenic Amyloid Accumulation





- APP – amyloid precursor protein
- Cleaved by β and γ-secretases
- $A\beta_{42}$ forms oligomers and plaques
- Toxic byproducts

AD = Alzheimer's Disease
Aβ = amyloid-beta
S-oligomers = soluble oligomers

Loscher W & Klein P. *CNS Drugs*. 2021

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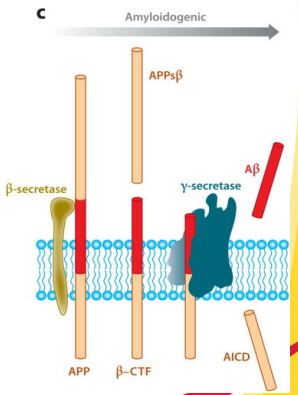
Amyloid physiology and pathology in Alzheimer's Disease

APP = amyloid precursor protein

CTF = C-terminus fragment

AICD = APP intracellular domain



van Dyck CH. *Biol Psychiatry*. 2018

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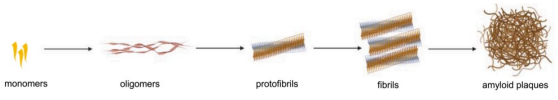
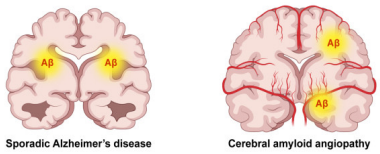
Amyloid physiology and pathology in Alzheimer's Disease

- Depending on amyloid-beta (Ab) site of cleavage and resultant length:
  - Ab40: vascular deposits – 10-20% (CAA)
  - **Ab42: aggregates with plaque formation – 10% (AD)**
  - Ab38: May not aggregate – 70-80%





CAA = cerebral amyloid angiopathy | AD = Alzheimer's disease

van Dyck CH. *Biol Psychiatry*. 2018

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AD Pathophysiology – Tau Hyperphosphorylation

- Tau is microtubule binding protein
- Phosphorylated sites on tau controls its binding to microtubules
- Hyperphosphorylation leads to dissociation from microtubules leading to tau oligomers and eventual formation of NFT (neurofibrillary tangles) > these potentiate neuronal damage and neurodegeneration
- These oligomers seed further tau misfolding, further propagating neurodegenerative and apoptotic processes (through nr2b activiation – excitotoxicity, ROS and mitochondrial dysfunction)
- Amyloid beta drives hyperphosphorylation, likely synergy

Loscher W & Klein P. *CNS Drugs*. 2021

AD = Alzheimer's Disease

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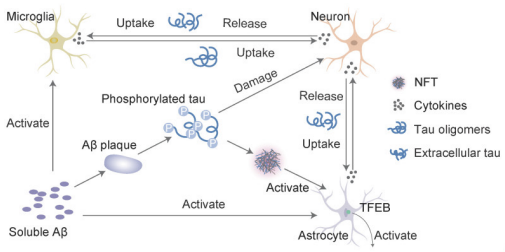
AD Pathophysiology – Tau Hyperphosphorylation



Loscher W & Klein P. *CNS Drugs*. 2021

AD = Alzheimer's Disease

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AD Pathophysiology – Additional pathogenic mechanisms

- Cholinergic neuronal degeneration leads to Ach deficiency and cognitive decline
- Neuroinflammation – microglia and astrocytes seem to be major players in progression/inflammation, activated by Ab and tau, modulated by genetic risk including ApoE and TREM2 > cytokines can damage neurons, bbb breakdown can lead to further inflammation
- BBB dysfunction, vascular abnormalities contribute to ab accumulation

Loscher W & Klein P. *CNS Drugs*. 2021

AD = Alzheimer's Disease

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