# Alzheimer’s Disease Clinical Protocol

A translational framework bridging molecular pathophysiology, biomarker diagnostics, and stage-gated pharmacological management.

# The modern epidemic of a century-old discovery

## 1906

German psychiatrist Alois Alzheimer identifies extracellular amyloid plaques and intracellular neurofibrillary tangles in 51-year-old Auguste Deter.

## 6.9M

Americans living with AD as of 2023.

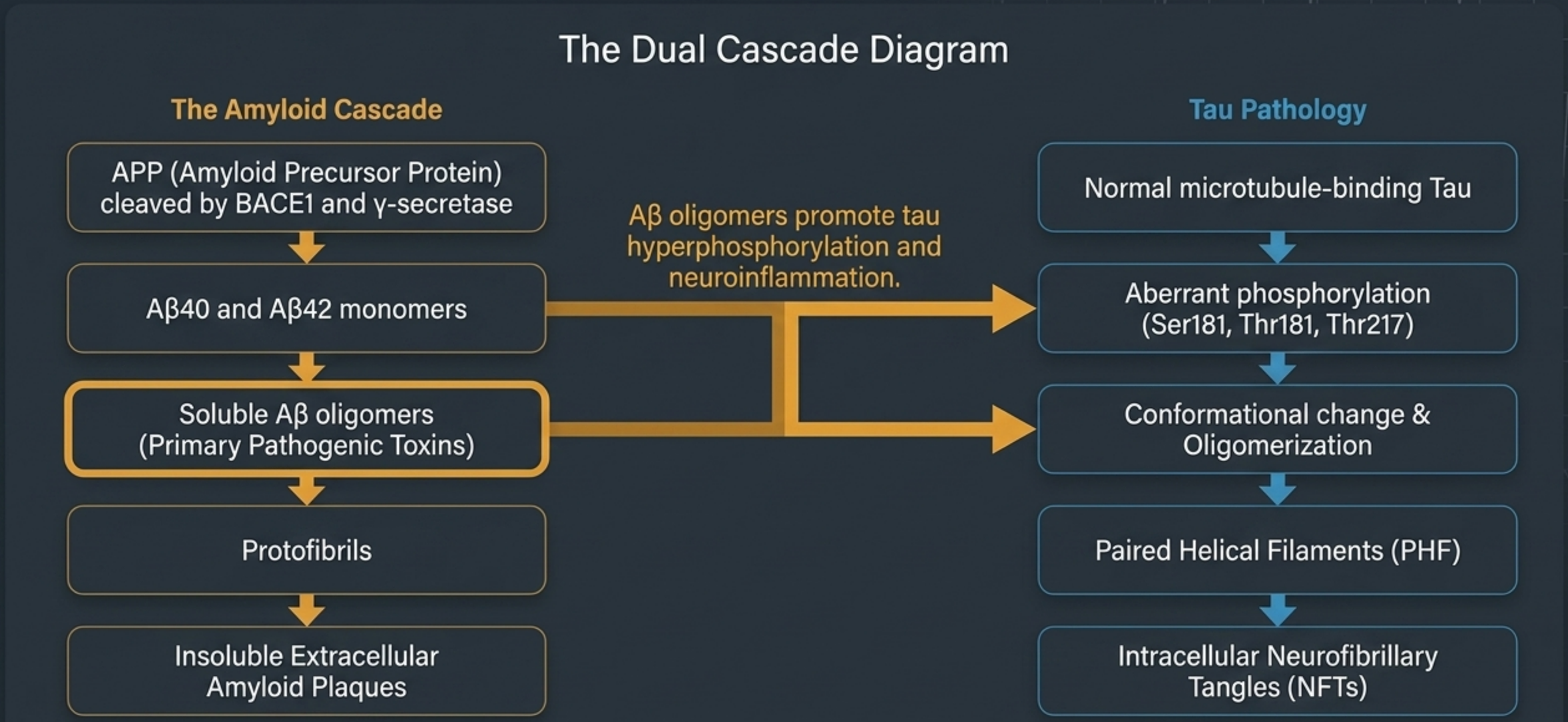
## 1:10

Adults age 65 and older diagnosed with Alzheimer's disease.

## $305B

Annual healthcare costs in the USA, with a maximum disease duration spanning up to 99 years.

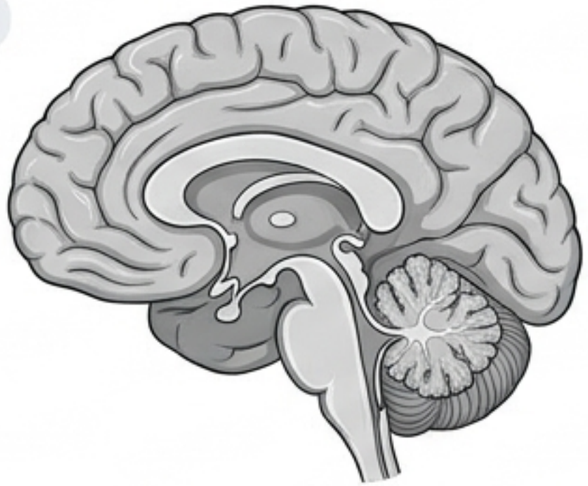
# The pathological dual cascade drives neuronal death



# Structural deterioration follows a predictable anatomical pathway

## The Atrophy Progression Model

1

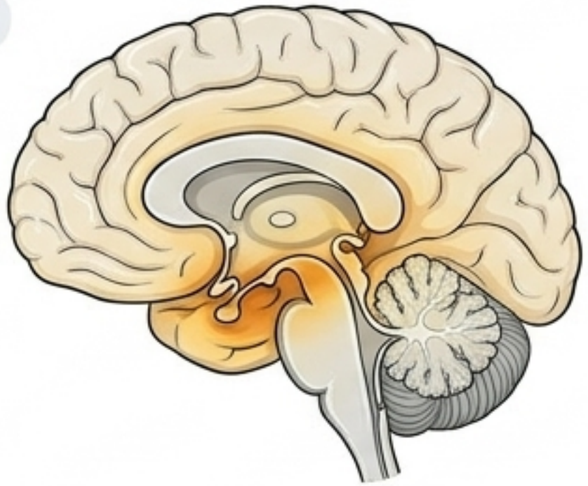


### Cognitively Normal

Brain volume: ~1400 $cm^3$

Clear, dense structural integrity.

2



### Mild Cognitive Impairment

Brain volume: ~1300 $cm^3$ (-7%)

Atrophy concentrated in the Entorhinal cortex and Hippocampus (Braak Stages I-IV).

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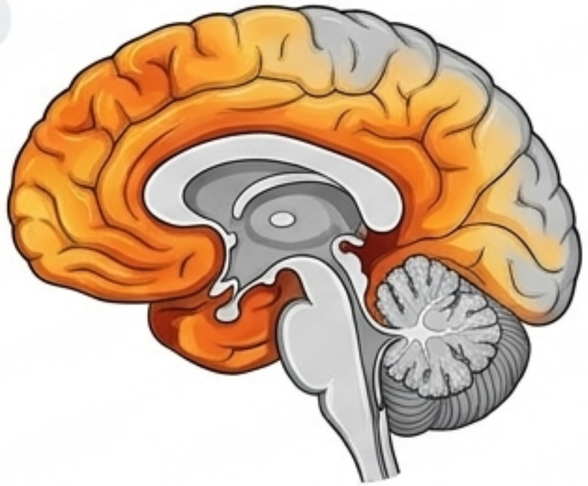


### Mild-Moderate Dementia

Brain volume: ~1100 $cm^3$ (-21%)

Volume loss spreads to temporal, parietal, and prefrontal cortices, with relative sparing of primary sensory regions.

# The NIA-AA biological classification framework establishes objective diagnosis

## Diagnostic Grid

### A (Amyloid Status)

**Pathology indicator:** Extracellular plaques

**CSF:** Aβ42 ↓

**Plasma:** p-tau181 ↑, p-tau217 ↑

**Imaging:** Amyloid PET +

### T (Tau Pathology)

**Pathology indicator:** Intracellular tangles

**CSF:** p-tau181 ↑, p-tau217 ↑

**Plasma:** p-tau181 ↑, p-tau217 ↑

**Imaging:** Tau PET +

### N (Neurodegeneration)

**Pathology indicator:** Neuronal loss / metabolic decline

**CSF:** Total tau ↑

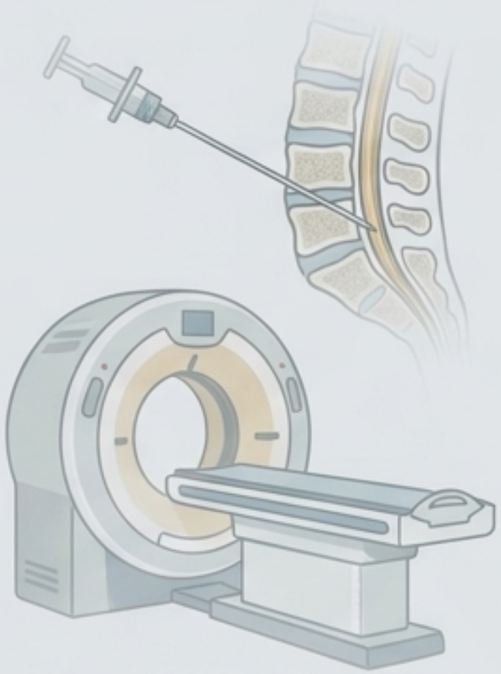
**Imaging:** Hippocampal atrophy on MRI, ↓ uptake on FDG-PET

**Biomarker confirmation (A+T+) fundamentally shifts AD from a purely syndromic clinical diagnosis to a defined biological state.**

# Blood-based biomarkers represent a paradigm shift in accessibility

## Legacy Diagnostic Approach

CSF Lumbar Puncture & PET Imaging



- Invasive
- High Cost
- Limited Accessibility
- Radiation Exposure

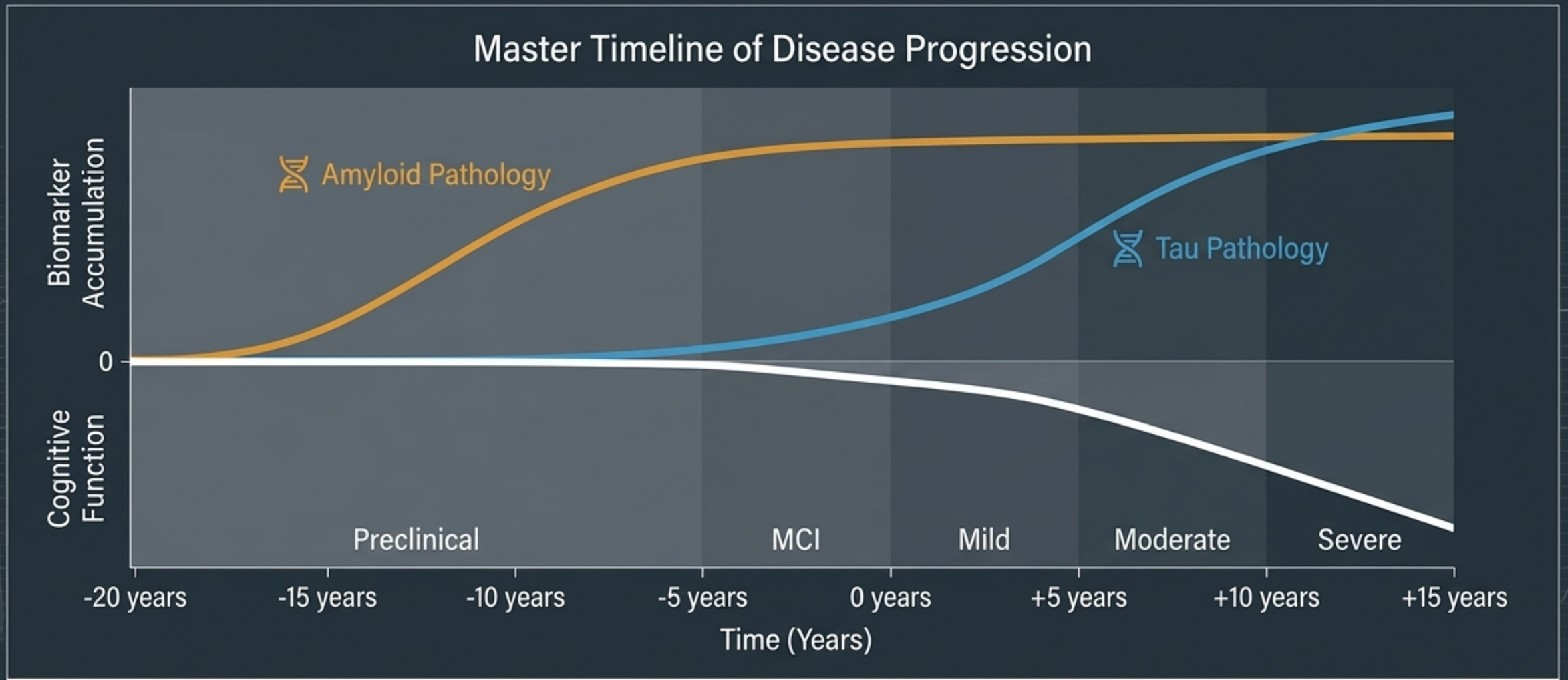
## Modern Plasma Approach

Focus on Phosphorylated tau-217 (p-tau217) and p-tau181.

Excellent concordance with PET imaging. p-tau217 demonstrates exceptionally high specificity for AD pathology.

Enables non-invasive, longitudinal assessment for preclinical identification and treatment monitoring.

# Silent pathology precedes clinical symptoms by decades




The divergence between biological onset and clinical onset defines the critical window for intervention.

# **Stage 1:** Preclinical Alzheimer's Disease

## Clinical Profile

**CDR Score:** 0

**Duration:** 10-20 years

**Cognition:** Normal on standard tests (MoCA).

**Function:** Fully independent.

## Biomarker Profile

**A+** (Amyloid positive)

**T±** (Tau emerging in transentorhinal cortex)

**N–** (No MRI atrophy)

## Clinical Protocol

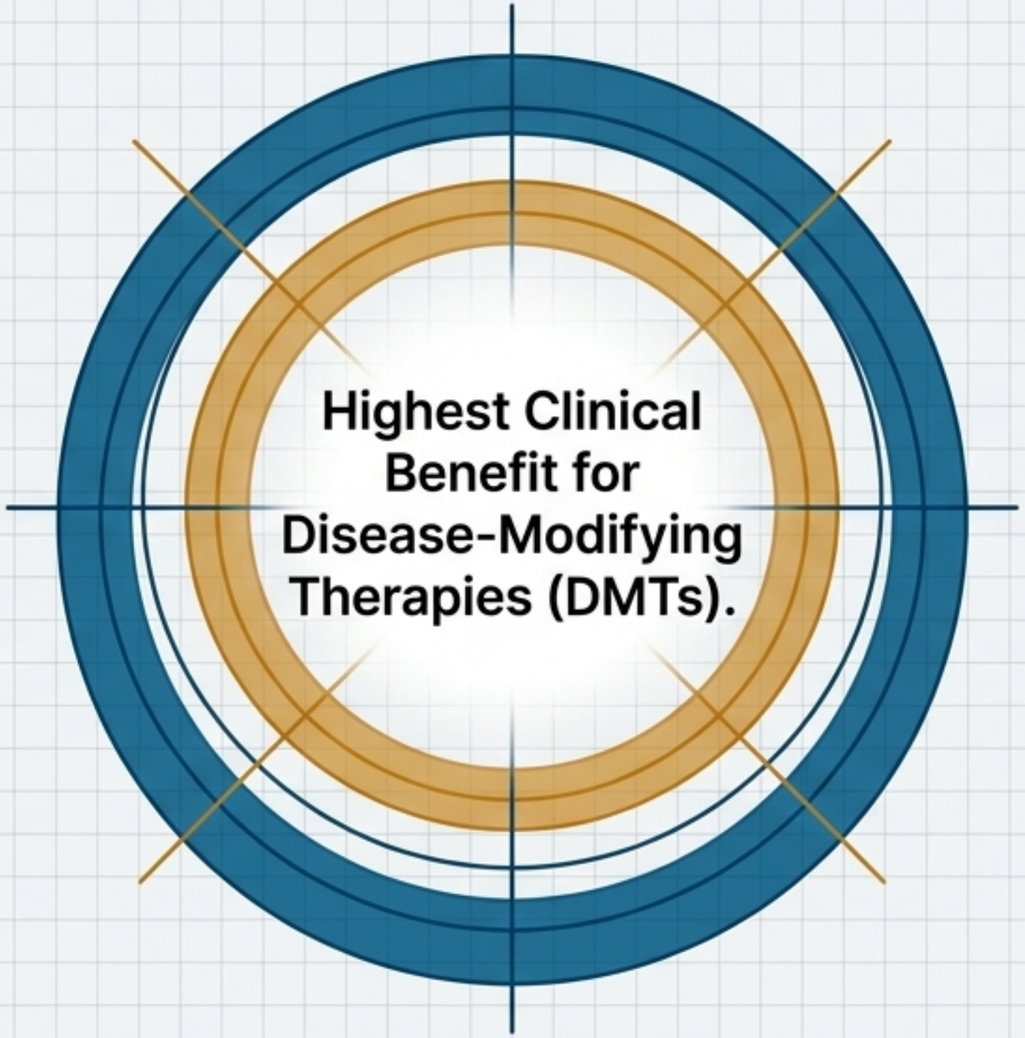
While no DMT is currently approved, aggressive cardiovascular risk reduction, cognitive engagement, and sleep optimization are strongly recommended.

APOE4 homozygotes with positive p-tau217 require close longitudinal monitoring.

# **Stage 2:** Mild Cognitive Impairment (MCI) marks the optimal therapeutic window

## Clinical Profile

- **CDR Score:** 0.5
- **Duration:** 3-7 years
- **Cognition:** Measurable episodic memory decline (typical MoCA 20–25).
- **Function:** Mostly independent, subtle impairment in complex IADLs (finances, travel).

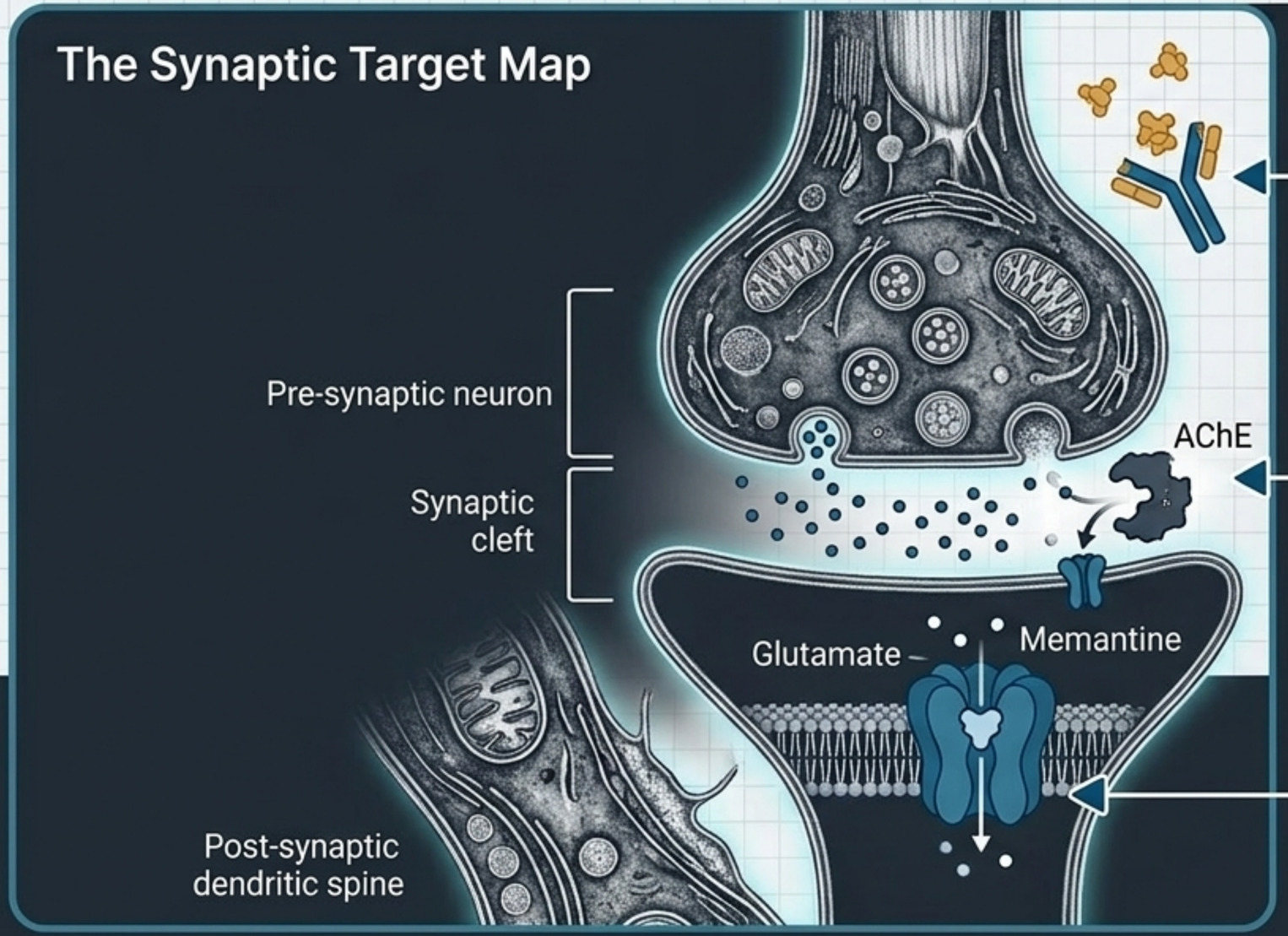



## Biomarker Profile

- **A+ T+ N±**
- **Hippocampal atrophy** becomes visible.
- **Conversion to dementia** ranges from 10-15% annually, drastically accelerated by an A+T+N+ profile.

# Pharmacological interventions map to distinct molecular and synaptic targets

## The Synaptic Target Map




**Monoclonal Antibodies (Lecanemab, Donanemab)** clear soluble and fibrillar Aβ species.

**Cholinesterase Inhibitors (Donepezil, Rivastigmine, Galantamine)** block AChE, increasing synaptic acetylcholine.

**Memantine** acts as a voltage-dependent NMDA receptor antagonist, preventing glutamate-induced excitotoxicity.

# Stage 2 & 3: Disease-Modifying Therapies (Amyloid Monoclonal Antibodies)

| | Lecanemab (Leqembi) | Donanemab (Kisunla) |
|---|---|---|
| **Mechanism** | Binds Aβ oligomers/protofibrils | Binds Phospho-tau N3pG + Aβ oligomers |
| **Clinical Benefit (18 mos)** | 27% slowing of decline | 35% slowing of decline |
| **Dosing** | 10 mg/kg IV Q2W | 10 mg/kg IV monthly, adaptive |
| **ARIA-E (Edema) Risk** | ~21% any grade; 3% symptomatic | ~24% any grade; 2% symptomatic |
| **ARIA-H (Hemorrhage) Risk** | ~17% any grade | ~12% any grade |

**Critical Safety Consideration:** APOE4 homozygosity (ε4/ε4) is the strongest risk factor for ARIA. Requires enhanced MRI monitoring (baseline, 6m, 12m) and strict shared decision-making.

# Stages 3 & 4: Mild to Moderate Dementia necessitates symptomatic polypharmacy

## Clinical Evolution

**Mild (CDR 1):**

- Clear memory impairment, temporal disorientation, requires assistance with IADLs.

**Moderate (CDR 2):**

- Dependent in ADLs, spatial disorientation. Neuropsychiatric symptoms peak (delusions, visual hallucinations, sundowning in 20-45% of patients).

## Pharmacological Strategy

**Baseline Therapy:**

- Initiate **Donepezil** (5-10 mg daily) to enhance cognition.
  Note: monitor for bradycardia. ⚠

**Escalation Pathway:**

- Add **Memantine** (target 20 mg daily) as disease progresses to moderate stage.
- The ChEI + Memantine combination is the evidence-based standard for moderate dementia.

**DMT Window:** The therapeutic window for amyloid monoclonal antibodies closes after the mild stage.

Stage 5: Severe Dementia marks the transition to palliative management

**Clinical Profile (CDR Score 3):**

- Minimal/absent verbal output. Total functional dependence. Immobile.
- Dysphagia and aspiration pneumonia (primary cause of death) dominate the clinical picture.

**Hospice Eligibility Gateway (FAST Scale)**

- FAST Stage 7a (inability to speak more than one word, ambulatory ability lost) predicts <6 month survival.
- FAST Stage 7c (inability to hold up head) yields a median survival of ~1.4 months.

**End-of-Life Protocol:**

Cease aggressive interventions. Prioritize comfort care, pain management, and dignity-preserving interventions over artificial nutrition (PEG tubes).

# **Iatrogenic risks:** Pharmacological contraindications in Alzheimer's management

## Anticholinergics

**Agents:** Diphenhydramine, oxybutynin, tricyclic antidepressants.
**Impact:** Blocks essential cholinergic transmission, directly antagonizing ChEI therapies, increasing delirium risk, and accelerating cognitive decline.

## Benzodiazepines

**Agents:** Lorazepam, Clonazepam, Alprazolam.

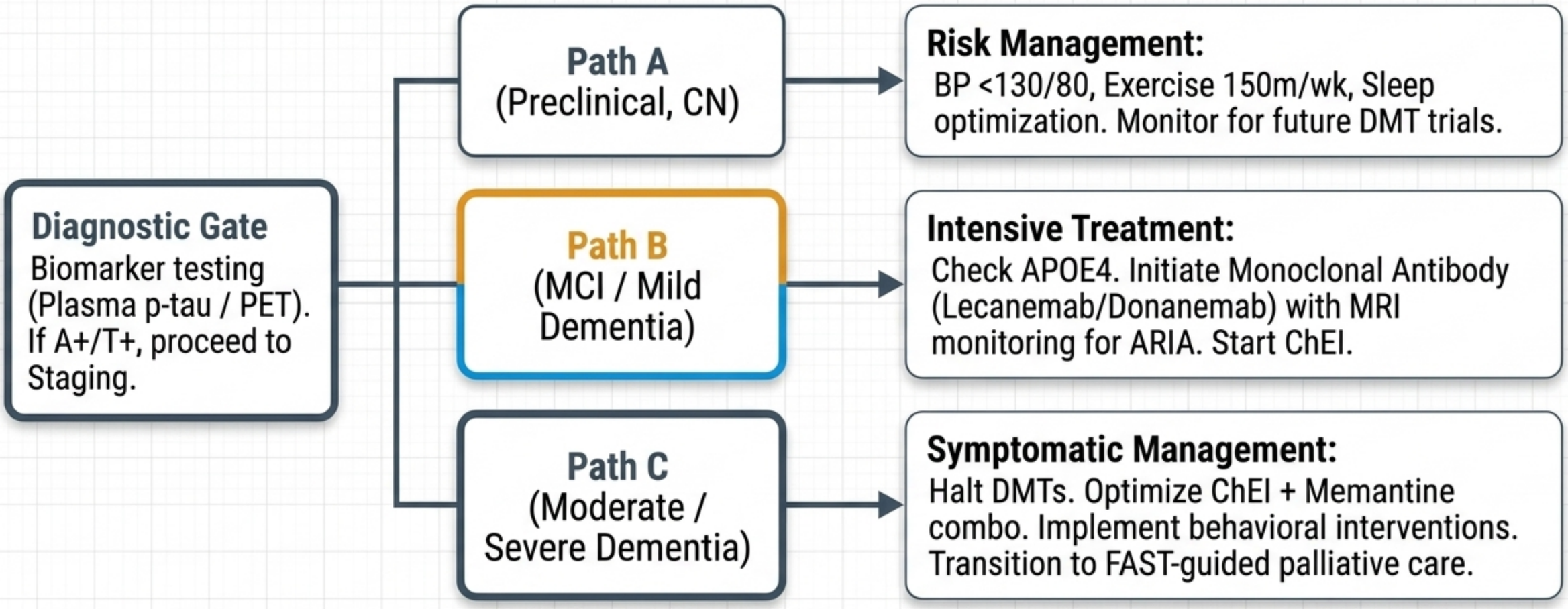
**Impact:** Chronic use strictly avoided. Dramatically increases fall risk, sedation, and delirium. For acute agitation, utilize environmental interventions first.

## Conventional Antipsychotics

**Agents:** Haloperidol, Chlorpromazine.

**Impact:** Black-box warning for increased mortality and stroke in elderly dementia patients. Use atypicals (Quetiapine, Aripiprazole) cautiously only for refractory, severe behavioral disturbances.

# The Alzheimer's Treatment Decision Tree




Early diagnosis enables optimal timing of interventions; biomarker monitoring dictates treatment intensity.