THE BIOMARKER CASCADE

Mapping Molecular Signatures to the Three Temporal Phases of Alzheimer's Disease

Amyloid · Tau · Neurodegeneration · Glial Reactivity
Synaptic Loss · Vascular · Metabolic

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Companion volume to the Collapse trilogy: Convergent Synaptic Collapse, Homeostatic Microglial Collapse, and Bioenergetic Collapse, and to The Tryptophan Partition.

Contents

Abstract

Alzheimer's disease is no longer diagnosed at the bedside alone; it is staged by a cascade of molecular signatures that begins two decades before the first complaint of forgetfulness and continues to evolve into the final years of life. The 2011 NIA-AA framework formalized the disease as a three-phase continuum — preclinical, prodromal/MCI, and dementia — and the 2018 ATN research framework (amyloid, tau, neurodegeneration) supplied the biomarker vocabulary in which that continuum is now operationalized. The intervening fifteen years have produced an extraordinary expansion of measurable variables: cerebrospinal fluid Aβ42/40 ratios with concordance to amyloid PET above 0.90; plasma p-tau217 assays that detect prodromal AD with sensitivities exceeding 0.95; neurofilament light chain as a generic axonal-injury readout valid across the entire disease span; glial fibrillary acidic protein as the earliest-rising plasma biomarker of reactive astrogliosis; soluble TREM2 as a microglial activation marker; neurogranin as a synaptic-loss marker; and the kynurenine-to-tryptophan ratio as an immunometabolic readout that couples peripheral inflammation to central monoaminergic decline. Each of these measurements has a *temporal signature* — a phase in which its trajectory is most informative — and the field's central organizational problem is now no longer whether biomarkers can detect AD but which biomarker, in which fluid, at which time, supplies the strongest signal for what therapeutic decision.

This dissertation advances the thesis that the biomarker cascade is best understood as a *staged signature problem*, in which each phase of Alzheimer's disease is characterized by the *first emergence* of a distinct molecular signature on top of the persisting earlier ones, and the staging is informative not because earlier markers disappear but because new markers come online while the earlier markers plateau, decline, or transition between fluids. The work is organized into seven analytical chapters. Chapter I traces the preclinical phase as the era of amyloid accrual, characterized by CSF Aβ42/40 decline, plasma Aβ42/40 decline, and amyloid PET positivity, with sTREM2 and GFAP emerging as the earliest non-amyloid markers. Chapter II treats the prodromal/MCI phase as the era of tau spread and synaptic loss, dominated by the p-tau isoform cascade (p-tau231 p-tau217 p-tau181 total tau) and the emergence of neurogranin, FDG-PET temporoparietal hypometabolism, and MRI hippocampal atrophy. Chapter III examines the dementia phase as the era of network collapse, characterized by sustained NfL elevation, advanced atrophy, persistent glial reactivity, and the emergence of vascular comorbidity markers. Chapter IV addresses the markers that do not fit ATN — the glial axis (GFAP, sTREM2, YKL-40), the synaptic axis (neurogranin, SNAP-25, synaptotagmin-1), the vascular axis (WMH, BBB-permeability indices), and the metabolic axis (kynurenine/tryptophan ratio, NAD+ precursors). Chapter V analyzes the plasma biomarker revolution and its consequences for population-level screening. Chapter VI maps the biomarker cascade onto the Collapse trilogy's three mechanistic axes (synaptic, microglial, bioenergetic), establishing the formal correspondence between clinically measurable variables and the

underlying disease infrastructure. Chapter VII develops the therapeutic implications: phase-specific trial design, the disappearance of pure "asymptomatic" trial cohorts as plasma biomarkers approach population screens, and the operationalization of secondary prevention.

The dissertation concludes that the biomarker cascade is not a passive recorder of an underlying disease but an *active staging instrument* — the choice of which marker to measure when defines which version of the disease the clinic is allowed to see. A unified framework in which biomarkers are organized by their first-emergence phase, by the fluid in which they are most informative, and by the mechanistic axis they index supplies the structural basis for the next decade of trial design and clinical practice.

Keywords: Alzheimer's disease, biomarkers, ATN framework, preclinical AD, mild cognitive impairment, plasma p-tau217, amyloid PET, neurofilament light, GFAP, sTREM2, neurogranin, kynurenine-to-tryptophan ratio, NIA-AA, secondary prevention

1. Introduction

1.1 The Research Problem

The clinical diagnosis of Alzheimer's disease, as Alois Alzheimer himself supplied it in 1907 with his case report of Auguste D., was a diagnosis of dementia confirmed by the post-mortem demonstration of senile plaques and neurofibrillary tangles. For most of the twentieth century, the diagnosis remained a clinicopathologic correlation visible only after death. The 1984 NINCDS-ADRDA criteria (McKhann et al., 1984) supplied the first standardized clinical diagnostic framework — "probable AD" and "possible AD" — but the underlying disease was still treated as a unitary clinical entity that began when symptoms began. The transformation of that view occurred between 1992 and 2011 in three steps: first, the amyloid cascade hypothesis (Hardy and Higgins, 1992; Hardy and Selkoe, 2002) articulated the proposition that the molecular pathology *precedes* the clinical syndrome by a measurable interval; second, the development of amyloid PET ligands ([^11C]PIB by Klunk et al., 2004) and CSF Aβ/tau assays (Blennow et al., 1995) supplied in vivo measurement of that molecular pathology; third, the 2011 NIA-AA criteria (Albert et al., 2011; McKhann et al., 2011; Sperling et al., 2011) formalized the staged continuum — preclinical, MCI, and dementia — as the operational framework in which AD is now understood.

The fifteen years since 2011 have produced what is arguably the largest expansion of disease-relevant measurement in the history of neurology. The 2018 NIA-AA Research Framework (Jack et al., 2018) reorganized AD biomarkers into the ATN classification: A for amyloid (CSF

Aβ42/40, amyloid PET), T for tau (CSF p-tau, tau PET), and N for neurodegeneration (CSF total tau, FDG-PET, MRI volumetrics). The plasma biomarker revolution that began with mass-spectrometric Aβ42/40 ratios (Schindler et al., 2019; Nakamura et al., 2018) and accelerated through plasma p-tau217 (Janelidze et al., 2020; Palmqvist et al., 2020; Karikari et al., 2020) has now placed AD-specific molecular measurement within reach of routine venipuncture. Glial markers (plasma GFAP, CSF sTREM2, CSF YKL-40), synaptic markers (CSF neurogranin, SNAP-25, synaptotagmin-1), and vascular markers (white matter hyperintensity volume, blood–brain barrier permeability indices) supply the dimensions that ATN omits. Each marker has a *first-emergence phase*, a *plateau phase*, and a *decline-or-divergence phase*, and these temporal signatures are themselves disease-stage indicators.

This dissertation addresses the question: **How does the constellation of available Alzheimer's biomarkers map onto the three temporal phases — preclinical, prodromal, and dementia — and what mechanistic, diagnostic, and therapeutic claims does that mapping support?** The thesis advanced is that each phase is characterized not by the disappearance of earlier markers but by the *first emergence* of a new layer of markers on top of those already present; that the choice of fluid in which a marker is measured (CSF, plasma, PET, MRI) determines the phase in which the marker is most informative; that the post-ATN markers — glial, synaptic, vascular, metabolic — supply the coupling variables that connect AD's molecular phenomena to its mechanistic infrastructure; and that the operationalization of secondary prevention requires a biomarker grammar organized not by disease vs. control but by phase vs. phase.

1.2 Significance

The significance of the reframing is fourfold. First, the staged-signature view supplies a vocabulary for trial design in which inclusion criteria are biomarker phases rather than clinical categories. The recent generation of anti-amyloid antibody trials — solanezumab, aducanumab, lecanemab, donanemab — has confirmed that the clinical effect of amyloid removal is largest in patients caught early, but the phase-specific reading is that *amyloid removal modifies the cascade only when administered while amyloid-driven downstream pathology is still in its first-emergence phase*. The biomarker grammar in which to evaluate that claim is a phase grammar, not a continuous-trajectory grammar.

Second, the framework supplies a principled answer to the long-standing question of "which biomarker first." The historical sequence of biomarker discovery — Aβ42 (1995), total tau (1995), p-tau181 (1999), p-tau217 (2020), GFAP (2019), neurogranin (2015), sTREM2 (2014), NfL (2017) — does not match the temporal sequence in which the markers become informative *in the disease*. Plasma GFAP, for example, rises in late preclinical AD before amyloid PET reaches its asymptote (Pereira et al., 2021; Benedet et al., 2021); the biomarker is "younger" by discovery but "older" by signal in the cascade. The phase-mapping in this dissertation is the first to attempt to systematically

separate these two orderings.

Third, the framework supplies a unifying interpretation of the otherwise disparate clinical observations that distinguish AD from related dementias. The frontotemporal-dementia, dementia-with-Lewy-bodies, and vascular-dementia syndromes share many of AD's downstream markers (NfL, GFAP, atrophy) but differ in the upstream phase-1 markers (amyloid, p-tau). The phase-mapping supplies the differential-diagnosis grammar in which AD is distinguished from its mimics by the *order* in which markers come online, not merely by their absolute levels.

Fourth, the framework supplies a mechanistic coupling to the Collapse trilogy. The Convergent Synaptic Collapse, Homeostatic Microglial Collapse, and Bioenergetic Collapse theses identify three mechanistic axes — synaptic-circuit failure, loss of microglial homeostatic identity, and bioenergetic-substrate collapse — but the trilogy did not systematically map clinically measurable biomarkers onto each axis. The present dissertation supplies that mapping: amyloid and tau index the synaptic axis (and its proteinopathic upstream drivers); GFAP, sTREM2, and YKL-40 index the microglial axis; FDG-PET, NfL, and the kynurenine/tryptophan ratio index the bioenergetic axis. The mapping closes the gap between the trilogy's mechanistic claims and the clinical surface on which those claims must be evaluated.

1.3 Scope and Limitations

This dissertation is a synthetic review, not a report of original experimental data. Its contribution is the integration of CSF, plasma, PET, and MRI biomarker literatures into a phase-organized framework, with the Collapse trilogy supplying the mechanistic vocabulary in which the markers are interpreted. The work draws principally on sporadic, late-onset AD because that population dominates the biomarker literature; the autosomal-dominant AD literature (DIAN cohort: Bateman et al., 2012) supplies the cleanest temporal sequence and is treated as a reference standard. Down syndrome AD (Lott and Head, 2019) is touched on as a third reference population in which the temporal sequence is compressed but otherwise comparable.

The thesis does not resolve the question of whether the biomarker cascade is causally hierarchical (Jack's hypothetical model: Jack et al., 2010) or whether the apparent hierarchy is a sampling artifact of the assays in current use. The framework is consistent with either reading. The work also does not address treatment-altered cascades (e.g., post-lecanemab amyloid clearance and downstream effects on tau and NfL) in depth; the lecanemab and donanemab evidence is addressed in Chapter VII as a phase-VII therapeutic test of the framework, not as a separate disease state.

2. Literature Review

2.1 From Clinicopathologic Diagnosis to the NIA-AA Framework

Alois Alzheimer's 1907 case report described the histopathology of senile plaques and neurofibrillary tangles in the brain of Auguste Deter; the diagnosis was confirmed post-mortem. For the next eight decades the diagnosis remained a clinicopathologic correlation, and clinical diagnosis during life used the syndromic criteria of probable AD (McKhann et al., 1984), which had a confirmed-at-autopsy positive predictive value of approximately 80% in expert clinical centers but considerably lower in general practice. The Khachaturian (1985) neuropathological criteria standardized post-mortem diagnosis, and the CERAD (Mirra et al., 1991) and NIA-Reagan (Hyman et al., 1997) criteria refined the histopathological staging.

The transformation from clinicopathologic to biomarker-based diagnosis began with three independent developments. First, the measurement of Aβ42 and total tau in cerebrospinal fluid (Motter et al., 1995; Blennow et al., 1995; Galasko et al., 1998) demonstrated that the molecular signatures of AD pathology were measurable in vivo, with Aβ42 decreased (reflecting parenchymal sequestration in plaques) and total tau increased (reflecting axonal injury). Second, the development of [^11C]Pittsburgh Compound B (Klunk et al., 2004) supplied the first amyloid PET ligand, allowing direct in vivo imaging of fibrillar Aβ deposition. Third, the longitudinal observation that CSF Aβ42 declines 15–25 years before symptom onset in autosomal-dominant AD (Bateman et al., 2012; Fagan et al., 2014) demonstrated that the molecular pathology preceded the clinical syndrome by a measurable interval.

The 2011 NIA-AA criteria (Albert et al., 2011; McKhann et al., 2011; Sperling et al., 2011) formalized the staged continuum: a preclinical stage (positive biomarkers, normal cognition), a prodromal/MCI stage (positive biomarkers, objective cognitive decline without functional impairment), and a dementia stage (positive biomarkers, dementia syndrome). The criteria were research-only at first but were rapidly adopted into clinical practice as biomarker access broadened. The 2018 NIA-AA Research Framework (Jack et al., 2018) reorganized the criteria around the ATN classification: amyloid, tau, neurodegeneration — three independent dimensions, each binary (positive or negative), generating eight possible biomarker profiles. Within ATN, AD is defined by A+T+ status regardless of N status; A+T-N+ is "Alzheimer's pathologic change"; A-T+N+ is "suspected non-AD pathology." The ATN framework therefore separates the etiologic biomarkers (A, T) from the topographic/severity biomarkers (N) and supplies the formal grammar in which biomarker-based diagnosis is now made.

2.2 The Preclinical Phase: Amyloid Accrual and the Silent Decade

The preclinical phase is operationally defined as biomarker-positive, cognitively normal. The earliest reliably measurable change is CSF Aβ42 decline, which precedes symptom onset by 15–25 years in autosomal-dominant AD (Bateman et al., 2012) and by an estimated 10–20 years in sporadic AD (Villemagne et al., 2013; Insel et al., 2019). The mechanism is parenchymal sequestration: as Aβ42 aggregates into plaques in the cortex, the soluble Aβ42 pool that exchanges with CSF declines. CSF Aβ40, which does not preferentially aggregate, is relatively preserved; the Aβ42/40 ratio is therefore a more robust marker than Aβ42 alone, correcting for inter-individual differences in total amyloid production (Hansson et al., 2019). The Aβ42/40 ratio has a concordance with amyloid PET above 0.90 in research cohorts (Janelidze et al., 2017).

Amyloid PET — initially with [^11C]PIB, later with [^18F]florbetapir, [^18F]florbetaben, and [^18F]flutemetamol — supplies a direct measurement of fibrillar Aβ deposition. The Centiloid scale (Klunk et al., 2015) normalizes amyloid PET measurements across tracers; values above 24 Centiloids are considered abnormal, with values above 100 reflecting advanced amyloid load. The temporal sequence runs from CSF Aβ42/40 decline (first) to amyloid PET positivity (second, with a delay of 5–10 years), and amyloid PET reaches its asymptote 5–10 years before symptom onset.

Plasma Aβ42/40 was first demonstrated to distinguish amyloid-positive from amyloid-negative individuals by Nakamura et al. (2018) using mass spectrometry and by Schindler et al. (2019) using a similar approach; the effect size is modest (10–15% decline in plasma Aβ42/40 with amyloid positivity) but the assay is now scalable. Plasma Aβ42/40 has lower discriminative power than CSF Aβ42/40 (AUC ~0.85 vs. ~0.95) but supplies the screening modality in which preclinical-phase detection at population scale is operationally feasible.

The non-amyloid markers that emerge in late preclinical phase include sTREM2 (Suárez-Calvet et al., 2016a, 2016b), GFAP (Benedet et al., 2021; Pereira et al., 2021), and the kynurenine/tryptophan ratio (Lim et al., 2017). Each of these markers reflects the response of non-neuronal compartments to early amyloid pathology — microglia for sTREM2, astrocytes for GFAP, and immunometabolic regulation for the kynurenine ratio.

2.3 The Prodromal/MCI Phase: Tau Spread and Synaptic Loss

The prodromal phase is operationally defined as biomarker-positive, with objective cognitive decline (typically a memory complaint with neuropsychological-test confirmation) but without functional impairment. The phase corresponds clinically to MCI due to AD. The dominant biomarker signature is the *p-tau cascade*, in which the phosphorylated tau isoforms appear in CSF and plasma in a specific temporal order: p-tau231 first (Ashton et al., 2021), followed by p-tau217 (Janelidze et al., 2020; Palmqvist et al., 2020), followed by p-tau181 (Karikari et al., 2020), with total tau elevation occurring later as axonal injury becomes generalized.

p-tau217 is the most clinically informative single marker for the prodromal phase. The plasma p-tau217 assay (Janelidze et al., 2020; Palmqvist et al., 2020) detects amyloid-positive individuals with AUC above 0.95 and detects tau PET positivity (which becomes abnormal in late preclinical/early prodromal phase) with comparable performance. The recent ALZpath and Lumipulse plasma p-tau217 assays have achieved clinically usable performance with central laboratory variability under 10% (Mielke et al., 2023; Brum et al., 2023). The 2024 update to the NIA-AA criteria (Jack et al., 2024) accepts plasma p-tau217 as a diagnostic biomarker on parity with CSF measurements for the first time.

Tau PET — with [^18F]flortaucipir and the next-generation MK-6240 and PI-2620 ligands — supplies the topographic dimension that CSF and plasma tau cannot. Braak staging in vivo (Schöll et al., 2016; Cho et al., 2016) demonstrates that tau pathology spreads in a stereotyped sequence from medial temporal lobe (Braak I–II) through limbic structures (III–IV) to isocortex (V–VI), and the topographic distribution at each tau PET timepoint maps to the cognitive domain expected to be impaired. Tau PET positivity in the medial temporal lobe is the earliest tau PET signal and emerges in late preclinical/early prodromal phase; isocortical tau PET positivity emerges in late prodromal/early dementia phase.

The neurodegeneration markers that emerge in prodromal phase include CSF and plasma NfL (Mattsson-Carlgren et al., 2020; Preische et al., 2019), CSF neurogranin (Kvartsberg et al., 2015; Portelius et al., 2018), FDG-PET temporoparietal hypometabolism (Mosconi et al., 2008), and MRI hippocampal atrophy (Jack et al., 1999; Frisoni et al., 2010). Each of these markers reflects a downstream consequence of tau and amyloid pathology — axonal injury (NfL), synaptic loss (neurogranin), regional metabolic decline (FDG-PET), and neuronal loss (atrophy).

2.4 The Dementia Phase: Network Collapse and Glial Reactivity

The dementia phase is operationally defined as biomarker-positive with dementia syndrome (cognitive impairment severe enough to impair daily function). The biomarker signatures of this phase are dominated by *downstream* markers rather than the upstream amyloid and tau signatures that established the diagnosis years earlier. CSF total tau is markedly elevated; plasma NfL reaches values comparable to acute axonal injury syndromes; MRI atrophy progresses from medial temporal lobe to global cortical involvement; FDG-PET hypometabolism is widespread; and glial markers (GFAP, YKL-40, sTREM2) reach sustained elevations.

Importantly, the upstream markers do not continue to track clinical progression in the dementia phase. Amyloid PET plateaus during late prodromal/early dementia phase (Jack et al., 2013) and does not predict the rate of cognitive decline within the dementia phase. CSF p-tau levels rise into prodromal phase and then plateau or decline as the number of tau-bearing neurons declines through neurodegeneration (cell death removes the source of secreted tau). The phase-mapping interpretation is that the upstream markers are *staging markers* of disease establishment but *not severity*

markers once the disease is established; severity within the dementia phase is indexed by N (atrophy, NfL, FDG-PET) and by glial reactivity (GFAP, sTREM2).

The dementia phase is also the phase in which *vascular* and *systemic-comorbidity* biomarkers acquire diagnostic and prognostic weight. White matter hyperintensities (WMH) on FLAIR MRI, blood–brain barrier permeability indices (CSF/serum albumin ratio, dynamic contrast-enhanced MRI), and pulse-wave indices of arterial stiffness all contribute to the rate of progression within the dementia phase even when amyloid and tau status are equivalent (Sweeney et al., 2018; Iturria-Medina et al., 2016). The Vascular Dimension paper of the Collapse trilogy (Truchard & Gustafsson, 2026) treats these markers as a fourth axis that is increasingly recognized as inseparable from the AD core.

2.5 The Plasma Biomarker Revolution

The 2018–2024 period saw the maturation of plasma-based AD biomarker assays from research curiosities to clinically deployable measurements. The Simoa (Single Molecule Array, Quanterix) and Lumipulse (Fujirebio) platforms, together with mass-spectrometric methods (Shimadzu, C2N), have produced plasma assays for Aβ42/40, p-tau181, p-tau217, p-tau231, GFAP, and NfL with sufficient analytical performance for clinical use. The key developments are: (i) plasma p-tau217 detects amyloid PET positivity with AUC > 0.95 (Palmqvist et al., 2020), (ii) plasma GFAP rises early in preclinical phase and tracks amyloid accumulation (Benedet et al., 2021; Pereira et al., 2021), (iii) plasma NfL is a generic axonal-injury marker that tracks neurodegeneration across the cascade and across non-AD dementias (Mattsson et al., 2017), and (iv) plasma Aβ42/40 by mass spectrometry detects amyloid PET positivity with AUC ~0.85 (Schindler et al., 2019).

The clinical implication is that AD biomarker measurement is no longer gated by lumbar puncture or PET access. A two-step screen — plasma p-tau217 as a high-sensitivity first-line test, followed by amyloid PET or CSF confirmation for the positive cases — is now feasible at primary-care scale (Hansson et al., 2023). The 2024 NIA-AA criteria (Jack et al., 2024) formalize this by accepting plasma p-tau217 as a diagnostic biomarker, and the FDA cleared the Lumipulse plasma p-tau217/Aβ42 ratio test in 2025.

2.6 Beyond ATN: The Glial, Synaptic, Vascular, and Metabolic Axes

The ATN framework's explicit limitation is its restriction to amyloid, tau, and neurodegeneration. The framework deliberately excluded markers that index the *response* to AD pathology — glial reactivity, synaptic loss, vascular dysfunction, immunometabolic shift — because the developers of the framework judged the evidence base insufficient in 2018. The intervening seven years have substantially closed that gap. The proposed expansion to ATN(X), where X indexes one or more of the response axes, is now under active consideration by the NIA-AA biomarker working groups.

The glial axis is indexed by plasma GFAP (astrocyte reactivity), CSF sTREM2 (microglial activation), and CSF YKL-40/CHI3L1 (chitinase-like astrocyte and microglial product). Each marker has a temporal signature: GFAP rises in late preclinical phase and tracks amyloid accumulation; sTREM2 rises during the transition from preclinical to prodromal phase; YKL-40 rises later, in prodromal/dementia phase, and tracks neurodegeneration rate (Craig-Schapiro et al., 2010; Suárez-Calvet et al., 2016a; Pereira et al., 2021).

The synaptic axis is indexed by CSF neurogranin (a postsynaptic dendritic-spine protein), CSF SNAP-25 (a presynaptic vesicular protein), and CSF synaptotagmin-1 (a presynaptic calcium sensor). Neurogranin is the best characterized and rises in late preclinical phase, tracking with future cognitive decline (Kvartsberg et al., 2015; Portelius et al., 2018; Tarawneh et al., 2016). The synaptic markers index the disease-relevant variable that ATN's N most poorly captures: synaptic dysfunction precedes overt neuronal death by years, and synaptic loss in AD is the substrate of the cognitive symptoms (Terry et al., 1991; DeKosky and Scheff, 1990).

The vascular axis is indexed by FLAIR-MRI WMH burden, CSF/serum albumin ratio (a crude BBB-integrity index), and dynamic contrast-enhanced MRI of BBB permeability. WMH burden is the most robust and is increasingly recognized as a contributor to AD progression rate even when not the primary etiology (Brickman et al., 2015; Lo and Jagust, 2012; Sweeney et al., 2018).

The metabolic axis is indexed by the plasma and CSF kynurenine-to-tryptophan ratio (KTR), reflecting inflammatory IDO induction; by plasma NAD+ precursors (NMN, NR, NAM) and the NAD+/NADH ratio (where measurable); and by FDG-PET as a topographic metabolic readout (Lim et al., 2017; van der Velpen et al., 2019; Truchard & Gustafsson, 2026, *The Tryptophan Partition*). The metabolic axis is the least operationalized of the four post-ATN axes but supplies the mechanistic coupling to the Bioenergetic Collapse and Homeostatic Microglial Collapse theses.

2.7 Gaps in the Literature

Five significant gaps motivate the present synthesis. First, the AD biomarker literature is organized predominantly by *marker* rather than by *phase*; reviews of any individual marker treat all three phases as a continuous trajectory rather than as discrete signature regimes. Second, the temporal-ordering question — which marker rises before which — has been addressed for individual marker pairs but not systematically across the full constellation. Third, the fluid-of-choice question — when a marker is most informative in CSF vs. plasma vs. PET — has been studied marker-by-marker but not integrated. Fourth, the mechanistic mapping of biomarkers to the underlying disease infrastructure remains largely informal; the explicit correspondence between, for example, CSF neurogranin and PV+ interneuron loss has not been quantitatively established. Fifth, the implications of the plasma biomarker revolution for trial design and clinical practice are still being absorbed, and the field lacks a unified framework for biomarker-defined inclusion criteria. This dissertation addresses each gap.

3. Methodology

3.1 Disciplinary Approach

This dissertation adopts a systems-level integrative review methodology, synthesizing primary experimental literature, large-cohort biomarker studies, clinical trial data, and theoretical frameworks across CSF/plasma analytical chemistry, neuroimaging, immunometabolism, and clinical neurology. The approach is consistent with the integrative dissertation tradition established for the Collapse trilogy.

3.2 Source Selection Criteria

Primary sources were selected for publication in peer-reviewed journals indexed in PubMed/MEDLINE, for sample sizes adequate to support claimed effect sizes, for use of validated assays with reported analytical performance, and for relevance to one or more of the three temporal phases. Large-cohort consortia (DIAN, ADNI, AIBL, BioFINDER, A4, IDEAS) are cited as the principal source of phase-temporal evidence because their longitudinal designs supply the within-subject trajectories that cross-sectional studies cannot. Review articles are cited for historiographical positioning but are not used as primary evidence for mechanistic claims.

3.3 Analytical Framework

The analysis proceeds through four levels of integration. At the **assay level**, the analytical characteristics of each marker (limit of detection, dynamic range, inter-assay variability, fluid compatibility) are characterized as the constraint on what the marker can clinically support. At the **physiologic level**, the marker is mapped to the cellular and subcellular process it reflects (e.g., neurogranin to postsynaptic-spine integrity, GFAP to astrocyte reactive state). At the **temporal level**, the marker is mapped to the AD phase in which it first emerges, plateaus, or declines, with reference to longitudinal-cohort data. At the **clinical level**, the marker is evaluated for its diagnostic, prognostic, or trial-stratification utility within each phase.

3.4 Citation Protocol

Citations follow APA 7th edition. Primary biomarker claims are cited to originating papers or to the consortium reports in which they were first established at scale. Where conflicting evidence exists, both sides are cited and the conflict is characterized.

4. Chapter I The Preclinical Phase: Amyloid Accrual and the Silent Decade

4.1 Defining the Phase

The preclinical phase of Alzheimer's disease is the interval — estimated at 15–25 years in length — during which AD molecular pathology is measurable in vivo but cognition remains within the normal range. The 2011 NIA-AA criteria (Sperling et al., 2011) operationally defined three preclinical sub-stages: Stage 1 (amyloid positivity alone), Stage 2 (amyloid plus evidence of neurodegeneration or tau), and Stage 3 (Stages 1–2 plus subtle cognitive change short of MCI). The 2018 framework (Jack et al., 2018) simplified this to "A+T-" (amyloid alone) and "A+T+" (amyloid plus tau) preclinical states. The 2024 update (Jack et al., 2024) accepts plasma p-tau217 as a sufficient T-marker, with the consequence that preclinical AD can now in principle be diagnosed from a venous blood sample.

The phase is operationally important because it is the *therapeutic window* in which secondary prevention is possible. The lecanemab and donanemab trials (van Dyck et al., 2023; Sims et al., 2023) demonstrated 25–35% slowing of cognitive decline in symptomatic early-AD patients; the AHEAD 3-45 trial (ongoing, results expected 2027) is testing the same drug in preclinical AD with the hypothesis that the effect size will be substantially larger when amyloid is removed before downstream tau pathology has been seeded.

4.2 CSF Aβ42/40: The Earliest Biomarker

CSF Aβ42 was the first AD biomarker to demonstrate preclinical-phase sensitivity. The mechanism is straightforward: as amyloid plaques sequester Aβ42 in cortical parenchyma, the soluble Aβ42 pool that exchanges with CSF declines. The decline is detectable approximately 15–25 years before symptom onset in autosomal-dominant AD (Bateman et al., 2012; the DIAN cohort) and is estimated at 10–20 years before symptom onset in sporadic AD (Villemagne et al., 2013). CSF Aβ42 alone is confounded by inter-individual variation in total amyloid production; the Aβ42/40 ratio corrects this confound by normalizing to Aβ40, which does not preferentially aggregate. The Aβ42/40 ratio has a concordance with amyloid PET above 0.90 across analytical platforms (Janelidze et al., 2017; Hansson et al., 2019). It is the current reference standard for amyloid biomarker positivity when amyloid PET is not available.

4.3 Amyloid PET: The Topographic Reference

Amyloid PET supplies a direct, topographic measurement of fibrillar Aβ deposition. The first-generation ligand, [^11C]PIB (Klunk et al., 2004), has a short half-life (20 minutes) requiring on-site cyclotron production; the second-generation [^18F] ligands — florbetapir (Amyvid), florbetaben (Neuraceq), and flutemetamol (Vizamyl) — have 110-minute half-lives and are now in routine clinical use. The Centiloid scale (Klunk et al., 2015) supplies a tracer-independent quantification: values below 12 Centiloids are normal, 12–24 are borderline, 24–50 are early positive, 50–100 are moderately positive, and >100 are advanced. The temporal trajectory in DIAN shows Centiloid values rising from 12 to 50 over approximately 10–15 years and plateauing thereafter. Sporadic AD shows a similar trajectory with greater inter-individual variation.

The clinical interpretation of amyloid PET in preclinical phase has shifted with the introduction of anti-amyloid therapy: a positive amyloid PET in a cognitively normal individual is now a candidate finding for secondary-prevention treatment in trials and, increasingly, in clinical practice. The shift has driven the development of plasma p-tau217 as a "pre-screen" that reduces the population referred for amyloid PET to those with high pre-test probability of positivity.

4.4 Plasma Aβ42/40: The Population-Scale Screen

Plasma Aβ42/40 was technically feasible from the early 2000s but achieved analytical performance sufficient for clinical use only with the high-precision mass spectrometric methods of Nakamura et al. (2018) and Schindler et al. (2019). The effect size of amyloid positivity on plasma Aβ42/40 is small — a 10–15% reduction — because the plasma pool is dominated by peripheral Aβ production from sources unrelated to brain amyloid. The clinical performance (AUC 0.85–0.90 for amyloid PET positivity) is sufficient for population screening but insufficient for definitive diagnosis. The C2N Diagnostics PrecivityAD assay and the comparable Quanterix and Roche assays are now in clinical use for amyloid status screening, typically in combination with plasma p-tau217 to improve specificity.

4.5 The Earliest Non-Amyloid Signals: sTREM2 and GFAP

The preclinical phase is not entirely characterized by amyloid biomarkers alone. Two markers rise in the late preclinical phase before amyloid PET reaches its asymptote and before any tau biomarker becomes positive: soluble TREM2 (sTREM2) in CSF and glial fibrillary acidic protein (GFAP) in plasma.

sTREM2 reflects microglial activation. TREM2 is a microglial transmembrane receptor whose ectodomain is shed by ADAM10/17 proteases into the CSF; CSF sTREM2 concentration tracks microglial-activation state. Suárez-Calvet et al. (2016a, 2016b) demonstrated that CSF sTREM2 is elevated in preclinical and prodromal AD, with the elevation peaking in early prodromal phase. The biological interpretation is that microglial activation — specifically, the transition toward the

disease-associated microglia (DAM) phenotype of Keren-Shaul et al. (2017) — is an early response to amyloid plaque accumulation and is detectable in CSF before clinical symptoms emerge.

Plasma GFAP reflects astrocyte reactivity. Benedet et al. (2021) and Pereira et al. (2021) demonstrated that plasma GFAP is elevated in preclinical AD and that the elevation tracks with amyloid PET centiloid values. The temporal sequence places GFAP elevation in the late preclinical phase, with the strongest tracking signal occurring during the amyloid accumulation phase itself rather than after amyloid PET plateaus. Plasma GFAP is the earliest plasma biomarker to rise specifically in response to AD pathology — earlier than plasma p-tau and earlier in its trajectory than plasma Aβ42/40 — and supplies the cleanest plasma signal of preclinical disease.

4.6 The Kynurenine-to-Tryptophan Ratio

A fourth marker that becomes informative in late preclinical phase is the plasma and CSF kynurenine-to-tryptophan ratio (KTR), reflecting inflammatory IDO induction. Lim et al. (2017) and van der Velpen et al. (2019) demonstrated that KTR is elevated in MCI due to AD and trends elevated in preclinical phase. The KTR couples peripheral inflammation to central monoaminergic decline (see *The Tryptophan Partition*, Truchard & Gustafsson, 2026) and supplies an immunometabolic readout that the conventional ATN framework does not capture. KTR is less specific to AD than amyloid biomarkers — it is also elevated in systemic infection, autoimmune disease, and depression — but it supplies a coupling variable that the AD-specific markers do not.

4.7 The Preclinical Phase Signature

The summary signature of the preclinical phase is therefore: CSF Aβ42/40 decline (first, ~20 years before symptoms), amyloid PET positivity (~10–15 years before symptoms), plasma Aβ42/40 decline (~10–15 years before symptoms, less robust), late-preclinical sTREM2 and plasma GFAP elevation (~5–10 years before symptoms), and a slow rise in KTR. Critically, p-tau biomarkers remain near normal in the preclinical phase; the transition to p-tau positivity defines the preclinical-to-prodromal phase boundary. The clinical reading of a preclinical-phase biomarker profile is that AD pathology is present, downstream tau pathology has not yet been seeded at population scale, and the therapeutic window for amyloid removal is still open.

5. Chapter II The Prodromal Phase: Tau Spread, Synaptic Loss, and the Onset of Clinical Decline

5.1 Defining the Phase

The prodromal phase is operationally defined as biomarker-positive (amyloid plus tau) with objective cognitive decline (memory or other cognitive complaint with neuropsychological-test confirmation) without functional impairment. The phase corresponds clinically to MCI due to AD (Albert et al., 2011) and is the phase in which most AD clinical trials currently enroll, including the symptomatic anti-amyloid trials (CLARITY-AD, TRAILBLAZER-ALZ 2). The phase typically lasts 3–7 years before transition to dementia, though substantial inter-individual variability exists.

The dominant biomarker signature of the prodromal phase is the *p-tau cascade*: phosphorylated tau isoforms appearing in CSF and plasma in a specific temporal order — p-tau231 (earliest), p-tau217, p-tau181, total tau (latest). The cascade is the basis of the modern operationalization of T-positivity in the ATN framework and is now extending into preclinical detection through the most sensitive of the assays (plasma p-tau217).

5.2 The p-Tau Cascade

Tau is a microtubule-associated protein whose physiologic function in axons is microtubule stabilization. Tau undergoes a stereotyped sequence of phosphorylation events under disease conditions, with phosphorylation at specific residues — Ser202/Thr205 (the AT8 epitope), Thr181, Thr217, Thr231 — preceding the formation of paired helical filaments and neurofibrillary tangles. The relative early elevation of p-tau217 vs. p-tau181 in plasma and CSF in early AD was first systematically established by Janelidze et al. (2020) and Palmqvist et al. (2020), and the earlier elevation of p-tau231 was established by Ashton et al. (2021).

The temporal sequence in DIAN and BioFINDER data places CSF p-tau231 elevation 10–20 years before symptom onset (overlapping with the late preclinical phase), CSF p-tau217 elevation 5–15 years before symptom onset, CSF p-tau181 elevation 5–10 years before symptom onset, and CSF total tau elevation 0–5 years before symptom onset (Janelidze et al., 2020; Suárez-Calvet et al., 2020; Ashton et al., 2021). The plasma p-tau measurements lag the CSF measurements by roughly 2–5 years but follow the same order.

p-tau217 is the most clinically informative single marker. Plasma p-tau217 detects amyloid PET positivity with AUC > 0.95 (Palmqvist et al., 2020), detects tau PET positivity with AUC > 0.90, and distinguishes AD from other dementias with AUC > 0.95 (Mattsson-Carlgren et al., 2020). The 2024 ALZpath and Lumipulse assays achieve clinically usable analytical performance, and the 2025 FDA clearance of the Lumipulse plasma p-tau217/Aβ42 ratio test made AD biomarker measurement available at primary-care scale.

5.3 Tau PET: The Topographic Reading

CSF and plasma p-tau measurements report a single number per fluid; they do not distinguish where in the brain the tau pathology is. Tau PET — with [^18F]flortaucipir (the first-generation ligand) and the next-generation MK-6240 and PI-2620 ligands — supplies that topographic information. The PET signal in vivo follows the Braak staging sequence established at autopsy by Braak and Braak (1991): medial temporal lobe (Braak I–II) first, limbic structures (Braak III–IV) second, isocortical regions (Braak V–VI) last (Schöll et al., 2016; Cho et al., 2016).

Tau PET positivity in the medial temporal lobe is the earliest tau PET signal and emerges during the preclinical-to-prodromal transition. Isocortical tau PET positivity emerges in late prodromal/early dementia phase. The amount of tau PET signal at any given timepoint correlates strongly with cognitive performance in the corresponding domain (medial temporal tau with episodic memory, posterior cingulate tau with default-mode-network function, frontal tau with executive function). The tau PET signal is therefore a *topographic* prognostic marker that the fluid measurements cannot supply.

5.4 Synaptic Markers: Neurogranin and SNAP-25

Synaptic loss is the proximal substrate of the cognitive symptoms of AD (Terry et al., 1991; DeKosky and Scheff, 1990). The disease-relevant variable that cognitive testing measures is not amyloid load per se but the functional integrity of cortical synapses — and synaptic loss is detectable in CSF before it is detectable as cortical atrophy on MRI.

CSF neurogranin (a postsynaptic dendritic-spine calmodulin-binding protein, principally expressed in cortical and hippocampal neurons) is the best-characterized fluid marker of synaptic loss. CSF neurogranin is elevated in preclinical and prodromal AD, with the elevation tracking future cognitive decline (Kvartsberg et al., 2015; Portelius et al., 2018; Tarawneh et al., 2016). The temporal signature places neurogranin elevation in late preclinical/early prodromal phase, with the strongest prognostic signal in early prodromal phase: a high CSF neurogranin in a CSF-positive MCI patient predicts faster conversion to dementia (typically 2–3 years vs. 5–7 years for low-neurogranin MCI).

CSF SNAP-25 (a presynaptic SNARE-complex protein) and synaptotagmin-1 (a presynaptic calcium sensor) supply complementary readouts of presynaptic function. Their elevation in CSF in AD is consistent with vesicular release of presynaptic-protein fragments under synaptic stress (Brinkmalm et al., 2014; Wang et al., 2018). The presynaptic and postsynaptic markers track together in AD but are differentially elevated in other dementias (e.g., neurogranin is relatively preserved in DLB), supplying differential-diagnosis information that ATN markers alone do not.

5.5 Neurofilament Light Chain: The Generic Neurodegeneration Marker

Neurofilament light chain (NfL) is a structural protein of large myelinated axons that is released into CSF and blood upon axonal injury or degeneration. NfL is *not* specific to AD — it is elevated in MS, ALS, traumatic brain injury, stroke, and frontotemporal dementia — but its non-specificity is its diagnostic strength: it is a generic axonal-injury index that tracks total neurodegenerative burden.

Plasma NfL rises in late prodromal and dementia phase in AD (Mattsson et al., 2017; Preische et al., 2019), with the elevation tracking cognitive decline and brain atrophy rates. In DIAN, plasma NfL is elevated 16–22 years before symptom onset and continues to rise through the dementia phase, providing a continuous trajectory variable that the binary amyloid and tau markers do not (Preische et al., 2019). The clinical use of plasma NfL is principally as a *progression* marker rather than a diagnostic marker: it does not distinguish AD from other dementias but it tracks the rate of disease progression once the diagnosis is established.

5.6 FDG-PET and MRI: The Imaging Neurodegeneration Markers

FDG-PET measures regional glucose metabolism and is the imaging equivalent of NfL's fluid measurement: a generic neurodegeneration marker. The characteristic AD pattern is temporoparietal hypometabolism, with posterior cingulate hypometabolism appearing earliest and inferior parietal/lateral temporal hypometabolism appearing later (Mosconi et al., 2008; Landau et al., 2010). The pattern is informative in prodromal AD (AUC for conversion to AD dementia ~0.85 within 2 years) and supplies a topographic prognostic readout that complements CSF/plasma neurodegeneration markers.

MRI volumetric measurement of hippocampal atrophy is the longest-established AD imaging biomarker (Jack et al., 1999; Frisoni et al., 2010). The hippocampal volume in early prodromal AD is 10–15% below age-matched controls and the rate of hippocampal volume loss is 3–5% per year, vs. 0.5–1% per year in controls. The hippocampal volume measurement is now augmented by entorhinal cortex measurement (which atrophies earlier than the hippocampus proper) and by global gray matter measurement (which captures the disease's progression beyond the medial temporal lobe).

5.7 The Prodromal Phase Signature

The summary signature of the prodromal phase is therefore: CSF p-tau231 and p-tau217 elevation, plasma p-tau217 elevation, medial-temporal tau PET positivity, CSF neurogranin elevation, FDG-PET temporoparietal hypometabolism, MRI hippocampal atrophy, plasma NfL elevation, persistent amyloid PET positivity and sTREM2/GFAP elevation from preclinical phase. The transition into dementia phase is marked by the spread of tau PET signal into isocortex, the plateau of CSF p-tau (as the source of secreted tau begins to decline through neuronal loss), and the acceleration of NfL and atrophy.

6. Chapter III The Dementia Phase: Network Collapse and Glial Reactivity

6.1 Defining the Phase

The dementia phase is operationally defined as biomarker-positive with dementia syndrome (cognitive impairment severe enough to impair daily function; CDR ≥ 1.0; MMSE typically < 24). The phase is the clinical-disease state in which AD has historically been diagnosed and is the phase in which most pharmacological intervention has been attempted. The phase typically lasts 6–10 years from diagnosis to death, with substantial variability driven by age at onset, vascular comorbidity, and APOE genotype.

The biomarker signature of the dementia phase is *downstream-dominant*: the upstream amyloid and tau markers plateau or decline as the disease consumes the neurons that produce them, while the downstream neurodegeneration and glial-reactivity markers continue to rise as the cascade reaches advanced stages. The phase's biomarker profile is therefore characterized more by the *plateau* of the upstream markers than by their continued accumulation, and by the *sustained elevation* of the downstream markers.

6.2 The Plateau of Upstream Markers

Amyloid PET reaches its asymptote during the late prodromal/early dementia phase and does not continue to rise meaningfully thereafter (Jack et al., 2013; Insel et al., 2019). The amyloid load is essentially set by the time of dementia diagnosis, with subsequent changes driven by anti-amyloid therapy rather than by natural progression. CSF Aβ42/40 reaches a floor by the same point. CSF p-tau levels rise into prodromal phase and then plateau or decline in dementia phase as the number of tau-secreting neurons declines — the mechanism is cell loss removing the source of secreted tau, leaving the residual tau-bearing neurons producing less total secretion (Mattsson-Carlgren et al., 2020).

The plateau of upstream markers has the practical implication that *the upstream markers do not track severity within the dementia phase*. A patient with mild AD dementia and a patient with severe AD dementia have similar amyloid PET centiloids and similar CSF p-tau values; the markers cannot distinguish them. The within-dementia-phase severity grading must be done with downstream markers — atrophy, NfL, FDG-PET — or with cognitive testing directly.

6.3 Plasma NfL: Sustained Elevation

Plasma NfL continues to rise through the dementia phase, with values 3–5x baseline in mild dementia and 10–20x baseline in severe dementia (Mattsson et al., 2017). The continued rise reflects the ongoing axonal-injury burden as the disease consumes cortical and white-matter axons. Plasma NfL is the best-validated plasma marker of disease severity within the dementia phase, and the rate of NfL rise predicts the rate of subsequent cognitive decline. NfL elevation in this phase is not specific to AD; comparable elevations are seen in advanced FTD, DLB, and vascular dementia, and the marker therefore reports total neurodegenerative burden rather than AD-specific severity.

6.4 MRI Atrophy: From Medial Temporal to Global

MRI atrophy in the dementia phase progresses from medial temporal lobe (already advanced in prodromal phase) to global cortical involvement. The atrophy pattern in early dementia phase is "AD-typical" — temporoparietal predominant, with relative preservation of primary motor and sensory cortices — and the pattern can support differential diagnosis from FTD (which shows frontal/anterior temporal atrophy) and from DLB (which shows relatively preserved cortical volume early). By moderate-to-severe dementia, the atrophy is global, and the imaging is no longer differentiating between AD and other late-stage dementias.

The atrophy rate in AD dementia is 2–4% global gray matter per year and 5–8% hippocampal per year, vs. <1% per year and <2% per year respectively in age-matched controls (Fox et al., 2000; Jack et al., 2008). The atrophy rate predicts subsequent cognitive decline and mortality. Cortical thickness measurements (FreeSurfer, ANTs) supply more sensitive regional measures than total volume.

6.5 Glial Reactivity: GFAP, sTREM2, YKL-40

The glial-reactivity markers reach their sustained elevation in dementia phase, though each rises along a distinct trajectory. Plasma GFAP — already elevated in late preclinical phase — continues to rise through prodromal and into dementia phase, reaching values 3–5x baseline in established dementia (Pereira et al., 2021). The continued rise reflects ongoing astrocyte reactivity in response to the persisting amyloid load and the growing neurodegeneration burden.

CSF sTREM2 follows a more complex trajectory: it rises in preclinical phase, peaks in early prodromal phase, and then declines in dementia phase as microglial number declines through age and disease-related microglial dysfunction. The dementia-phase decline in sTREM2 is interpreted as a *loss of microglial protective capacity* — the microglia that were responding to early amyloid pathology have transitioned into dysfunctional states (the disease-associated microglia of Keren-Shaul et al., 2017; the dystrophic microglia of Streit et al., 2009) and are no longer producing the active TREM2 shedding that drives sTREM2 elevation.

CSF YKL-40/CHI3L1 is elevated principally in dementia phase, reflecting reactive astrocyte and microglial activity in established disease (Craig-Schapiro et al., 2010). It supplies a marker of *advanced* neuroinflammation that complements the earlier-rising GFAP and sTREM2.

6.6 Vascular Comorbidity Markers

The dementia phase is the phase in which vascular comorbidity becomes a major contributor to clinical progression rate. White matter hyperintensity (WMH) burden on FLAIR MRI is the most widely measured vascular marker; large WMH volumes predict faster cognitive decline within AD dementia even when amyloid and tau status are matched (Brickman et al., 2015). Cerebral microbleeds (visible on susceptibility-weighted MRI) supply a related vascular readout and are particularly relevant in the context of anti-amyloid therapy (where they predict ARIA-H risk).

Blood–brain barrier integrity, measured by CSF/serum albumin ratio (Q-albumin) or by dynamic contrast-enhanced MRI (Sweeney et al., 2018; Iturria-Medina et al., 2016), is increasingly recognized as a contributor to AD progression. Elevated Q-albumin in AD dementia predicts faster decline and is hypothesized to reflect the pericyte and endothelial dysfunction that the Vascular Dimension paper (Truchard & Gustafsson, 2026) treats as a fourth Collapse axis.

6.7 The Dementia Phase Signature

The summary signature of the dementia phase is therefore: plateau or decline of amyloid PET and CSF p-tau (with continued amyloid PET positivity), sustained and rising plasma NfL, progressive MRI atrophy from medial temporal to global, sustained plasma GFAP elevation, declining sTREM2 (microglial dysfunction), rising YKL-40 (advanced glial reactivity), accumulating WMH and Q-albumin (vascular comorbidity), persistent KTR elevation (immunometabolic), and broad FDG-PET hypometabolism. The clinical reading is that the disease has shifted from a *driver-dominant* state (in which amyloid and tau are actively accumulating) to a *downstream-dominant* state (in which the consequences of accumulated pathology dominate, and severity is reported by neurodegeneration and glial-reactivity markers rather than by the proteinopathic upstream markers).

7. Chapter IV Beyond ATN: Glial, Synaptic, Vascular, and Metabolic Markers Across the Cascade

7.1 The Limits of ATN

The ATN framework's explicit restriction to amyloid, tau, and neurodegeneration was justified in 2018 by the maturity of the evidence base for each axis. In the seven years since, the evidence base for four additional axes — glial, synaptic, vascular, metabolic — has substantially expanded, and each axis now supplies a clinically informative dimension that ATN does not capture. The 2024 NIA-AA criteria explicitly acknowledged this and identified the glial axis (specifically plasma GFAP) as a candidate for inclusion in a future expanded framework. The expansion proposal "ATN(X)" — in which X indexes one or more of the response axes — is now under active discussion.

The four response axes share a structural property: each indexes the *response* of a specific compartment to the AD core pathology rather than the core pathology itself. Glial markers index the response of astrocytes and microglia. Synaptic markers index the response of neuronal synapses. Vascular markers index the response of cerebral vasculature. Metabolic markers index the systemic immunometabolic state. The four together supply the *response phenotype* of AD, distinct from the core proteinopathy that defines it.

7.2 The Glial Axis: GFAP, sTREM2, YKL-40

The glial axis is the most clinically advanced of the response axes. Plasma GFAP — already discussed in Chapters I and III — is the earliest-rising and most clinically useful single glial marker, with elevation detectable in late preclinical phase and continued rise through prodromal and dementia phases. The Pereira et al. (2021) and Benedet et al. (2021) studies established that plasma GFAP tracks with amyloid PET load and supplies prognostic information beyond plasma p-tau217 in mixed cohorts.

CSF sTREM2 has a more complex trajectory — rising in preclinical, peaking in early prodromal, declining in dementia — that itself supplies phase information: a high sTREM2 in a biomarker-positive individual suggests early-phase disease, while a low sTREM2 in a biomarker-positive individual suggests advanced microglial dysfunction. The Heslegrave et al. (2016) and Suárez-Calvet et al. (2019) studies established the trajectory in large cohorts.

CSF YKL-40 (chitinase-3-like 1) supplies a marker of advanced glial activation and is principally elevated in dementia phase. YKL-40 elevation in CSF is consistent across AD, ALS, MS, and traumatic brain injury, indicating that it reports a generic advanced neuroinflammation state rather than an AD-specific signal (Craig-Schapiro et al., 2010; Olsson et al., 2016).

The clinical implication is that the glial axis supplies a *phase-resolved* readout: plasma GFAP for amyloid-coupled astrocyte response (preclinical-onward), CSF sTREM2 for microglial activation peaking in prodromal phase, and CSF YKL-40 for advanced inflammation in dementia phase. The three together supply a neuroinflammatory staging that is independent of amyloid and tau.

7.3 The Synaptic Axis: Neurogranin, SNAP-25, Synaptotagmin-1

The synaptic axis indexes the disease-relevant variable that cognitive testing measures: synaptic functional integrity. CSF neurogranin is the best-characterized marker, with elevation in preclinical and prodromal phase tracking future cognitive decline. The Kvartsberg et al. (2015) and Portelius et al. (2018) studies established CSF neurogranin as a synaptic marker with diagnostic and prognostic value, and the Tarawneh et al. (2016) study demonstrated that CSF neurogranin predicts cognitive decline beyond what amyloid and tau markers predict.

CSF SNAP-25 and synaptotagmin-1 supply presynaptic markers complementary to the postsynaptic neurogranin (Brinkmalm et al., 2014; Wang et al., 2018). The presynaptic markers are particularly informative in differential diagnosis: SNAP-25 is preferentially elevated in AD over DLB, while synaptotagmin-1 is preferentially elevated in early synaptopathic states. The combined synaptic-marker panel supplies a richer readout of synaptic state than any single marker.

The synaptic axis maps directly to the Convergent Synaptic Collapse thesis (Truchard & Gustafsson, 2026): the dissertation's claim that PV+ interneurons, perineuronal nets, and gamma-frequency oscillations constitute a convergent infrastructure on which AD acts is operationally testable through synaptic biomarker measurements. Specifically, CSF parvalbumin (still in research-assay development) and CSF aggrecan (a perineuronal-net core protein) would supply the most direct biomarker readout of the CSC framework's central claims.

7.4 The Vascular Axis: WMH, BBB Permeability, Pulse-Wave Indices

The vascular axis indexes the response of cerebral vasculature to age, hypertension, diabetes, and AD-specific cerebral amyloid angiopathy. WMH burden on FLAIR MRI is the most widely measured marker and is elevated even in preclinical AD; the Brickman et al. (2015) and Lo and Jagust (2012) studies established that WMH burden predicts AD progression rate independent of amyloid and tau status.

Blood–brain barrier permeability — measured by CSF/serum albumin ratio (Q-albumin) or by dynamic contrast-enhanced MRI — is elevated in AD and supplies a more proximal measure of vascular dysfunction. The Sweeney et al. (2018) and Nation et al. (2019) studies demonstrated that BBB breakdown in the hippocampus precedes overt AD pathology, supplying evidence that vascular dysfunction is upstream rather than downstream of cognitive decline in at least a subset of cases.

The Vascular Dimension paper of the Collapse trilogy (Truchard & Gustafsson, 2026) develops the case for treating vascular dysfunction as a fourth Collapse axis, coupled to the synaptic, microglial, and bioenergetic axes through pericyte–endothelial–microglial signaling. The vascular biomarkers — WMH, Q-albumin, DCE-MRI permeability, pulse-wave velocity — supply the operational readout for that fourth axis.

7.5 The Metabolic Axis: KTR and NAD+ Precursors

The metabolic axis is the least operationalized of the four response axes but supplies the most direct coupling to the Bioenergetic Collapse thesis. The plasma and CSF kynurenine-to-tryptophan ratio (KTR) reflects inflammatory IDO induction and is elevated in MCI due to AD (Lim et al., 2017; van der Velpen et al., 2019; Sorgdrager et al., 2019). The KTR couples peripheral inflammation to central monoaminergic decline and to the de novo NAD+ biosynthesis arm; the *Tryptophan Partition* dissertation (Truchard & Gustafsson, 2026) develops the full mechanistic framework.

Plasma NAD+ precursors (NMN, NR, NAM) and downstream metabolites (1-methylnicotinamide, methylnicotinamide-oxide) supply readouts of NAD+ metabolism. The methods for plasma NAD+ precursor measurement have matured substantially since 2020 (Migaud et al., 2024; Liu et al., 2018), and small-cohort studies suggest reductions in NAD+ precursor availability in AD. The clinical utility of NAD+ metabolic measurement remains under investigation, and the markers are not yet routine, but they supply the most direct readout of the Bioenergetic Collapse axis.

FDG-PET (already discussed in Chapter II) supplies the imaging-based metabolic readout: regional glucose hypometabolism in temporoparietal cortex, posterior cingulate, and lateral parietal areas. FDG-PET is the most clinically available metabolic marker and is routinely used in AD diagnosis.

7.6 Cross-Axis Coupling

The four response axes are not independent; they are coupled through the underlying mechanistic infrastructure. Glial reactivity (GFAP, sTREM2) and metabolic shift (KTR) are coupled through neuroinflammatory IDO induction. Synaptic loss (neurogranin) and bioenergetic stress (KTR, NAD+ depletion) are coupled through PV+-interneuron metabolic demand (Kann et al., 2014; Truchard & Gustafsson, 2026, *Convergent Synaptic Collapse*). Vascular dysfunction (WMH, Q-albumin) and microglial state (sTREM2, GFAP) are coupled through pericyte–microglial signaling.

The cross-axis coupling has the practical consequence that an extended biomarker panel — ATN(GSVM), where G is glial, S is synaptic, V is vascular, and M is metabolic — supplies a richer phenotypic characterization than ATN alone. The seven-axis panel (or some clinically tractable subset) is the natural endpoint of the post-ATN biomarker development trajectory and is the framework on which the next decade of trial design will likely be organized.

8. Chapter V The Plasma Biomarker Revolution and the Democratization of Early Detection

8.1 The Pre-Plasma Era

For most of the AD biomarker era — from the 1995 establishment of CSF Aβ42 measurement through 2018 — definitive AD biomarker measurement required CSF (via lumbar puncture) or PET (with cyclotron-produced or unit-dose [^18F] tracers). Both modalities are limited in access: lumbar puncture is performed in specialized centers, requires patient consent for a moderately invasive procedure, and is contraindicated in patients on anticoagulation or with intracranial mass effect; PET is performed in centers with the relevant imaging infrastructure, costs $3,000–$6,000 per scan, and is reimbursed only in defined clinical contexts (Medicare CMS-1418-F policy, post-2022). The consequence is that, throughout this era, AD biomarker measurement was effectively rationed to memory-clinic populations and to clinical-trial enrollees.

The pre-plasma era was therefore an era in which the *biomarker-defined disease* and the *clinically diagnosed disease* were largely the same population, distinguished only by the small minority of clinically diagnosed AD patients who underwent biomarker confirmation and by the small minority of preclinical cohorts (DIAN, A4, AHEAD 3-45) in which biomarker measurement preceded clinical diagnosis. The population-level epidemiology of preclinical AD was estimated from the cohort studies and modeled from autopsy series; it was not directly measured.

8.2 The Plasma Aβ42/40 Wave (2018–2020)

The first wave of the plasma revolution began in 2018 with the high-precision mass spectrometric measurement of plasma Aβ42/40 (Nakamura et al., 2018; Schindler et al., 2019). The effect size of amyloid positivity on plasma Aβ42/40 is small — a 10–15% reduction — and the AUC for amyloid PET positivity is 0.85–0.90. The clinical performance is sufficient for population-level screening but insufficient for definitive diagnosis. The C2N Diagnostics PrecivityAD assay, FDA-cleared in 2020, was the first commercial plasma Aβ assay; it is used principally as a high-NPV ruling-out test in symptomatic populations.

8.3 The Plasma p-Tau217 Wave (2020–2024)

The second and more consequential wave began in 2020 with the demonstration that plasma p-tau217 detects amyloid PET positivity with AUC > 0.95 (Palmqvist et al., 2020; Janelidze et al., 2020). The effect size of amyloid positivity on plasma p-tau217 is large — a 3–5x elevation — because p-tau217 is preferentially elevated by AD pathology and is much less affected by peripheral processes than Aβ. The clinical performance is sufficient for *diagnostic* rather than merely screening use, and the marker has been adopted as the first-line plasma test in memory-clinic practice.

The 2023 publications of the ALZpath (Mielke et al., 2023) and Lumipulse (Brum et al., 2023) plasma p-tau217 assays demonstrated clinically usable analytical performance at scale, with central laboratory variability under 10% and clinical-grade quality control. The 2025 FDA clearance of the Lumipulse plasma p-tau217/Aβ42 ratio test for AD diagnosis made high-quality plasma AD biomarker measurement available in primary-care laboratory networks.

8.4 The Plasma GFAP Adjunct

Plasma GFAP — already discussed in Chapter I — supplies a complementary readout to plasma p-tau217. GFAP is the earliest-rising plasma AD biomarker, with elevation detectable in late preclinical phase before p-tau217 becomes positive (Benedet et al., 2021; Pereira et al., 2021). The combination of plasma GFAP plus plasma p-tau217 supplies a two-marker panel that captures preclinical-phase signal (GFAP) and prodromal-phase signal (p-tau217); the AUCs for amyloid PET positivity and for prediction of clinical AD progression are both improved over either marker alone.

8.5 Plasma NfL: The Generic Progression Marker

Plasma NfL — discussed in Chapter II — supplies the third workhorse plasma marker. NfL is non-specific to AD but tracks total neurodegenerative burden and supplies a continuous-trajectory variable that the binary amyloid and tau markers do not. The clinical use of plasma NfL in AD is principally as a progression marker after diagnosis is established, with serial NfL measurements supplying a quantitative readout of disease activity that can be used to assess treatment response or to predict short-term decline.

8.6 The Two-Step Screen and Population-Scale Detection

The practical consequence of the plasma revolution is the feasibility of a two-step screening strategy for AD: plasma p-tau217 (plus GFAP, optionally) as a high-sensitivity first-line test, followed by amyloid PET or CSF confirmation for the positive cases. The Hansson et al. (2023) BioFINDER analysis demonstrated that a two-step plasma confirmatory strategy can identify amyloid-positive individuals at primary-care scale with positive predictive value > 0.85 and at one-third the cost of an amyloid-PET-first strategy.

The clinical implementation of this strategy is now under active development. The U.S. Medicare CMS has signaled interest in covering plasma AD biomarker tests in symptomatic populations; the U.K. NHS has begun pilot implementation in memory clinics; and several European national health systems are developing screening pathways. The clinical-trial implications are equally substantial: enrollment in symptomatic AD trials can now be biomarker-confirmed at primary-care scale, and enrollment in preclinical trials can be biomarker-pre-screened at population scale.

8.7 The Disappearance of "Asymptomatic" Cohorts

A subtler implication of the plasma revolution is the disappearance, in any operational sense, of a pure "asymptomatic" preclinical cohort. As plasma p-tau217 testing extends into primary-care practice, the population of biomarker-positive but cognitively normal individuals will, for the first time, be systematically identified. The clinical and ethical implications are substantial: should asymptomatic biomarker-positive individuals be informed of their status? Should they be offered treatment? Should they be enrolled in monitoring programs?

The current consensus (Rabinovici et al., 2024) is that asymptomatic biomarker-positive individuals should not routinely be tested outside research contexts because the available treatments (lecanemab, donanemab) are not FDA-approved for preclinical AD. The AHEAD 3-45 trial results (expected 2027) will likely shift this consensus: if amyloid removal in preclinical AD substantially reduces progression to MCI, the case for routine screening and treatment in asymptomatic biomarker-positive populations becomes substantial, and the clinical landscape will reorganize around a fundamentally different model of AD as a chronic preclinical disease analogous to hypertension or hyperlipidemia.

9. Chapter VI Mapping the Biomarker Cascade to the Collapse Trilogy

9.1 The Trilogy's Three Axes

The Collapse trilogy identifies three mechanistic axes of AD: a synaptic-circuit axis (PV+ interneurons, perineuronal nets, gamma oscillations), a microglial-state axis (loss of TGF-β/SMAD-maintained homeostatic identity), and a bioenergetic-substrate axis (mitochondrial quality-control failure, NAD+ depletion, autophagy-lysosomal collapse). The trilogy's claim is that each axis supplies a convergent infrastructure on which the disease-specific molecular drivers (Aβ, tau) act, and that the three axes are coupled through TREM2-PI3K-AKT-mTOR microglial support, v-ATPase ATP-dependent lysosomal acidification, and PV+ interneuron energetics.

The biomarker cascade developed in this dissertation supplies the *clinical readout* of the three axes. Each axis is operationalized through a specific subset of biomarkers, and the temporal phase in which the corresponding markers come online determines when the underlying axis becomes clinically measurable.

9.2 The Synaptic Axis

The synaptic axis is operationalized through:

- **Direct markers**: CSF neurogranin (postsynaptic), CSF SNAP-25 and synaptotagmin-1 (presynaptic). Neurogranin emergence in late preclinical phase indexes the *first* synaptic loss; SNAP-25/synaptotagmin-1 emergence in prodromal phase indexes presynaptic-functional collapse. - **Indirect/imaging markers**: FDG-PET temporoparietal hypometabolism (regional synaptic function), MRI hippocampal atrophy (downstream from synaptic loss), tau PET (synaptic-tau accumulation in axons and synaptic terminals). - **Specific to the CSC framework**: CSF parvalbumin (PV+-interneuron loss; research assay) and CSF aggrecan (perineuronal-net core protein; research assay). These markers would supply the most direct readout of the CSC framework's central claim that PV+ interneurons and PNNs are the convergent substrate of AD; their development for clinical use is a priority for the next decade.

The temporal sequence of synaptic-axis markers — neurogranin (late preclinical) SNAP-25/synaptotagmin-1 (prodromal) FDG-PET (prodromal) atrophy (prodromal-dementia) cognitive symptoms (prodromal-dementia) — supplies the operational sequence in which the synaptic axis is recognized.

9.3 The Microglial Axis

The microglial axis is operationalized through:

- **Direct markers**: CSF sTREM2 (microglial activation), plasma GFAP (astrocyte reactivity; coupled to microglial state through cytokine signaling), CSF YKL-40 (advanced microglial/astrocyte activation), plasma sTREM2 (emerging in research, less established than CSF). - **Indirect markers**: KTR (inflammatory IDO induction in microglia and peripheral monocytes),

plasma cytokines (IL-6, TNF-α, IL-1β; less specific but supportive). - **Specific to the HMC framework**: CSF or plasma TGF-β1, CSF SMAD3 phosphorylation (research methods), and microglial-state transcriptomic profiling from CSF-isolated microglia (emerging research methodology). These would supply the most direct readout of the Homeostatic Microglial Collapse thesis's central claim that loss of TGF-β/SMAD-maintained homeostatic identity is the upstream microglial-state transition.

The temporal sequence — plasma GFAP (late preclinical) CSF sTREM2 rise (preclinical-prodromal transition) CSF sTREM2 peak (early prodromal) KTR rise (prodromal) CSF YKL-40 rise (dementia) CSF sTREM2 decline (dementia) — supplies a phase-resolved readout of microglial-state evolution.

9.4 The Bioenergetic Axis

The bioenergetic axis is operationalized through:

- **Direct markers**: KTR (immunometabolic state), plasma NAD+ precursors (research-grade), plasma 1-methylnicotinamide (NAD+ degradation product), CSF lactate (anaerobic metabolic shift), plasma BHB (ketogenic capacity index). - **Indirect/imaging markers**: FDG-PET (regional glucose metabolism), MRS measurement of brain NAA (mitochondrial proxy), DTI/MRI measures of axonal integrity (downstream from mitochondrial dysfunction). - **Specific to the BC framework**: plasma p-tau and amyloid biomarkers indirectly reflect the proteostatic component of the bioenergetic axis (mitophagy and macroautophagy failure produce proteinopathy), and the LC-specific [^11C]MeNER PET or neuromelanin-sensitive MRI supply LC-specific readouts of the locus coeruleus pathway that the BC framework identifies as the earliest site of AD pathology.

The temporal sequence — LC neuromelanin signal decline (very early, preclinical) KTR rise (preclinical-prodromal) FDG-PET hypometabolism (prodromal) plasma NAD+ precursor decline (prodromal-dementia) CSF lactate elevation (dementia) — supplies a phase-resolved readout of bioenergetic decline.

9.5 The Coupling: Where Biomarkers Cross Axes

The trilogy's coupling claims (TREM2-mTOR microglial energetics, v-ATPase ATP-dependent lysosomal acidification, PV+ interneuron metabolic demand) are operationally testable through cross-axis biomarker correlation. Specifically:

- **CSF sTREM2 (microglial) × KTR (bioenergetic)**: should be positively correlated, with the correlation reflecting the immunometabolic coupling between microglial activation and inflammatory IDO induction. - **CSF neurogranin (synaptic) × FDG-PET (bioenergetic)**: should be positively correlated, with the correlation reflecting PV+ interneuron metabolic demand

as the substrate of synaptic loss. - **WMH (vascular) × CSF sTREM2 (microglial)**: should be positively correlated, with the correlation reflecting pericyte–microglial coupling.

Cross-axis biomarker correlation in large cohorts has been incompletely characterized; the BioFINDER, ADNI, and DIAN cohorts have collected the relevant marker data and could in principle support the analysis. The cross-axis correlations are the operational test of the trilogy's coupling claims and are a priority for the next phase of the methodology.

9.6 The Phase × Axis Matrix

The integration of the trilogy's three axes (plus the vascular and proteinopathy axes) with the cascade's three phases (preclinical, prodromal, dementia) generates a phase × axis matrix in which each cell is populated by the dominant biomarker readout for that phase × axis combination. The matrix is the natural endpoint of the integration developed in this dissertation:

- **Preclinical × Synaptic**: CSF neurogranin (emerging) - **Preclinical × Microglial**: plasma GFAP, CSF sTREM2 (early elevation) - **Preclinical × Bioenergetic**: LC neuromelanin signal decline, mild KTR rise - **Preclinical × Vascular**: early WMH (modest), Q-albumin (modest) - **Preclinical × Proteinopathy (A/T)**: CSF Aβ42/40 decline, amyloid PET positive, plasma p-tau231 emerging - **Prodromal × Synaptic**: CSF neurogranin (established), SNAP-25, FDG-PET, hippocampal atrophy - **Prodromal × Microglial**: CSF sTREM2 peak, plasma GFAP rising, KTR rising - **Prodromal × Bioenergetic**: FDG-PET hypometabolism, plasma NAD+ precursor decline - **Prodromal × Vascular**: WMH accumulation, BBB-permeability increase - **Prodromal × Proteinopathy**: plasma p-tau217 elevation, CSF p-tau181/217/231 elevation, tau PET medial-temporal - **Dementia × Synaptic**: advanced atrophy, generalized FDG-PET hypometabolism, plasma NfL elevation - **Dementia × Microglial**: sustained plasma GFAP, CSF sTREM2 decline (dysfunction), CSF YKL-40 elevation - **Dementia × Bioenergetic**: CSF lactate elevation, plasma NAD+ depletion, broad FDG-PET hypometabolism - **Dementia × Vascular**: WMH burden, Q-albumin elevation, cerebral microbleeds - **Dementia × Proteinopathy**: amyloid PET plateau, CSF p-tau plateau, tau PET isocortical

The matrix supplies the operational vocabulary in which biomarker-guided staging and trial design will be conducted in the next decade.

10. Chapter VII Therapeutic Windows, Trial Design, and the Operationalization of Secondary Prevention

10.1 The Phase-Window Concept

The phase-mapping developed in the preceding chapters has direct implications for therapeutic-window targeting. Each AD-modifying intervention has a *window* in which its effect size is largest, and the window is defined not by clinical category (preclinical, MCI, dementia) but by biomarker phase. The anti-amyloid antibodies (lecanemab, donanemab) have their largest effect sizes in early symptomatic AD — the prodromal-to-early-dementia transition — because that is the phase in which amyloid pathology is still actively driving downstream cascade events. Anti-tau approaches (currently in trial: zagotenemab, semorinemab, JNJ-63733657) are expected to have larger effect sizes earlier — late preclinical to early prodromal — because tau pathology is still spreading and the spread is the mechanism by which the cascade propagates. Anti-inflammatory and metabolic approaches may have effects across the full cascade, with secondary-prevention effects expected to be largest in preclinical phase.

The phase-window concept reorganizes trial design from "AD" or "MCI due to AD" inclusion criteria to "biomarker-phase X" inclusion criteria. The current generation of AD trials is in transition toward this framework: the lecanemab Phase 3 (CLARITY-AD) used biomarker-confirmed early AD (MCI/mild dementia with amyloid PET or CSF positivity); the AHEAD 3-45 trial uses biomarker-confirmed preclinical AD with sub-stratification by amyloid PET burden. The next-generation trials are expected to use plasma p-tau217 thresholds for inclusion and plasma p-tau217 × plasma GFAP × plasma NfL panels for stratification.

10.2 The Lecanemab/Donanemab Phase Test

The 2023 CLARITY-AD (lecanemab; van Dyck et al., 2023) and TRAILBLAZER-ALZ 2 (donanemab; Sims et al., 2023) trials are the first phase-window tests of an AD-modifying intervention. Both trials enrolled biomarker-confirmed early AD (MCI/mild dementia, amyloid-PET-positive or CSF-positive) and both demonstrated 25–35% slowing of cognitive decline. The TRAILBLAZER-ALZ 2 trial additionally stratified by tau PET load and demonstrated larger effect sizes in low-tau strata, consistent with the phase-window hypothesis (earlier in cascade = larger effect).

The biomarker effects observed in CLARITY-AD and TRAILBLAZER-ALZ 2 supply the first systematic dataset on the cascade's response to upstream intervention. Amyloid PET clearance was dramatic (60–80% reduction in centiloid value at 18 months in donanemab); plasma p-tau217 declined substantially (30–50% reduction); plasma GFAP declined modestly (10–20%); plasma NfL was unchanged or modestly elevated (consistent with the antibody-related amyloid-clearance neurodegeneration secondary to ARIA, balanced against reduced ongoing pathology). The pattern supports the cascade's hypothesized causal hierarchy: removing the upstream driver (amyloid) reduces the next-downstream marker (p-tau217), the next (GFAP), but not the most downstream (NfL).

10.3 The Preclinical Trial: AHEAD 3-45 and the Secondary-Prevention Question

The AHEAD 3-45 trial (ongoing, results expected 2027) is the first systematic test of secondary prevention in preclinical AD. The trial enrolls cognitively normal, amyloid-PET-positive individuals stratified by amyloid burden: A3 stratum (low amyloid, Centiloid 20–40) and A45 stratum (moderate-to-high amyloid, Centiloid > 40). The primary endpoint is cognitive decline on the Preclinical Alzheimer Cognitive Composite (PACC-5) at 4 years.

The trial's results will resolve several first-order questions: (i) does early amyloid removal prevent the seeding of downstream tau pathology, (ii) does the effect size in preclinical AD exceed the effect size in prodromal/early-dementia AD, and (iii) is the safety profile of lecanemab acceptable in cognitively normal populations with much longer expected treatment durations than the CLARITY-AD population. If the trial demonstrates a substantial effect, the AD treatment landscape will reorganize around preclinical detection and secondary prevention, with profound implications for plasma screening, clinical-pathway design, and population-level cost-effectiveness.

10.4 Anti-Tau and the Prodromal Window

The anti-tau therapeutic class — currently dominated by anti-tau antibodies (semorinemab, zagotenemab, JNJ-63733657, BIIB080) — is positioned for the prodromal window. Tau spread, by the propagation mechanism documented in cell and animal models (Clavaguera et al., 2009; Liu et al., 2012), is the mechanism by which AD pathology progresses from medial temporal lobe through limbic structures into isocortex. The intervention point is the phase in which tau is actively spreading and the topographic distribution is still limited — this is the prodromal phase by current cascade mapping.

The first-generation anti-tau antibody trials (Phase 2 semorinemab in MCI; tilavonemab in early AD) showed minimal cognitive effects but the trials were small, the antibodies were directed at N-terminal tau (likely the wrong epitope), and the biomarker effects were not systematically measured. The current Phase 2/3 trials (BIIB080 antisense oligonucleotide; JNJ-63733657 antibody against middle-domain tau) are expected to supply more definitive tests in the next 2–4 years.

10.5 The Glial and Metabolic Therapeutic Surfaces

The glial and metabolic therapeutic surfaces are less mature than the proteinopathy-targeting surfaces but supply complementary intervention points. Microglial-state stabilizers — agonist anti-TREM2 antibodies (AL002 by Alector; ATV-TREM2 by Denali Therapeutics) — are in Phase 2 trials with the hypothesis that sustaining microglial protective activity during disease progression will slow neurodegeneration. The phase window for these interventions is hypothesized to be preclinical-to-prodromal, the window in which microglial activation is still capable of protective function before transitioning to the dysfunctional dementia-phase state.

Metabolic interventions — NAD+ precursors (nicotinamide riboside, nicotinamide mononucleotide), IDO inhibitors (epacadostat, INCB024360), KMO inhibitors (CHDI-340246) — are at earlier stages of clinical evaluation in AD specifically (though NR is in Phase 2/3 in PD with the NIH-funded NR-SAFE trial). The phase window for these interventions is hypothesized to span the cascade, with secondary-prevention effects in preclinical phase and disease-modifying effects in prodromal/early-dementia phase.

10.6 The Combination-Therapy Argument

The phase × axis matrix developed in Chapter VI implies that monotherapy targeting any single axis at any single phase will produce limited effect sizes because the cascade is multi-axis and multi-phase. The implied therapeutic strategy is *combination therapy* — for example, anti-amyloid antibody in preclinical phase to prevent seeding, plus anti-tau antibody in prodromal phase to slow spread, plus a microglial-state stabilizer across the cascade to maintain protective function, plus a metabolic support (NAD+ precursor or KMO inhibitor) to address the bioenergetic axis. The combination strategy is consistent with the precedent of multi-axis treatment in hypertension, hyperlipidemia, and HIV.

The first systematic combination-therapy trial is in design as of 2026 (the AHEAD-COMBO concept, not yet announced) and is expected to combine lecanemab (anti-amyloid) with an anti-tau antibody in preclinical AD. The trial's design depends on biomarker stratification by phase × axis, and the framework developed in this dissertation supplies the operational vocabulary for that stratification.

10.7 The Falsifiable Predictions

The phase-mapping framework supplies several falsifiable predictions for the next 5–10 years of trial data:

Prediction 1. In any biomarker-positive cohort, the effect size of anti-amyloid intervention will decrease monotonically across the phase sequence preclinical prodromal dementia. The AHEAD 3-45 trial will test this directly. If effect sizes are larger in dementia than in prodromal, the framework's phase-window hypothesis is falsified.

Prediction 2. Plasma p-tau217 will decline within 12 months of anti-amyloid antibody treatment regardless of clinical stage, but the magnitude of plasma p-tau217 decline will correlate with subsequent cognitive benefit. If plasma p-tau217 declines without subsequent cognitive benefit, the framework's coupling between biomarker dynamics and clinical outcome is weakened.

Prediction 3. Plasma NfL will be largely unaffected by anti-amyloid intervention but will be affected by anti-tau and microglial-state intervention. If NfL declines with anti-amyloid intervention beyond what amyloid clearance alone would predict, the framework's hierarchical cascade model is

enriched but not falsified; if NfL is affected by no intervention class, the cascade's coupling is weaker than hypothesized.

Prediction 4. Combination therapy (anti-amyloid plus anti-tau plus glial/metabolic) in preclinical AD will produce effect sizes substantially exceeding the additive expectation of the component monotherapies. If combinations are merely additive, the cross-axis coupling claimed by the trilogy is weakened.

Prediction 5. Population-scale plasma p-tau217 screening will identify preclinical AD at prevalence 3–5x the current clinically diagnosed prevalence within a decade of routine deployment. If the prevalence is lower, the preclinical-phase population is smaller than the cascade hypothesis suggests; if higher, the operational definitions of phase boundaries will require revision.

11. Conclusion

This dissertation has advanced the thesis that Alzheimer's disease biomarkers are best understood as a staged signature problem, with each of the three temporal phases (preclinical, prodromal, dementia) characterized by the first emergence of a distinct constellation of molecular markers on top of those already established. The preclinical phase is the era of amyloid accrual, characterized by CSF and plasma Aβ42/40 decline, amyloid PET positivity, and the late-preclinical emergence of plasma GFAP, CSF sTREM2, and the kynurenine-to-tryptophan ratio. The prodromal phase is the era of tau spread and synaptic loss, dominated by the p-tau cascade (p-tau231 p-tau217 p-tau181 total tau) and the emergence of CSF neurogranin, FDG-PET temporoparietal hypometabolism, MRI hippocampal atrophy, and plasma NfL. The dementia phase is the era of network collapse, characterized by the plateau of upstream markers, sustained downstream marker elevation (NfL, atrophy, GFAP), the decline of CSF sTREM2 (microglial dysfunction), the elevation of CSF YKL-40 (advanced glial reactivity), and the accumulation of vascular comorbidity markers.

The framework supplies four principal contributions. First, it identifies the *fluid-of-choice* question — when each marker is most informative in CSF, plasma, PET, or MRI — as a phase-dependent question, with markers transitioning between fluids and modalities as the disease progresses. Second, it extends the ATN framework with four response axes (glial, synaptic, vascular, metabolic), each operationalized through specific biomarker constellations, and supplies a unified phase × axis matrix in which the trilogy's mechanistic claims can be tested. Third, it maps the biomarker cascade onto the Collapse trilogy's three mechanistic axes (synaptic, microglial, bioenergetic) plus the vascular and proteinopathy axes, supplying the operational readout of the trilogy's central claims.

Fourth, it derives the therapeutic-window implications of the cascade for trial design and supplies the falsifiable predictions on which the framework is testable.

The dissertation's central scientific conclusion is that the biomarker cascade is not a passive recorder of an underlying disease but an active staging instrument: the choice of which marker to measure when defines which version of the disease the clinic is allowed to see. A biomarker grammar organized by first-emergence phase, by fluid of choice, by mechanistic axis, and by therapeutic-window implication supplies the structural basis for the next decade of AD trial design and clinical practice. The plasma biomarker revolution has placed AD-specific molecular measurement within reach of population-scale screening; the operationalization of secondary prevention will, within the next five years, transform AD from a clinical-syndrome disease into a chronic preclinical disease analogous in management to hypertension or hyperlipidemia. The biomarker cascade framework developed here is intended as the conceptual scaffolding for that transformation.

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End of Dissertation