The Neurovascular-Neuroinflammatory Continuum

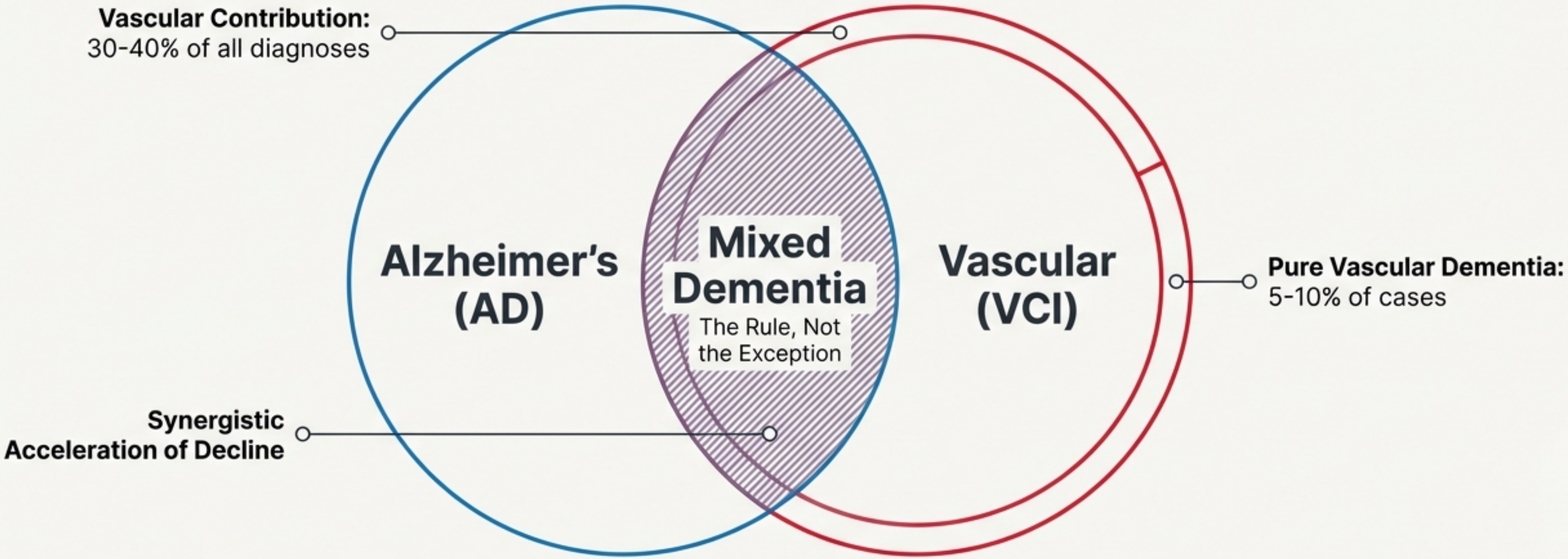
Precision Phenotyping for Non-Amyloid Dementia

- Beyond the ‘Rule-Out’ Diagnosis
- Targeting the ‘A- T- N+’ Gap
- From Structural Injury to Active Dysregulation

Prepared for Dr. James Truchard and Benjamin Gustafsson
Drafted by Gemini3.0

The Myth of the Binary

The historical separation of Alzheimer's and Vascular pathology is contradicted by modern data.



Reality: "Pure" pathology is a statistical rarity in the aging brain.

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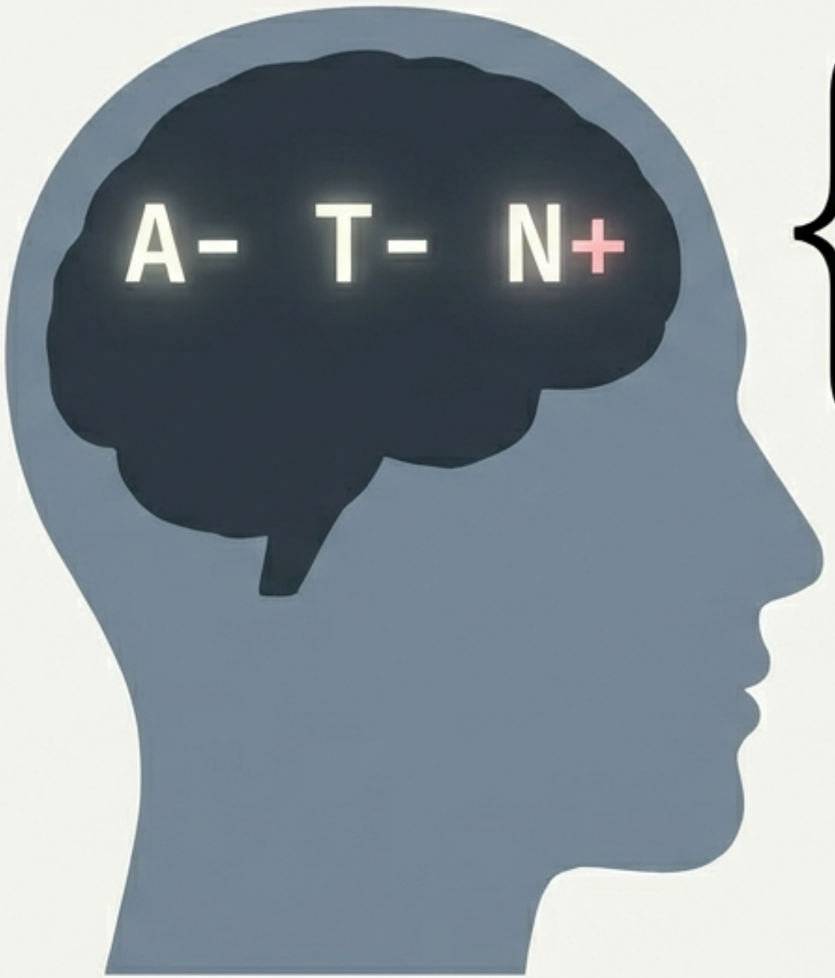
The “Amyloid-Negative” Orphan

Defining the patient who falls through the cracks.



A- (Amyloid Negative)

T- (Tau Negative)

N+ (Neurodegeneration Present)

The Suspects

1. Pure Vascular Cognitive Impairment (VCI)
2. LATE (TDP-43 Proteinopathy)
3. Rare Etiologies

THE CLINICAL QUESTION

If it is not plaques (Amyloid) or tangles (Tau), **what is driving the neurodegeneration?**

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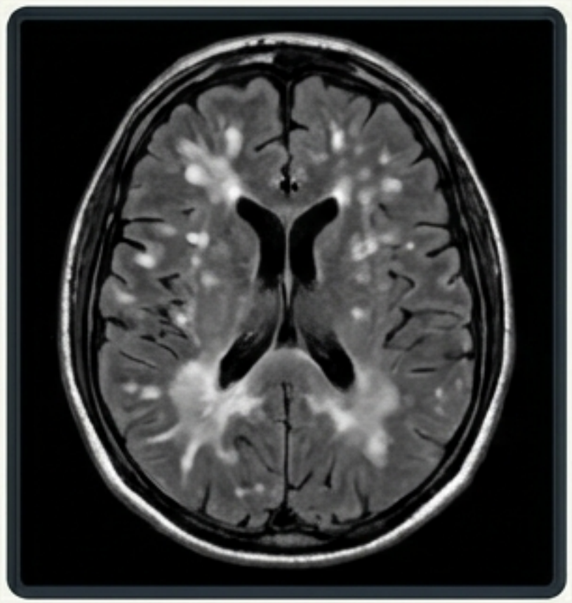
The Clinico-Radiological Paradox

Why standard MRI is a blunt instrument.

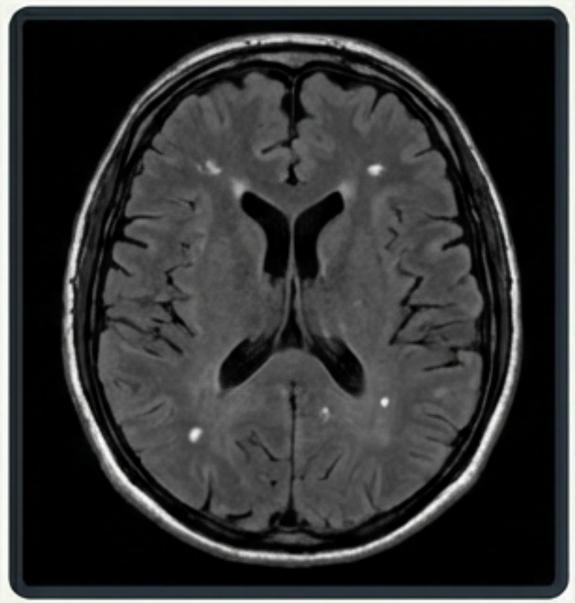
Scan A: Extensive WMH Burden



Patient Status: Cognitively Normal

?

Scan B: Mild WMH Burden



Patient Status: Severe Executive Dysfunction

The Limitation: White Matter Hyperintensity (WMH) volume is non-specific.

- Fails to distinguish ischemic vs. inflammatory etiology.
- Misses diffuse damage in ‘Normal Appearing White Matter’.
- We must see beyond the lesion.

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The Vascular-Immune Hypothesis

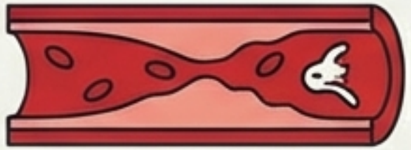
Vascular injury is an active inflammatory process, not just a scar.

RISK FACTORS

Hypertension, Diabetes

TRIGGER

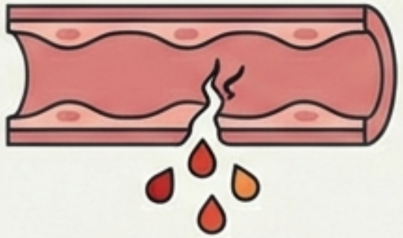
Endothelial Dysfunction & Hypoxia



HIF-1α Upregulation

BREACH

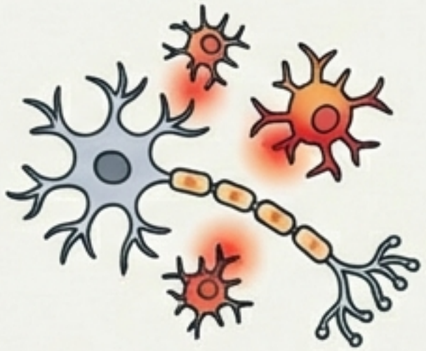
BBB Leakage



Serum Protein Extravasation

RESPONSE

Neuroinflammation



Microglia Activation

Vascular — Inflammatory

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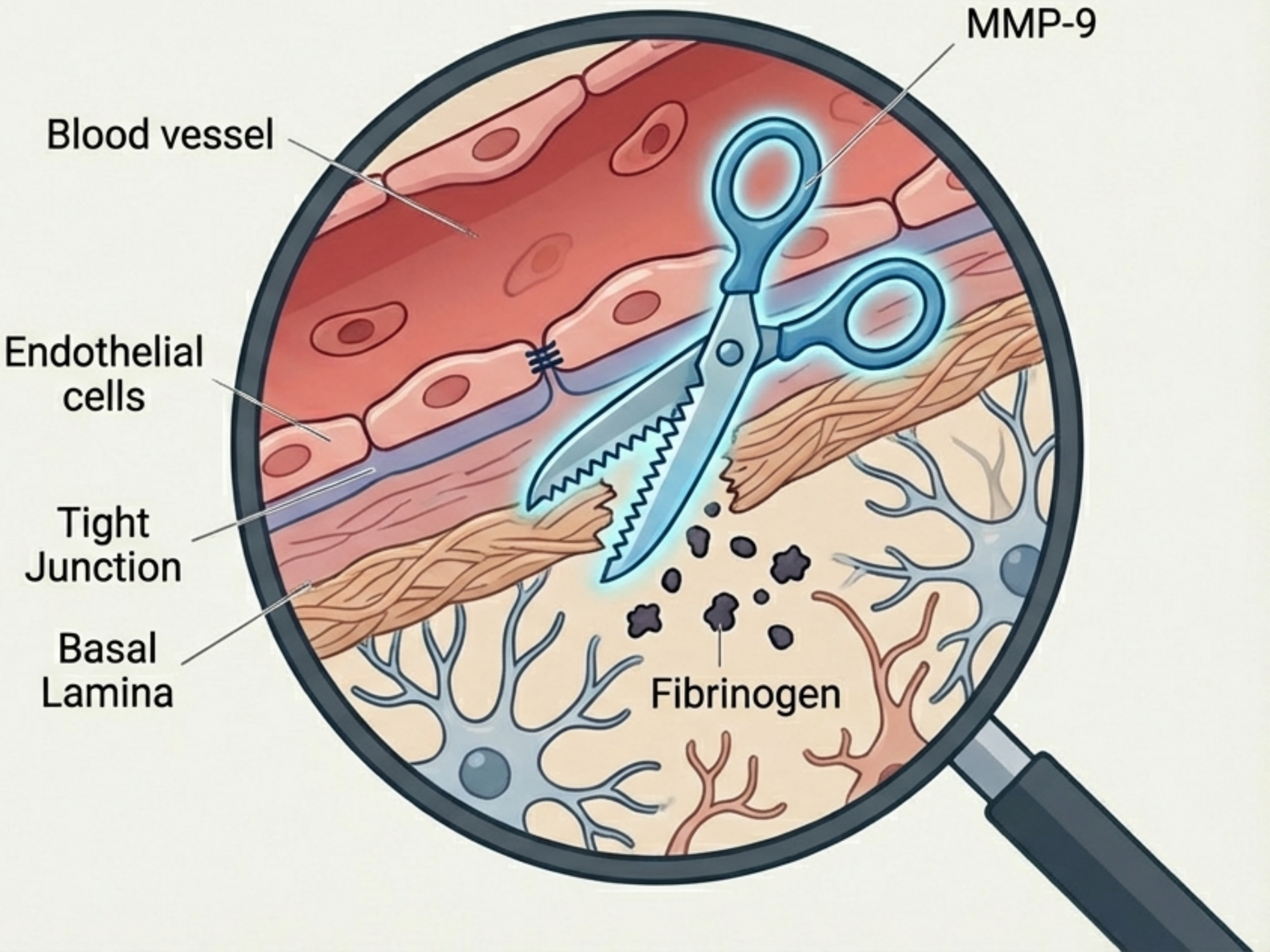
The Molecular Culprit: MMP-9

Mechanisms of Barrier Breakdown

- 1. Chronic Hypoxia triggers MMP-9 release.
- 2. MMP-9 degrades Type IV Collagen and Laminin.
- 3. Tight Junctions fail, leading to fluid leakage (Vasogenic Edema).
- Result: The “Angiogenic-Inflammatory” signature of VCI.



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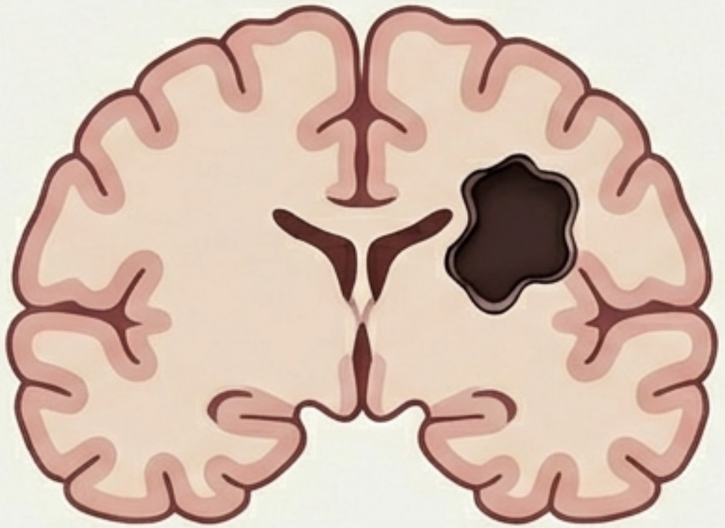
The Consequence: Diffuse Disintegration

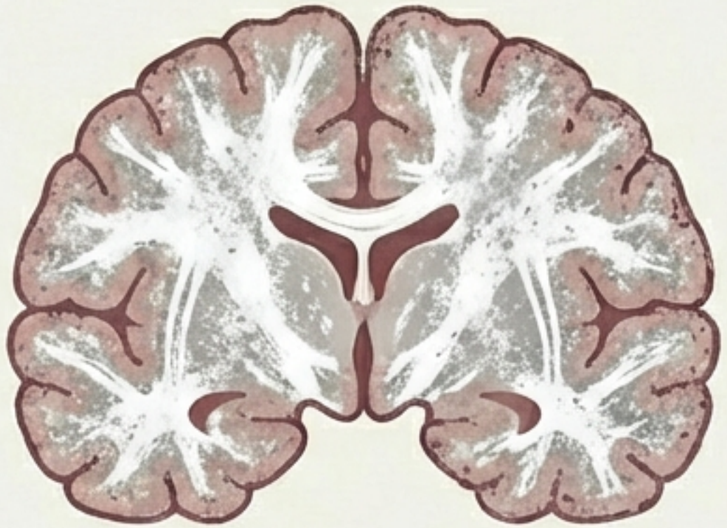
Microstructural failure beyond the visible lesion.

Macro-Infarct



Visible Stroke / Necrosis. Focal damage.

Micro-Structural Disintegration



Diffuse Demyelination / Apoptosis. Global fragility.

Pathology: Inflammaging

Oligodendrocytes are sensitive to oxidative stress, leading to widespread loss of myelin integrity invisible to standard MRI.

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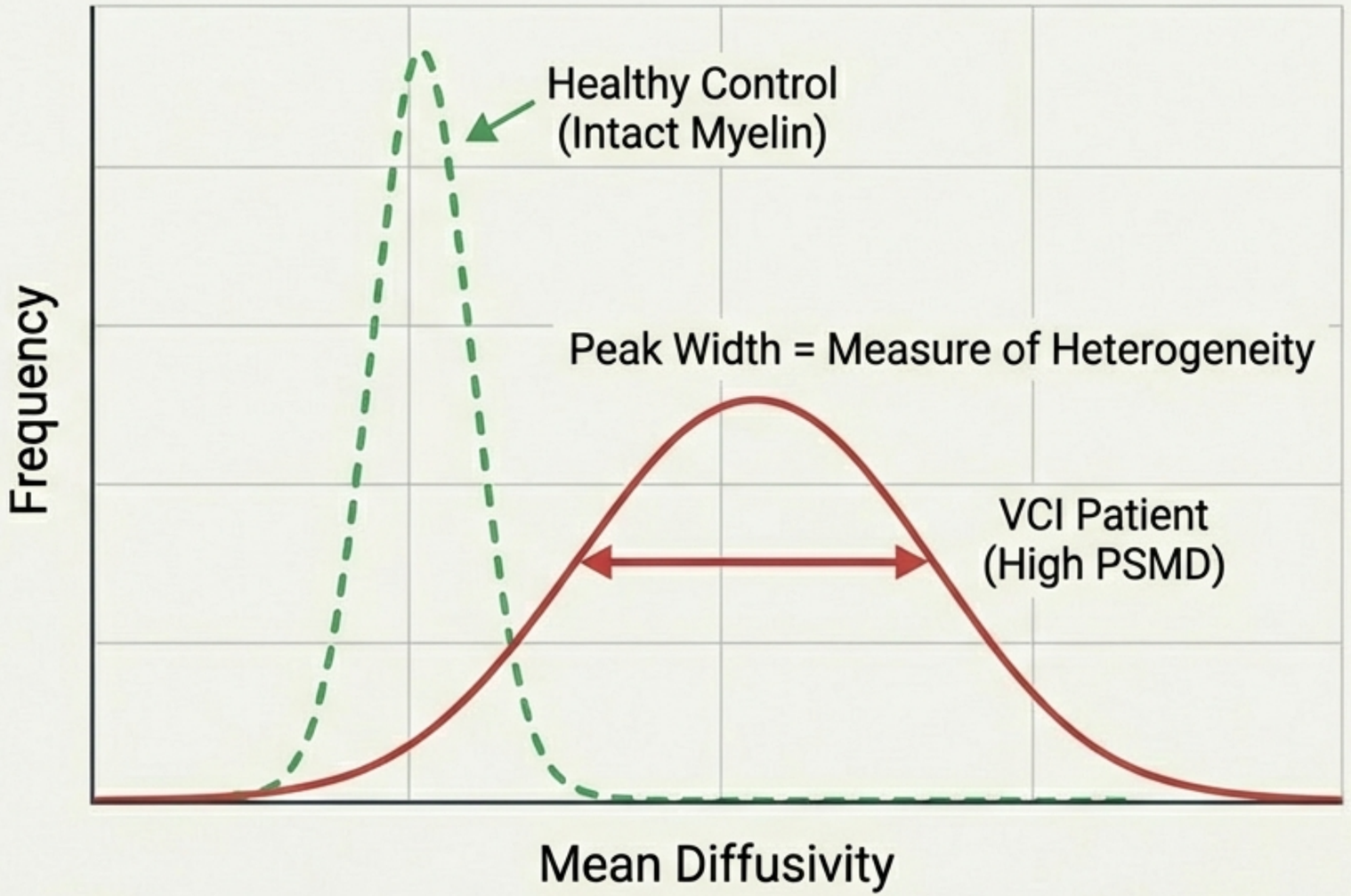
The New Lens: PSMD

Peak Width of Skeletonized Mean Diffusivity



Why PSMD wins:

- Measures the ‘messiness’ of water movement.
- Correlates strongly with Processing Speed (VCI hallmark).
- The ‘Geiger Counter’ for white matter burden.

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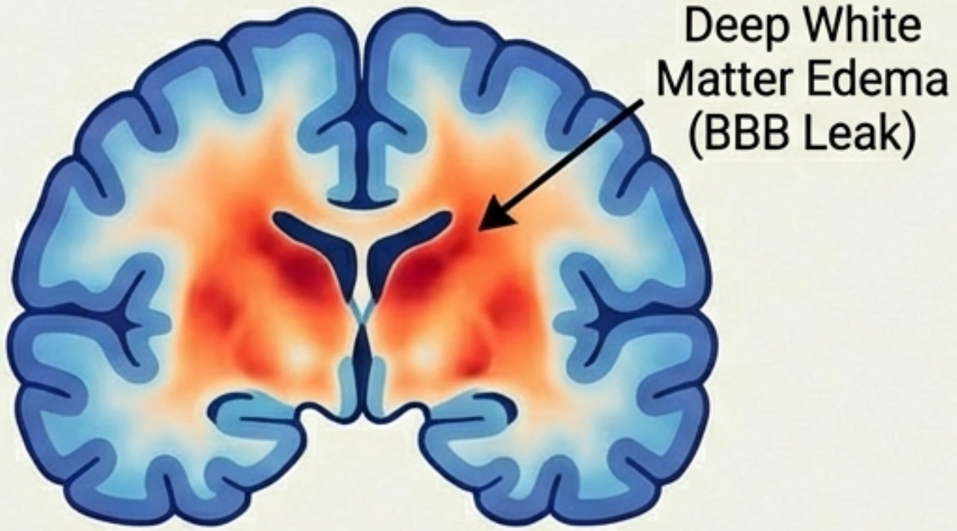
Mapping Inflammation & Clearance

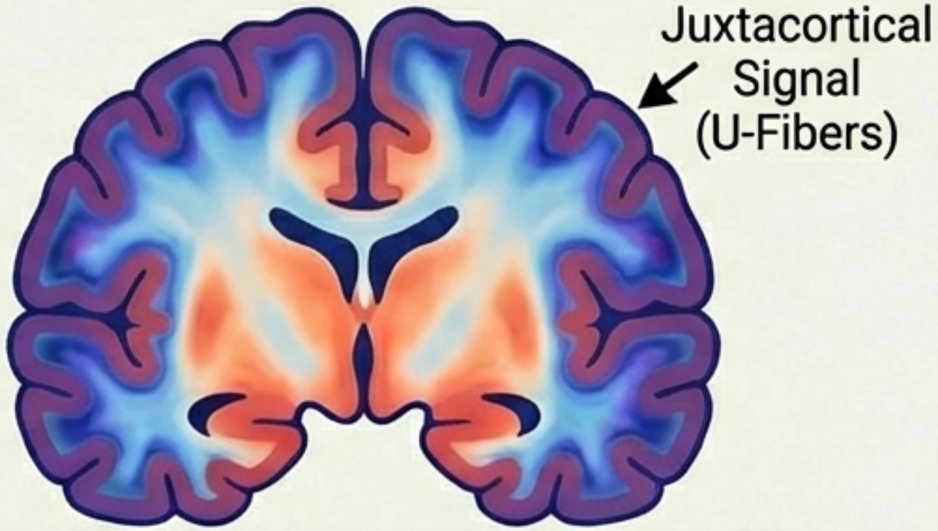
Geography distinguishes etiology.

The VCI Signature



Low DTI-ALPS (Glymphatic Failure)

The AD Signature



Reflects cortical neurodegeneration spreading inward.

Vascular Failure Profile = High Deep Free-Water + Low Glymphatic Clearance

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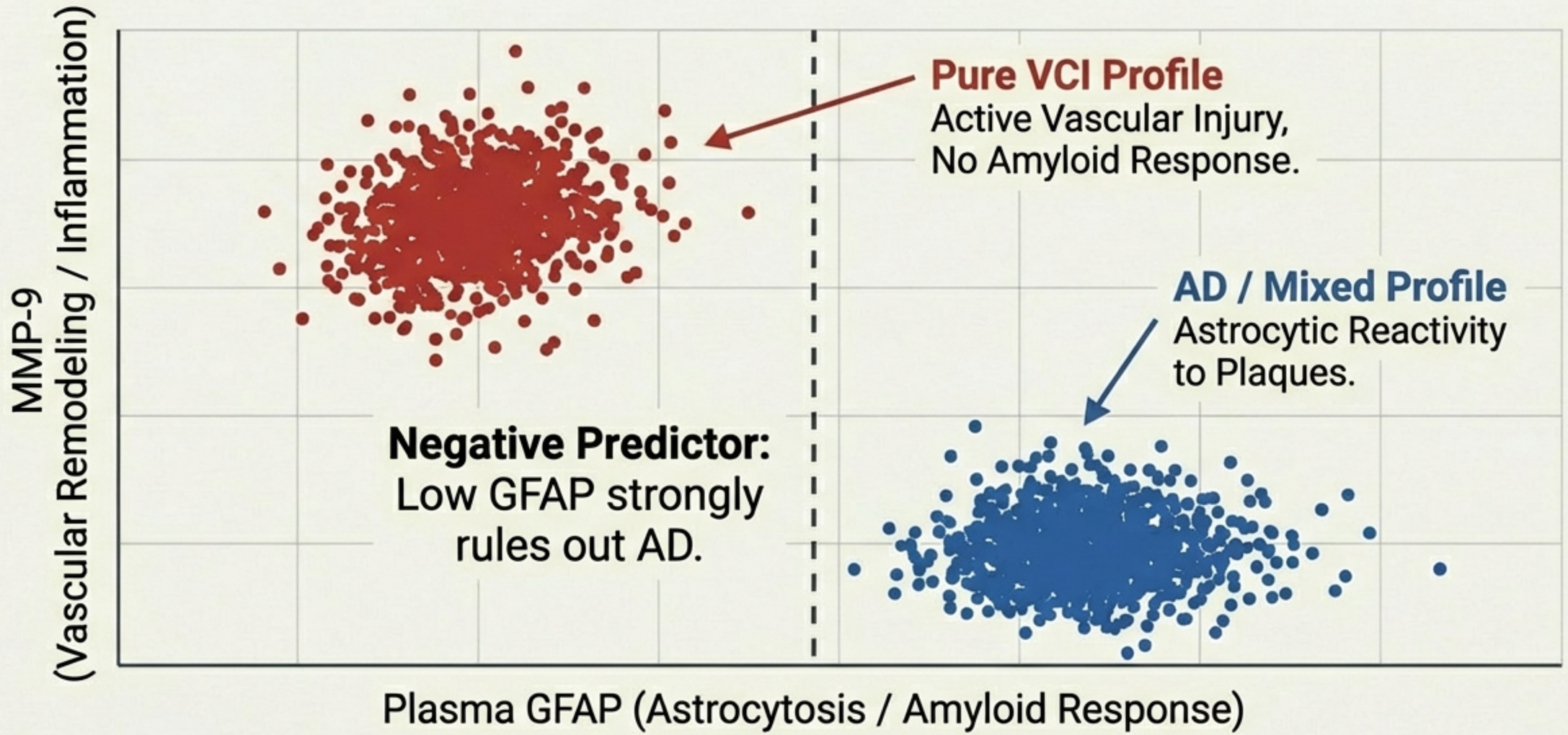
The Fluid Fingerprint

Biochemical differentiation: MMP-9 vs. GFAP



Supportive Markers: PlGF (Angiogenesis) elevated in VCI.

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The Mimic: LATE-NC

Limbic-predominant Age-related TDP-43 Encephalopathy

The Vascular-Atrophy Mismatch

LATE Profile

Severe memory loss with healthy vessels.

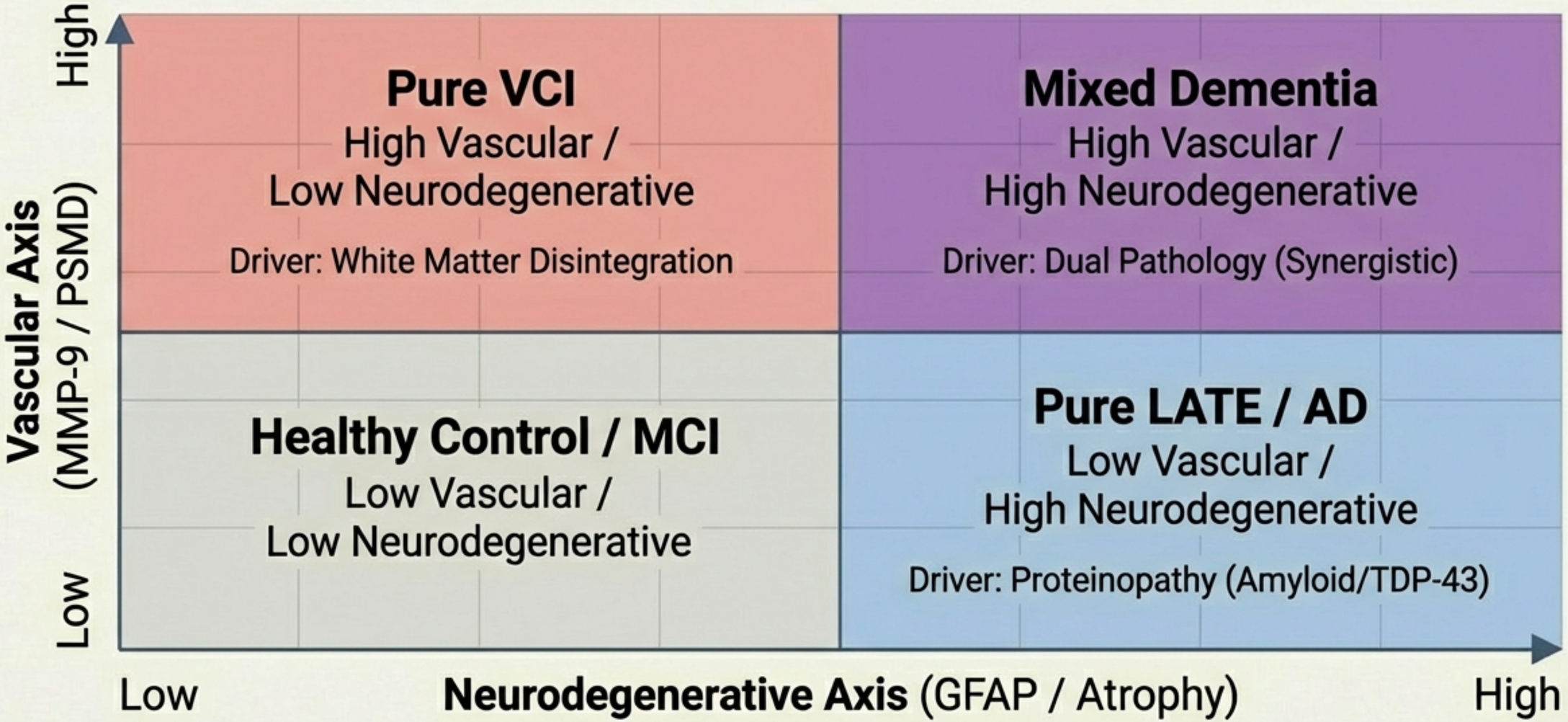
VCI Profile

Dysexecutive syndrome with damaged vessels.

Target Demographic: The Oldest-Old (>80 years). Often misdiagnosed as Alzheimer's.

The Integrated Diagnostic Matrix

Precision Phenotyping on Two Axes



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Profiles in the “A-” Cohort

Stratifying the Amyloid-Negative Patient

Clinical Card

Profile A: Pure VCI

- PSMD: High
- MMP-9: High
- GFAP: Low

Angiogenic-Inflammatory VCI

Clinical Card

Profile B: Pure LATE

- PSMD: Low
- MMP-9: Normal
- Atrophy: Severe (Hippocampal)

TDP-43 Encephalopathy

Clinical Card

Profile C: Mixed (VCI + LATE)

- PSMD: High
- MMP-9: High
- Atrophy: Severe

Dual Pathology

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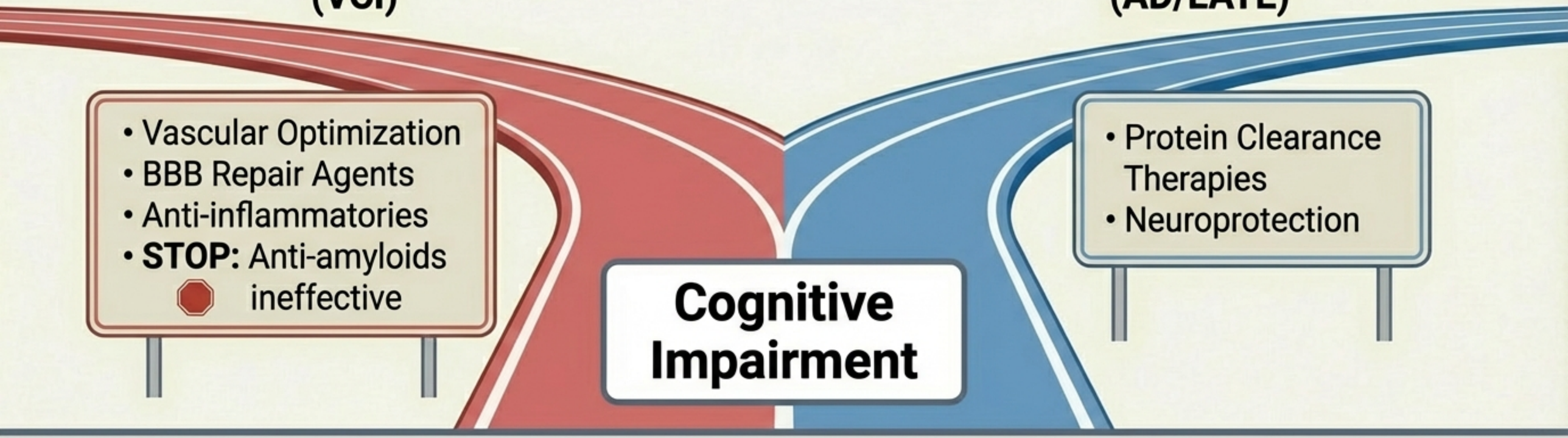
Implications for Treatment & Trials

Diagnosis dictates destination.



The Trial Problem: Current trials dilute efficacy by mixing these populations. Precision phenotyping is the prerequisite for successful therapeutics.

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The Future of Phenotyping

From broad labels to biological precision.

1. The Vascular-Immune Hypothesis provides the mechanism.
2. PSMD + MMP-9 + GFAP provides the fingerprint.
3. We can now resolve the “Gray Zone” of dementia.

Moving from Dementia to Precision Neurology.

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