# Distinguishing Causes of Dementia

## What's New?

DATE: February 9, 2026 PRESENTED BY: Peter S. Pressman, MD, OHSU Aging and Alzheimer's Disease Research Center

# Why "What's New" Matters Now

1. **Blood biomarkers are FDA-cleared**

   pTau181/217 now available for primary care

2. **New LBD diagnostic tools**

   Skin biopsy and RT-QuIC/SAA now clinically available

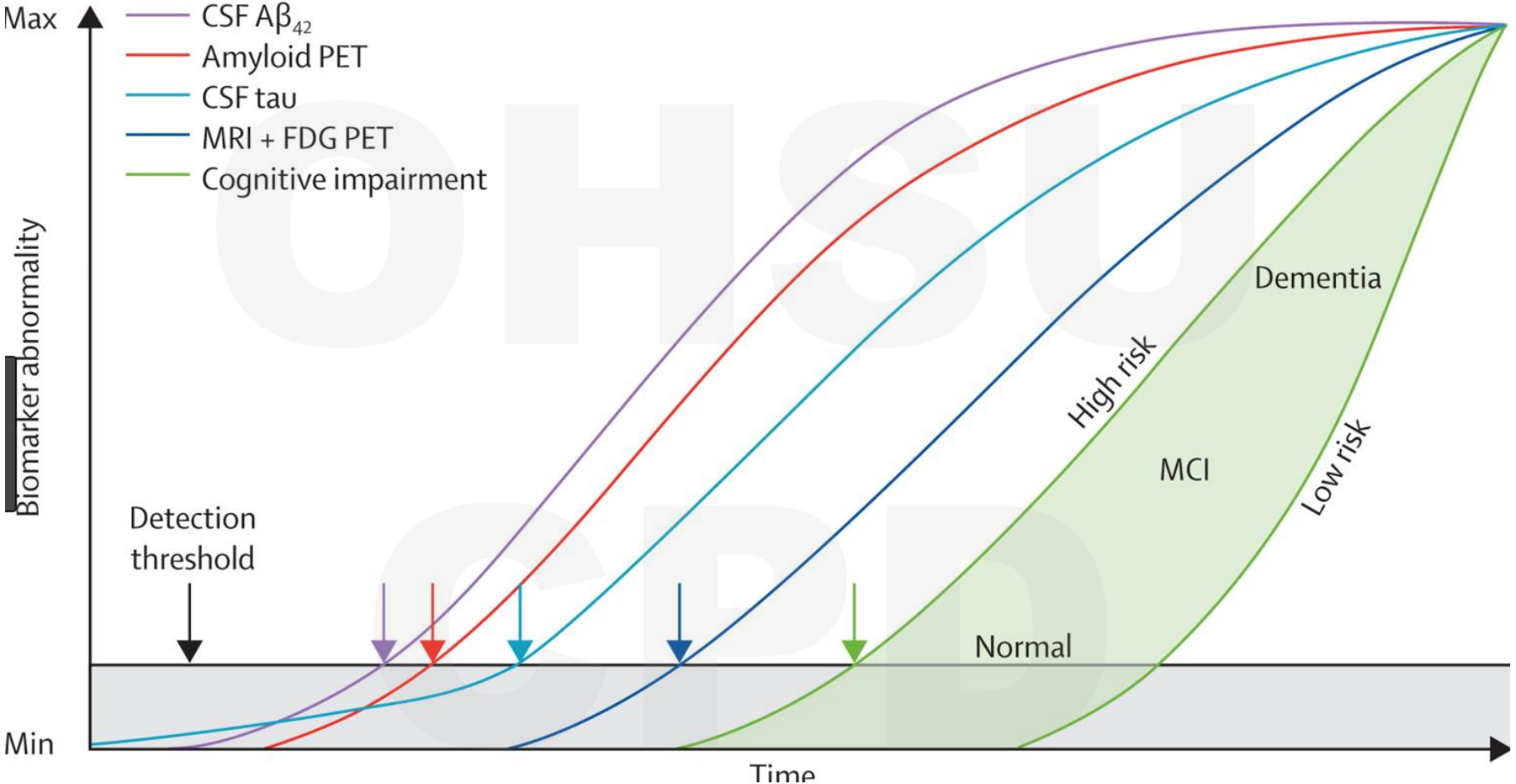
3. **NfL distinguishes FTD from psychiatric mimics**

   NIC-FTD 2020 consensus recommendations

Getting it right has treatment implications – even without amyloid therapies.

# Learning Objectives

- Apply FDA-cleared blood biomarkers in clinical practice
- Use new diagnostic biomarkers for LBD (skin biopsy, SAA)
- Apply NIC-FTD 2020 recommendations and NfL to distinguish bvFTD from psychiatric disorders
- Recognize reversible causes and modifiable risk factors (Lancet 2024)


Max
CSF Aβ42
Amyloid PET
CSF tau
MRI + FDG PET
Cognitive impairment
Biomarker abnormality
Detection threshold
Normal
High risk
MCI
Low risk
Dementia
Min
Time

Jack 2010

# NIA-AA 2024 — Biological Definition of AD

**AD is now defined biologically — clinical symptoms not required for diagnosis**

## ATN Framework

A+T+N = AD pathology present, regardless of symptoms

CONTROVERSY: Critics argue asymptomatic + biomarker positive = "at risk," not "disease"

**PCP TAKEAWAY: Biomarker confirmation now required before anti-amyloid therapy**

*Source: Jack CR Jr, et al. Alzheimers Dement. 2024;20(8):5352-5374*

SECTION 1

# Blood Biomarkers

# FDA Clearances — Timeline

**May 2025**

## Lumipulse G pTau217/Aβ1-42 ratio

First FDA-cleared blood test for AD

**Oct 2025**

## Roche Elecsys pTau181

Cleared for primary care as rule-out test

**Jan 2026**

## Billing codes finalized

Expected Medicare reimbursement pathway

*Sources: FDA clearance announcements; Fujirebio; JCI 2025*

# What the Tests Actually Tell You

| Biomarker | Performance | Best Use |
|---|---|---|
| pTau217 | AUC 0.90-0.97 | Best overall performer — rises in response to amyloid |
| pTau181 | 97% NPV | Excellent rule-out — if negative, AD very unlikely |
| NfL | Non-specific | HIGHER in FTD than AD — key differentiator |

**CLINICAL PEARL**

Consider pTau217 as a sensitive marker of Alzheimer's pathology.

*Source: Barthélemy NR, et al. Nat Med. 2024; JCI Oct 2025*

# Two-Threshold Interpretation Model

| NEGATIVE | POSITIVE | INTERMEDIATE |
| --- | --- | --- |
| **AD very unlikely** | **AD pathology likely** | **~20% of results** |
| → Investigate other causes | → Consider PET/CSF if treatment candidate | → Requires additional testing |

*Source: DETeCD-ADRD Guidelines 2025; JCI 2025*

# CRITICAL CAVEATS:

## Racial Disparities (Rutgers, Feb 2025)

| Metric | White Pts | Black Pts |
|---|---|---|
| Sensitivity | 90.3% | 73.7% |
| PPV | 87% | 58% |

**A positive test in a Black patient may be essentially a coin flip (58% PPV)**

Confirmatory PET/CSF mandatory before treatment

## Kidney Function (Vanderbilt)

Even mild CKD breaks NfL predictive value. Check eGFR before interpreting.

## Other Comorbidities

Diabetes, HTN, prior stroke, TBI all elevate biomarkers independently.

## Population Screening (Karolinska)

Low PPV in asymptomatic populations. Not suitable as standalone screening.

# Coverage and Access Update

- ✓ FDA clearance opens door to Medicare coverage
- ✓ CPT billing codes being finalized for January 2026
- ⚠ Advisory panel recommended $130/test (vs. proposed $17)
- ⚠ LDTs (PrecivityAD2) remain largely out-of-pocket ~$1,200-1,450

PRACTICAL TIP: Check current coverage; consider for patients who would be treatment candidates if positive

*Source: CMS Clinical Lab Fee Schedule; UsAgainstAlzheimer's advocacy*

# 2025 Appropriate Use Criteria for AD Biomarkers

### AA Clinical Practice Guidelines (AAIC July 2025)

- ≥90% sens + ≥75% spec → **Triage tool** (negative rules out AD)
- ≥90% sens + ≥90% spec → **May substitute** for CSF/PET

### SNMMI/AA PET Criteria (January 2025)

First revision since 2013—17 clinical scenarios:

- Amyloid AND tau PET recommendations
- AAT treatment eligibility
- Monitoring during therapy

### ✓ APPROPRIATE USE

Symptomatic patients being evaluated for cognitive impairment

## Interpreting Results

### ✗ NOT APPROPRIATE

- Screening asymptomatic individuals
- "Worried well" without objective impairment
- Population-level screening (low PPV)

### Key Principle

*"Blood tests are triage tools—a negative result is highly reliable. Positives require specialist evaluation and confirmatory testing before treatment."*

Sources: AA Clinical Practice Guidelines, AAIC 2025; SNMMI/AA Appropriate Use Criteria, Jan 2025

# Blood-Based Biomarkers: 2025 FDA Clearances

FDA CLEARED MAY 2025

## Fujirebio Lumipulse

**Measures:** p-tau217 / Ab42 ratio

**Use:** Symptomatic patients 55+

**Access:** Quest, LabCorp

**Best for:** Rule-in AND rule-out in symptomatic patients

FDA CLEARED OCTOBER 2025

## Roche Elecsys

**Measures:** pTau181

**Use:** Primary care screening

**NPV:** 97.9%

**Best for:** Rule-OUT in primary care. Negative = redirect workup.

SECTION 2

# Lewy Body Dementia

## New Diagnostic Biomarkers

# The LBD Diagnostic Problem

**50-80%**

Clinical diagnosis accuracy

**3.6 yrs**

Average time to diagnosis

**50%**

Experience severe neuroleptic reactions

**NEW: We now have biological confirmation methods**

*Source: DLB Consortium; CND Life Sciences*

# Lewy Body Composite Risk Score

Physical findings

Clinical symptoms

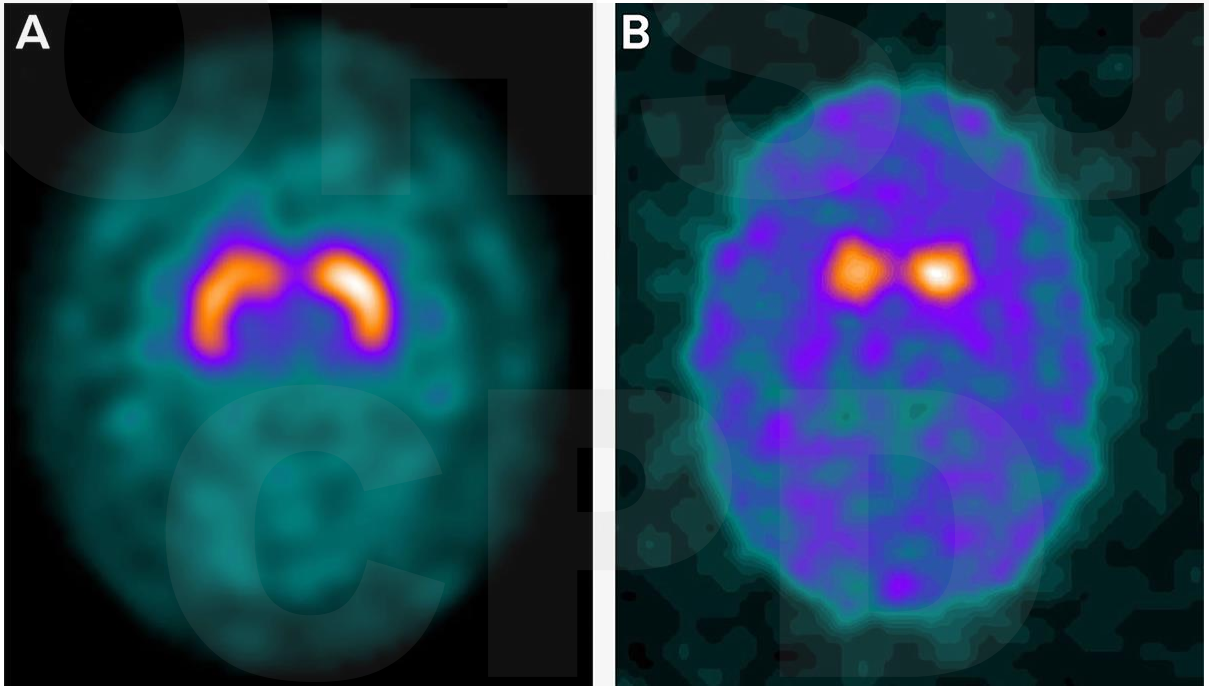
| **Please rate the following physical findings being present or absent for the past 6 months and symptoms as being present or absent for at least 3 times over the past 6 months. Does the patient…** | **Yes** | **No** |
|---|---|---|
| Have slowness in initiating and maintaining movement or have frequent hesitations or pauses during movement? | | |
| Have rigidity (with or without cogwheeling) on passive range of motion in any of the 4 extremities? | | |
| Have a loss of postural stability (balance) with or without frequent falls? | | |
| Have a tremor at rest in any of the 4 extremities or head? | | |
| Have excessive daytime sleepiness and/or seem drowsy and lethargic when awake? | | |
| Have episodes of illogical thinking or incoherent, random thoughts? | | |
| Have frequent staring spells or periods of blank looks? | | |
| Have visual hallucinations (see things not really there)? | | |
| Appear to act out his/her dreams (kick, punch, thrash, shout or scream)? | | |
| Have orthostatic hypotension or other signs of autonomic insufficiency? | | |
| **TOTAL SCORE** | | |



Using the cutoff of 3 or greater, the LBCRS was able to discriminate:

| | **DLB vs. AD** | **DLB vs any dementia** | **MCI DLB vs MCI AD** |
|---|---|---|---|
| Area Under Curve | 0.94 (0.90-0.97) | 0.94 (0.91-0.98) | 0.96 (0.91-1.0) |
| Sensitivity | 94.2 | 97.9 | 100 |
| Specificity | 78.2 | 86.1 | 72.9 |
| Positive Likelihood Ratio | 4.1 | 7.0 | 3.2 |
| Negative Likelihood Ratio | 0.08 | 0.02 | 0.0 |

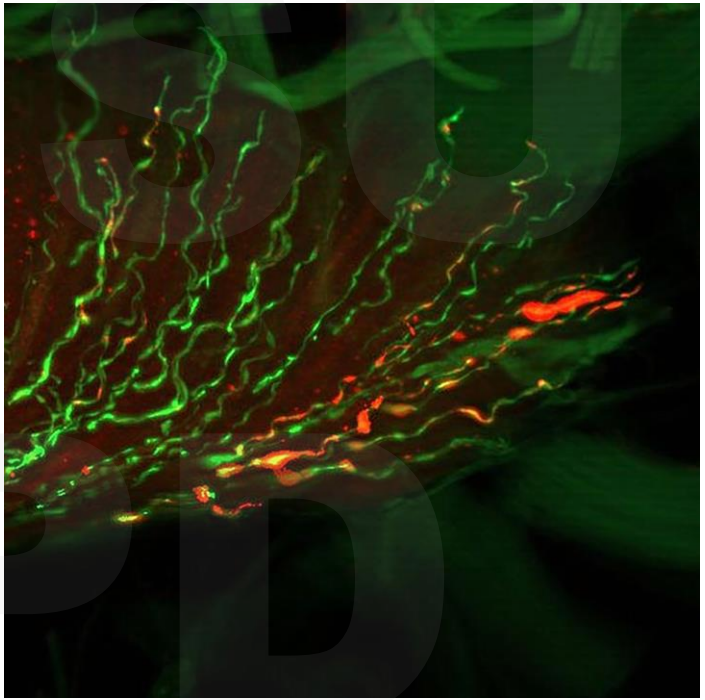
# DAT scan




Galvin Continuum 2024

# Newer Tests in LBD

- CSF: Reduced in LBD, elevated in AD; seeding assays (e.g., RT-QuIC) are FDA-cleared.
- Skin: Biopsies detect phosphorylated α-synuclein; FDA-cleared assay available.
- Plasma: Elevated α-synuclein correlates with disease progression; methods still experimental.
- PET: No clinical ligands yet; promising tracers in development.



Galvin Continuum 2024

# Skin Biopsy for α-Synuclein — NOW AVAILABLE

**Syn-One Test (CND Life Sciences) — NIH "Top Promising Medical Finding 2024"**

| | | |
|---|---|---|
| **Sensitivity** | **93-100%** | across synucleinopathies (PD, DLB, MSA, PAF) |
| **Specificity** | **>95%** | zero false positives in non-synucleinopathy controls |
| **Coverage** | **Medicare** | participating provider; commercial coverage expanding |

*Source: Gibbons CH, et al. JAMA. 2024;331(15):1298-1306*

# Skin Biopsy — Clinical Utility Data

**80%** Changes diagnosis when result supports suspected diagnosis

**52%** Annual increase in P-SYN deposition — potential trial endpoint

**31%** Of MCI patients tested positive → may predict conversion to DLB

*Source: Frontiers Neurol. 2024; Neurology 2025 abstracts*

# RT-QuIC / Seed Amplification Assay — CSF

Detects misfolded α-synuclein protein seeds in CSF

| DLB vs. Controls | MCI-LB (Prodromal) |
| --- | --- |
| Sensitivity 95% | Sensitivity 95% |
| Specificity 98% | Specificity 97% |

Also works on skin, olfactory mucosa — less invasive options emerging
Same-day assay now available (<12 hours vs. previous 48+ hours)

*Source: Rossi M, et al. Acta Neuropathol. 2020; npj Biosensing 2025*

# Combining Biomarkers for AD vs. LBD

**p-tau181/217**

Rules in/out
AD pathology

**α-Synuclein SAA**

Rules in/out
Lewy pathology

**CO-PATHOLOGY COMMON: ~20% of AD patients show α-synuclein positivity**

**CLINICAL APPROACH: Test for both when presentation unclear**

*Source: Alz Dement. 2025; McWilliam et al.*

# When to Order Skin Biopsy / SAA

**Order when:**

- 1+ core DLB features with diagnostic uncertainty
- Atypical parkinsonism — CBD vs. PSP vs. DLB unclear
- Before antipsychotic in dementia patient with any LBD red flags
- RBD + cognitive symptoms (prodromal workup)

**Where to order:** Syn-One Test via CND Life Sciences | CSF SAA increasingly available through academic centers

SECTION 3

# Frontotemporal Dementia

## NIC-FTD 2020 & Neurofilament Light

# The FTD Diagnostic Challenge

**50%**

Initially misdiagnosed as psychiatric disorder

**3.6 yrs**

Average time to correct diagnosis

**13-51%**

See psychiatrist first; labeled depression, bipolar, schizophrenia

Until 2020: No consensus on how to distinguish bvFTD from psychiatric mimics

**NOW: NIC-FTD 2020 provides standardized approach**

*Source: AFTD; NIC-FTD 2020*

# NIC-FTD 2020 Consensus Recommendations

*Neuropsychiatric International Consortium for FTD — 45 experts, 15 countries*

1. Chronologically-ordered history from knowledgeable informant
2. Formal social cognition testing in neuropsych battery
3. 3D-T1 MRI with standardized visual atrophy rating scales
4. Serum or CSF NfL to differentiate bvFTD from psychiatric disorders
5. C9orf72 screening in all possible/probable bvFTD cases

*Source: Brain. 2020 (NIC-FTD); Pressman PS, et al. J Neuropsychiatry Clin Neurosci. 2021*

# Neurofilament Light Chain (NfL) in FTD

*NfL = marker of axonal damage — released with neurodegeneration*

| | |
|---|---|
| **FTD vs Controls** | AUC 0.84 |
| **bvFTD vs Psychiatric** | Significantly elevated in bvFTD |
| **FTD vs AD** | NfL higher in FTD than AD |
| **Presymptomatic** | Rises before clinical symptoms |

CAVEAT: Accuracy decreases in patients >60 due to age-related NfL increase

# NfL — Clinical Applications

| | |
|---|---|
| **Distinguishing FTD vs. AD** | NfL higher in FTD than AD |
| **Distinguishing bvFTD vs. Psychiatric** | NfL much higher in bvFTD |
| **Monitoring genetic FTD** | Predicts conversion to symptomatic disease |
| **Prognosis** | Baseline NfL correlates with rate of decline |

**COMBINED: NfL + p-tau181 achieves AUC ~0.90 for AD vs. FTD**

*Source: Mol Neurodegeneration. 2025; Int J Mol Sci. 2025*

# Practical FTD vs. Psychiatric Approach

1. Structured history — family history of ALS/dementia? Progressive course?
2. Formal social cognition testing (emotion recognition, theory of mind)
3. 3D-T1 MRI with visual rating scales
4. Serum NfL — if markedly elevated, favors neurodegeneration
5. Consider C9orf72 genetic testing — especially if psychiatric features prominent
6. If still uncertain → Neurology/Memory Clinic referral

*Source: NIC-FTD 2020 algorithm*

# Red Flags for C9orf72

- Very slow progression ("phenocopy")
- Prominent psychotic symptoms
- Family history of ALS or dementia
- Minimal atrophy on MRI early in disease

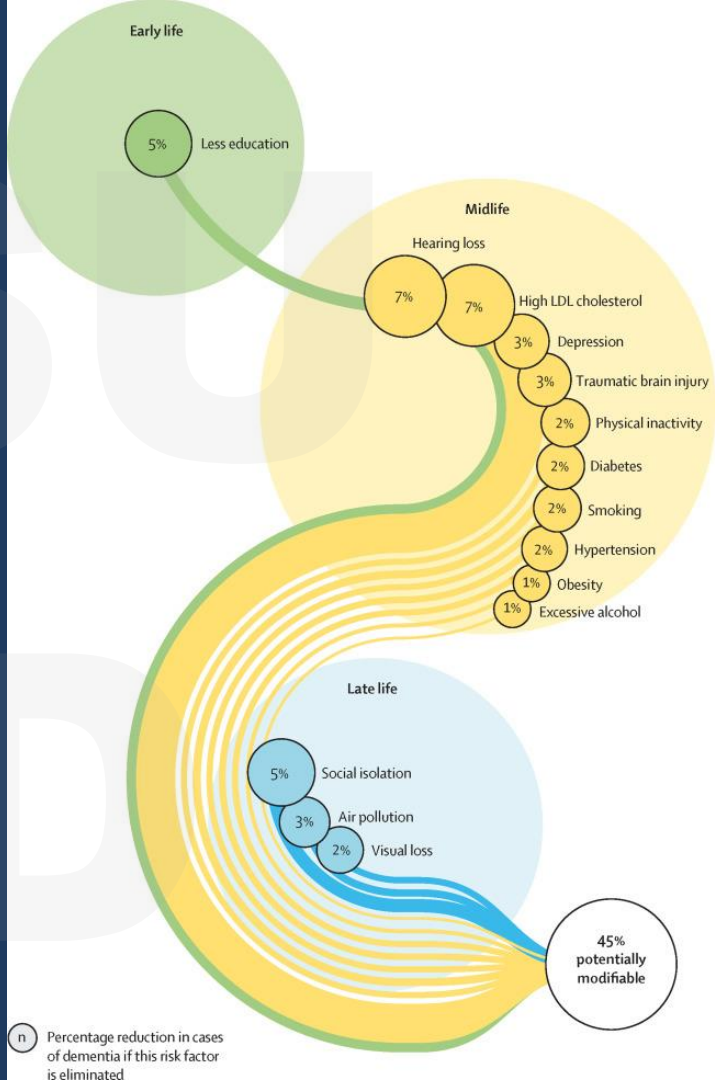
**RECOMMENDATION: Screen C9orf72 in ALL possible/probable bvFTD cases**

*Source: NIC-FTD 2020; GENFI consortium*

SECTION 4

# New Modifiable Risk Factors

Lancet Commission 2024



# Lancet Commission 2024 Update

**45%**

of dementia cases attributable to 14 modifiable factors

**Two NEW additions for 2024:**

- Vision loss (2% PAF)
- High LDL cholesterol (2% PAF)

***Message: "Be ambitious about prevention"***

*Source: Livingston G, et al. Lancet. 2024;404:572-628*

# Vision Loss — New Modifiable Factor

**67%**
of adults >70
have vision loss

**RR 1.47**
dementia risk
(meta-analysis)

**90%**
of vision loss
is treatable

**Specific conditions:**

Cataracts: 17% increased risk | Diabetic retinopathy: 34% increased risk

**ACTION: Annual eye exams; cataract surgery; correct refractive errors**

*Source: Lancet 2024; JAMA Intern Med. 2022 (cataract study)*

# Hearing Loss — ACHIEVE Trial Update

**ACHIEVE Trial 2023**

**48%**

slower cognitive decline
in high-risk subgroup

**2025 Secondary Analysis**

**61.6%**

slower decline in
top quartile risk

Hearing loss = largest single modifiable factor (7% PAF)

Dose-response: Every 10 dB decrease → 4-24% increased dementia risk

**ACTION: Screen hearing; amplification referral**

*Source: Lin FR, et al. Lancet. 2023;402:786-797; 2025 secondary analysis*

# Peripheral Neuropathy — Emerging Evidence

| | |
|---|---|
| **OR 1.40** | PN associated with MCI in diabetes (ARIC-NCS study) |
| **OR 1.33** | PN associated with MCI overall |
| **4.3x** | Increased dementia risk: Type 2 DM + DPN vs. diabetes without DPN |

Mechanisms: Shared metabolic pathways, reduced mobility, sensory deprivation

**ACTION: Monofilament testing; optimize glycemic control**

*Source: Neurology. 2022 (Brenowitz); Endocrine. 2025; Diabetes. 2025*

# When to Order Which NEW Test

| Clinical Scenario | NEW Test to Consider |
| --- | --- |
| Cognitive decline, uncertain if AD | **pTau181 (rule-out) or pTau217** |
| Suspected LBD (hallucinations, RBD, parkinsonism) | **Skin biopsy (Syn-One) or CSF SAA** |
| Young-onset behavior change, psych treatment failure | **Serum NfL + C9orf72 testing** |
| Dementia patient before ANY antipsychotic | **Skin biopsy if LBD not ruled out** |

SECTION 5

# Treatable Contributors

# Reframing "Reversible Dementia"

**Traditional Definition**

**5-19%**

"reversible"
(B12, NPH, hypothyroidism)

**Expanded Definition**

**30%+**

treatable contributors
(meds, sleep, hearing, pain, depression)

*"Drugs are the most reversible factors contributing to these syndromes. Reversing even one factor contributing to a geriatric syndrome can be enough to alleviate it."*

— Australian Prescriber 2022

**Goal: Optimize cognition, not necessarily "cure" dementia**

*Source: Lancet Commission 2024 (45% attributable to modifiable factors)*

# Medications — The Most Reversible Factor

**61%** of memory clinic patients on anticholinergics

**24%** with ACB score ≥3 (high burden)

**13%** increased cognitive impairment risk per ACB point

**54%** increased dementia risk with cumulative strong anticholinergic use

Common culprits: diphenhydramine, oxybutynin, TCAs, first-gen antihistamines

**ACTION: Calculate ACB score; deprescribe where possible**

# Pain

**45-56%**
of dementia patients have chronic pain

**HR 1.42**
dementia risk associated with pain

**Pain is undertreated in cognitive impairment — patients can't report effectively**

Mechanisms: Inflammation, medication effects, sleep disruption, reduced activity

**ACTION: Systematically assess and treat pain in all dementia patients**

*Source: Eur J Ageing 2024 meta-analysis; JAMA Intern Med 2017*

# Sleep Disorders — 30-80% Prevalence

## Obstructive Sleep Apnea

30-80% prevalence in dementia populations
CPAP → documented executive function improvement
Glymphatic clearance mechanism: sleep clears amyloid

## Insomnia & Sleep Fragmentation

CBT-I preferred over sedative-hypnotics (which worsen cognition)

**REMEMBER: RBD = prodromal synucleinopathy — 73% convert by 12 years**

**ACTION: Screen for sleep disorders; consider sleep study; treat OSA**

# Depression and "Pseudodementia"

**48-52%**

of depressed elderly meet MCI criteria

**53%**

reverse with depression treatment

**33%**

convert to true dementia (strong predictor)

**CLINICAL PEARL**

Pseudodementia patients are distressed about their symptoms; AD patients often lack insight — the discrepancy is diagnostic

**ACTION: Screen with PHQ-9/GDS; treat depression even if comorbid dementia**

*Source: Gen Psychiatr 2023; StatPearls 2025*

# Delirium Superimposed on Dementia

**49%**

prevalence in hospitalized dementia

**Often attributed to "just the dementia" — WRONG**
Accelerates cognitive trajectory
Increases mortality
**ALWAYS treatable when identified**

**ACTION: Use CAM or 4AT at care transitions; educate caregivers on warning signs**

**The Systematic Checklist — for EVERY cognitive complaint:**

☐ Medication review (ACB) ☐ Pain ☐ Hearing ☐ Vision ☐ Depression ☐ Sleep ☐ Delirium ☐ Standard labs ☐ Imaging

*Source: Han QYC, et al. J Am Med Dir Assoc. 2022;23(1):23-32*

SECTION 6

# Rapidly Progressive Dementia

Autoimmune & Prion — NEW Diagnostics

# RT-QuIC for Prion Disease — NOW AVAILABLE

**May 2024: Mayo Clinic launched clinical RT-QuIC assay for CJD**

**Sensitivity**

**87-92%**

**Specificity**

**98-100%**

**Key advance:** Distinguishes prion disease from treatable autoimmune causes and rapidly progressive AD

Now part of CDC diagnostic criteria for probable CJD

Mayo RPD Panel: Combines RT-QuIC + AD biomarkers (Aβ, tau) + t-Tau/p-Tau ratio in single CSF panel

*Source: Mayo Clinic Labs 2024-2025; CDC 2018/2021 criteria*

# Autoimmune Encephalitis as Dementia Mimic

**Up to 13%**

of non-CJD RPD in specialist clinics = autoimmune

**81%**

of anti-NMDAR encephalitis achieve significant recovery

## LGI1 Encephalitis

Up to 50% of patients >45 years fulfill dementia criteria

71% present with cognitive decline — not prominent seizures

May lack classic features: no seizures, normal MRI, normal CSF

**Clue: Hyponatremia (SIADH pattern)**

**Highly treatable — early immunotherapy predicts outcome**

*Source: Br J Psychiatry 2024; Lancet Neurol 2024*

# Antibody Testing — What's Changed

**OBSOLETE**

**VGKC-complex antibody testing alone**

Up to 5% of healthy controls are positive

**CURRENT STANDARD**

**Direct LGI1 and CASPR2 cell-based assays**

"Double negative" VGKC = NOT clinically meaningful

**"Seronegative AE" often means incomplete testing — need CSF + serum, tissue + CBA**

Newer antibodies to know: GFAP (astrocytopathy), Neurochondrin, Septin-7, IgLON5

**Red Flags for Autoimmune (vs. Neurodegenerative):**

Subacute onset (<3 months) | Seizures | Hyponatremia | CSF pleocytosis | Medial temporal T2 signal

*Source: Lancet Neurology 2023 — Graus et al. updated position*

# Rapidly Progressive Dementia — NEW Tools

*When progression is weeks-months (not years):*

| Clinical Picture | NEW Test |
|---|---|
| Classic CJD (myoclonus, ataxia, cortical ribboning) | **RT-QuIC CSF** |
| Subacute cognitive + seizures + temporal MRI signal | **LGI1/CASPR2 antibodies** |
| Subacute encephalopathy, any age | **AE panel (tissue + CBA)** |
| Rapidly progressive + psychiatric features | **NMDAR, GABA-B antibodies** |

**Autoimmune causes are TREATABLE — worth screening in all RPD**

# Take-Home Messages — What's Actually NEW

1. Blood biomarkers are HERE — pTau181 FDA-cleared for primary care (Oct 2025)
2. LBD has biological confirmation — Skin biopsy 93-100% sensitive
3. NfL helps distinguish FTD from psychiatric mimics — NIC-FTD 2020 standard
4. Vision loss + LDL cholesterol now modifiable factors — Lancet 2024
5. 30%+ have treatable contributors — medications, sleep, pain, depression
6. RT-QuIC + autoimmune panels — don't miss treatable RPD

**You can act on ALL of these in primary care TODAY.**