The Certain Uncertainty of an Alzheimer Disease Diagnosis

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The advent of monoclonal antiamyloid antibody (mAb) therapy for Alzheimer disease (AD) has thrust diagnostic criteria into the spotlight, with critical implications for patient care. Primary care practitioners are now on the front lines of this challenge, driven by specialist wait times, direct-to-consumer tests, and patient requests for biomarker testing. The stakes are high, as mAb therapy can alter the disease course but also carries risks for cerebral edema and hemorrhage.

Consider 2 actual cases. Physician A is a 53-year-old asymptomatic woman with dementia in both parents and an APOE ε4/ε4 genotype, which is associated with high lifetime risk for AD. Her Mini-Mental State Examination (MMSE) score is 30 out of 30, her magnetic resonance imaging (MRI) scan is normal, and neurocognitive testing places her at the 61st percentile for her age, without deficits. However, her cerebrospinal fluid (CSF) shows an abnormal level of amyloid, a key AD biomarker, while her p-tau level, another critical marker, is normal. What is her diagnosis, and is mAb therapy indicated?

In contrast, Architect B is a 65-year-old woman who has progressive cognitive and functional loss meeting clinical criteria for dementia and an APOE ε3/ε4 genotype. Her MMSE score is 26 out of 30. Neurocognitive testing places her at the 32nd percentile for her age, with deficits in recall (first percentile), language, and executive function. Her MRI scan shows mild white-matter changes without hippocampal atrophy. Both an amyloid positron emission tomography (PET) scan and CSF reveal an abnormal amyloid level, but her CSF p-tau level is normal. Does she have AD, and is she eligible for mAb therapy?

The answers depend on the diagnostic framework applied: the Alzheimer's Association (AA-2024) criteria, or the International Working Group (IWG-2024) criteria (1–3). The AA-2024 criteria define AD by amyloid positivity alone (via CSF, PET, or serum), so both patients have AD under this framework. However, only symptomatic patients, such as Architect B, are eligible for mAb therapy (2). With the stricter IWG-2024 criteria, which require cognitive impairment plus both amyloid and tau positivity, neither patient qualifies for diagnosis or therapy (3). Physician A, despite her high risk for AD, was not eligible for mAb therapy under either framework. The classifications differentially weight tau and symptoms, with AA-2024 focusing on biological detection and IWG-2024 requiring a clinicopathologic diagnosis (1). The frameworks only converge in classic cases with cognitive impairment, tau positivity, and amyloid positivity.

This discordance has real-world implications. In a cohort of nearly 1200 people with cognitive and CSF data from the AD neuroimaging database, applying different diagnostic criteria caused a 42% diagnostic discordance rate (4). The AA-2018 criteria classified 25% to 40% of cognitively intact persons and 60% to 70% of symptomatic persons with AD. The IWG-2021 criteria diagnosed 0% of cognitively intact persons and 33% to 40% of symptomatic persons, as would the IWG-2024 criteria (4). The gap widened to 79% among amyloid-positive, tau-negative persons like Physician A and Architect B (4).

Beyond diagnostic discordance between the frameworks, 3 limitations of available diagnostic tools challenge accurate diagnosis: biomarker limitations, variation in cognitive assessments, and omission of copathology and genetics.

First, amyloid positivity may be pathologic, but it is not specific for AD. Its prevalence increases sharply with age; roughly one quarter of adults in their 70s and nearly half in their 80s have amyloid, yet most remain cognitively intact (5, 6). Conversely, tau pathology, while not as sensitive a biomarker early in the disease course, correlates more closely with clinical progression. Tau increases only modestly with age even among amyloid-positive persons (from 17% at age 60 years to 22% at age 80 years) (6, 7). Relying on a single biomarker risks diagnostic misclassification: Focusing on amyloid alone may lead to overlabeling (AA-2024, Architect B), while focusing on tau alone may lead to underdiagnosis (IWG-2024, Physician A).

This tension is amplified by the rise of blood-based biomarkers. Although indispensable for screening, they have a false-positive rate of 9% to 12% (higher for some assays) (8). Even so, blood biomarkers correlate better (88%) with CSF or PET amyloid pathology than clinical diagnosis by generalists (61%) and specialists (73%) (8). Such tests should not be a stand-in for diagnosis, and discordant results should prompt further assessment to avoid inaccurate labeling.

Second, identifying cognitive impairment is challenging. Although mAb therapy is approved only for symptomatic, amyloid-positive persons (MMSE score of 22 to 30), cognitive performance varies widely with education and baseline intellect. Physician A's higher cognitive reserve may mask early decline, with a good score despite pathology. A person with identical pathology but lower reserve may score poorly, precluding treatment eligibility. Rigid cognitive cutoffs without context risk both undertreatment and overtreatment.

Finally, current criteria do not incorporate copathology and genotype into the diagnostic algorithm, moving beyond a binary, positive-or-negative biomarker paradigm. Pure AD pathology is uncommon; comorbidities such as cerebrovascular disease, Lewy bodies,

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and TDP-43 pathology almost always coexist, shaping prognosis and treatment response (9). This is critical where copathology may be the main cause of impairment.

Similarly, integrating genetics is crucial. APOE ε4 homozygosity confers a lifetime AD risk of approximately 60%—akin to *BRCA1* in breast cancer, where genetics guides intervention (1). Moving beyond a binary, biomarker-defined diagnosis to a probabilistic model (mirroring oncology) that integrates age, genetics, comorbid pathology, lifestyle, and clinical trajectory better reflects the complexity of AD and ensures that treatments are targeted to patients who are likely to benefit (1).

Applying these principles in practice clarifies management of Physician A and Architect B. Physician A weighed her high genetic risk and amyloid positivity against her asymptomatic and tau-negative state. Although she was asymptomatic, she chose off-label mAb therapy. This was based on a probabilistic assessment of her risk and data suggesting benefit from mAb therapy in asymptomatic autosomal dominant AD mutation carriers (10).

Architect B was diagnosed with limbic-predominant, age-related TDP-43 encephalopathy without hippocampal atrophy. Tau negativity and lack of hippocampal atrophy suggested AD pathology was not the primary driver of her deficits. She met the AA-2024 criteria for AD, but not the IWG-2024 criteria. Despite amyloid positivity, the patient, her family, and her internal medicine physician elected to forgo mAb therapy given its unlikely benefit. Such nuanced, partnered decision making helps all involved understand disease complexity and prognostic implications.

For practitioners, 3 principles can help to navigate uncertainty. First, they should avoid diagnosing AD by amyloid positivity alone in asymptomatic persons; in symptomatic persons, they should confirm blood biomarker positivity with CSF or PET if feasible, although the AA-2024 criteria allow for blood biomarker–based diagnosis. Second, biomarker discordance, and the amyloid-positive/tau-negative state, likely warrant further evaluation. Finally, practitioners should integrate APOE genotype, cognitive reserve, and comorbidities to form a probabilistic, personalized assessment that targets therapy to patients who are most likely to benefit.

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