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The arrival of monoclonal antibodies targeting amyloid-beta, such as lecanemab and donanemab, has redefined the treatment landscape for Alzheimer's disease (AD). These agents modestly slow cognitive and functional decline, but patient responses vary. Recent 2024 and 2025 findings have clarified which patients are most likely to benefit based on clinical stage, biomarkers, imaging, and genetic or comorbid profiles.

Early Stage Disease Is Key

The most reliable predictor of benefit is clinical stage. Patients with mild cognitive impairment (MCI) or mild AD dementia (Clinical Dementia Rating [CDR] 0.5–1.0) experience the greatest slowing of decline. Moderate-stage patients derive less benefit, particularly those with high tau pathology. In both the Clarity AD and TRAILBLAZER-ALZ 2 trials, significant slowing of decline was seen predominantly in the early symptomatic phase. These results underscore the importance of early detection, appropriate staging, and timely initiation of treatment.

Tau Pathology and Response

Baseline tau pathology, measured by CSF p-tau217 or tau PET imaging, is among the strongest predictors of therapeutic efficacy. Patients with low-to-intermediate tau burden demonstrate the greatest cognitive benefit. In fact, in open-label extensions of lecanemab, individuals with minimal tau pathology not only avoided decline but in some cases improved over three years. Conversely, patients with advanced tau pathology experienced a limited response, suggesting the underlying disease may be too far progressed for amyloid-targeting agents alone to have substantial impact. Tau burden therefore serves as both a staging and prognostic tool in therapeutic decision-making.

Biomarker Trends Reflect Treatment Impact

Fluid biomarkers in CSF and plasma help confirm biological response and support clinical observations:

- **p-tau217 and GFAP**: These markers of tau pathology and astrocytic activation decline significantly with treatment, suggesting mitigation of downstream neurodegeneration and inflammation.
- **Aβ42/40 ratio**: As plaques are cleared, more soluble Aβ becomes measurable in CSF and plasma, indicating target engagement. Though useful biochemically, this marker is not sufficient for predicting clinical outcomes.
- **Neurofilament light (NfL)**: Rising plasma NfL levels correlate with neuroaxonal injury and cognitive decline. Slower increases in NfL over time correlate with improved outcomes, positioning NfL as a dynamic marker of disease progression and response.

Neuroimaging Predictors Neuroimaging adds another dimension to identifying responders:

- **Tau PET**: Lower baseline tau burden is predictive of response, and treatment with anti-amyloid antibodies slows the accumulation of tau pathology, particularly in early-stage patients.

- **Amyloid PET**: While amyloid clearance occurs consistently, the degree of amyloid positivity at baseline does not differentiate responders. However, PET imaging is still crucial for initial diagnosis and determining therapy eligibility.
- **MRI**: MRI markers like hippocampal volume loss or cortical thinning are not predictive in early stages. More critical is the detection of microbleeds or superficial siderosis, which raise the risk of ARIA and limit the safety and feasibility of anti-amyloid therapy. Patients with heavy CAA involvement should be excluded from therapy due to bleeding risk and adverse events.

Clinical and Genetic Factors

Clinical and genetic profiles also shape therapeutic outcomes:

- **APOE ε4 status**: Carriers of this allele, especially homozygotes, are at increased risk for ARIA-E and require more careful monitoring. Nonetheless, APOE ε4 status does not preclude cognitive benefit, although effects may be attenuated.
- **Sex differences**: Data from Clarity AD suggest that male patients may experience greater benefit, though this requires further validation in future trials.
- **Age**: Trials have demonstrated efficacy across older adult populations, with no consistent difference in therapeutic effect between age groups. However, the presence of mixed pathologies in very old patients may influence real-world response.

Who Should Not Receive Therapy?

Anti-amyloid therapy is not indicated for all individuals with AD pathology. Contraindications include:

- Moderate-to-severe dementia stages.
- Extensive tau pathology on PET or CSF.
- Significant evidence of CAA on MRI, including superficial siderosis or more than four microbleeds.
- Use of anticoagulants due to elevated risk of ARIA-H.
- Coexisting neurodegenerative conditions that would dilute the specific benefits of amyloid clearance.

The "Goldilocks" Responders

Patients who are most likely to benefit from anti-amyloid monoclonal antibodies can be characterized by the following profile:

- Clinical presentation of MCI or mild AD dementia.
- Biomarker-confirmed amyloid positivity via PET or CSF.
- Low to intermediate tau burden, without advanced tangle pathology.

- No significant MRI abnormalities suggestive of CAA.
- Not taking anticoagulants and able to tolerate possible ARIA side effects.
- Possibly male, not homozygous for APOE ε4, and with a slower progression of plasma NfL.

Summary of Predictors of Response:

- Low tau burden (CSF or Tau-PET) predicts greater response to therapy.
- Early-stage disease (CDR 0.5–1) shows best response.
- Early therapy initiation (onset of symptoms) improves likelihood of clinical stabilization or improvement.
- Slower NfL rise = slower decline.
- Declines in p-tau181, p-tau217 and GFAP confirm engagement.
- Increases CSF Aβ42/40 ratio increases confirm engagement.
- Amyloid clearance (PET) aligns with biomarker shifts but less so with clinical stratification.
- Male sex may enhance response (Clarity AD subgroup).
- APOE ε4 non-carriers may benefit more.
- MRI CAA markers = higher ARIA risk and lower tolerance.
- Minimal comorbid neurovascular pathology supports better cognitive outcomes.
- Mild brain atrophy does not alter efficacy.
- Age does not significantly modify benefit.

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