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As Alzheimer's disease (AD) research shifts from symptomatic diagnosis to early detection and prevention, biomarkers have emerged as essential tools for understanding and tracking disease progression. In 2016, Clifford R. Jack Jr. and colleagues introduced the **A/T/N framework**-a biologically based classification system designed to categorize individuals according to the presence or absence of core AD-related pathologies. This framework offers a **clear, agnostic, and inclusive** model for describing disease biology across the full spectrum of cognitive aging, regardless of clinical symptoms.

What Is the A/T/N Framework?

The A/T/N system organizes seven established AD biomarkers into **three binary categories**:

- **A (Amyloid pathology)**:
  - Measured via **amyloid PET** or **CSF Aβ42** levels.
  - A positive (A^+) result indicates the presence of **β-amyloid plaques**, a hallmark of AD.
- **T (Tau pathology)**:
  - Measured through **CSF phosphorylated tau (p-tau)** or **tau PET imaging**.
  - A positive (T^+) result signals **neurofibrillary tangle pathology**.
- **N (Neurodegeneration or neuronal injury)**:
  - Identified via **CSF total tau**, **FDG-PET hypometabolism**, or **MRI-detected atrophy** in AD-characteristic brain regions.
  - A positive (N^+) result suggests active **neuronal dysfunction or loss**.

Each individual is scored as **positive or negative** for each category, resulting in biomarker profiles such as **$A^+/T^+/N^-$** or **$A^-/T^-/N^+$**.

Why Was the A/T/N System Developed?

The framework addresses several longstanding challenges in AD research:

- **Agnostic to clinical symptoms**: It enables biomarker categorization independent of cognitive status, allowing use across preclinical, MCI, and dementia stages.
- **Clarity and simplicity**: Unlike previous systems tied to diagnostic labels (e.g., "probable AD" or "prodromal AD"), A/T/N strictly describes **biological processes**, not syndromes.
- **Scalability across studies**: The binary format makes it useful in large-scale longitudinal and epidemiological studies, where diagnostic criteria often vary.
- **Flexibility for expansion**: The model allows for future incorporation of additional categories, such as vascular pathology (V) or synaptic dysfunction (S), as new biomarkers emerge.

How Are A/T/N Biomarkers Measured?

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AT(N) Framework for Alzheimer's Disease

	A Amyloid	T Tau	N Neurodegeneration
Screening	Serum $A\beta_{42}/40$ ratio	Serum p-tau_{181} or p-tau_{217}	Neurofilament light chain
Confirmator	CSF CSF p-tau ratio CSF $A\beta_{42}$ or Amyloid PET	CSF p-tau_{181} CSF total tau	Neuron-specific enolase Structural brain imaging
FAQ	**Can a single biomarker definitively confirm AD?** No, the highest certainty requires A, T and N positivity.		

Reference: Jack CR Jr, et al. *Alzheimers Dement*. 2018:14(4)

Imaging biomarkers provide spatial information, while CSF biomarkers quantify disease burden but lack topographic detail. Each offers complementary insights.

Clinical Relevance and Use Cases

Individuals with **A^+/T^+** profiles are biologically classified as having **Alzheimer's disease**, even if they are cognitively normal.

Those with **$A^-/T^+/N^+$** are more likely to have **non-Alzheimer tauopathies**, such as **primary age-related tauopathy (PART)**.

An **$A^-/T^-/N^+$** profile may indicate **non-AD neurodegeneration**, such as cerebrovascular disease or hippocampal sclerosis.

The framework facilitates **early identification**, **risk stratification**, and **clinical trial enrollment**, especially as **disease-modifying therapies** become available for early AD.

The A/T/N/C Model: Adding Clinical Stage

To enhance clinical utility, a fourth dimension-**C (Cognition)**-can be added:

- **Cn** = Normal cognition
- **Cm** = Mild cognitive impairment

- **Cd** = Dementia

Thus, a profile such as **$A^+/T^+/N^+/Cm$** describes a patient with biomarker-confirmed AD and mild cognitive impairment.

Limitations and Ongoing Challenges

Biomarker cutoffs can vary by method and population, raising concerns about standardization.

Overlap with other pathologies is common, especially in older adults with mixed etiologies.

Some biomarker results may be **discordant** or fall near thresholds, complicating interpretation.

The framework doesn't yet fully capture **individual variability**, including genetic risk, resilience, or comorbid conditions.

The Path Forward

The A/T/N framework has laid the groundwork for a **biologically grounded definition of Alzheimer's disease**. It is now influencing regulatory standards, drug development, and real-world implementation of biomarker-supported diagnoses. Future enhancements may include:

- Integration of **blood-based biomarkers** (e.g., plasma Aβ42/40, p-tau217, neurofilament light).
- Addition of **vascular (V)** and **synaptic (S)** biomarkers.
- Enhanced **staging models** that combine molecular data with clinical phenotype and prognosis.

Conclusion

The A/T/N framework represents a transformative shift in how we define and study Alzheimer's disease. By moving beyond symptom-based diagnosis and focusing on the biology of disease, it enables earlier intervention, clearer communication, and more precise research. As diagnostic tools evolve and become more accessible, A/T/N will play a central role in the future of dementia care.