NIA-AA Revised Criteria for Diagnosis and Staging of AD: Impact on Clinical Trials and Clinical Practice

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Disclosures

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Outline

- Clinical staging
- Integrated biological and clinical staging
- Multi-modal biomarker profiles and identification of copathology
- Treatment effects
- Impact on Clinical Trials and Clinical Practice

Clinical staging

- Applies only to those with biological AD
- Only change from 2018 is addition of stage 0
  - Deterministic gene (ADAD and DSAD); no clinical change and biomarker normal
  - Consistent with Neuronal Synuclein Disease and Huntington Dz
- Risk alleles not included in staging. Risk alleles define risk, not clinical stage of AD

Clinical staging for individuals on the AD continuum

Stage 0 Asymptomatic, deterministic gene

No evidence of clinical change. Biomarkers still in normal range

Stage 1 Asymptomatic, biomarker evidence only

Performance within expected range on objective cognitive tests.

No evidence of recent cognitive decline or new symptoms

Stage 2 Transitional decline: Mild detectable change, but minimal impact on daily function

Normal performance within expected range on objective cognitive tests.

Decline from previous level of cognitive or neurobehavioral function, that represents a change from individual baseline within past 1-3 years, and has been persistent for at least 6 months.

May be documented by evidence of subtle decline on longitudinal cognitive testing which may involve memory or other cognitive domains but performance still within normal range

May be documented through subjective report of cognitive decline (SCD)

May be documented with recent onset change in mood, anxiety, motivation not explained by life events

Remains fully independent with no or minimal functional impact on daily life activities (ADL)

Clinical staging for individuals on the AD continuum

Stage 3 Cognitive impairment with early functional impact

Performance in the impaired/abnormal range on objective cognitive tests

Evidence of decline from baseline, documented by the individual's report or by observer (e.g. study partner) report or by change on longitudinal cognitive testing or neurobehavioral behavioral assessments.

Performs daily life activities independently but cognitive difficulty may result in detectable functional impact on complex activities of daily life, i.e., may take more time or be less efficient but still can complete, either self-reported or corroborated by observer.

Stage 4 Dementia with mild functional impairment

Progressive cognitive and mild functional impairment on instrumental ADL with independence in basic ADL

Stage 5 Dementia with moderate functional impairment

Progressive cognitive and moderate functional impairment on basic ADLs requiring assistance

Stage 6 Dementia with severe functional impairment

Progressive cognitive and severe functional impairment on dependence for basic ADLs

Integrated biological (letters) and clinical (numbers) staging

	Stage 0	clinical Stage 1	clinical Stage 2	clinical Stage 3	clinical Stages 4-6
Initial biological stage (A)	X	1A	2A	3A	4-6A
Early biological stage (B)	X	1B	2B	3B	4-6B
Intermediate biological stage (C)	X	1C	2C	3C	4-6C
Advanced biological stage (D)	X	1D	2D	3D	4-6D

Biomarker profiles vs biological staging

- Biological staging of AD
  - Only core biomarkers
  - Applies only to individuals in whom AD has been diagnosed by core biomarkers
- Biomarker profiles - carried forward from 2018
  - May employ core and non-core biomarkers to characterize the general pathophysiologic state of an individual beyond or in addition to the presence of AD
  - Are applicable to all individuals in the population

Biomarker profiles

- Full multimodal biomarker profile
  - ATNISV (+/- or a continuous quantitative scale for each category)

Biomarker category	CSF or plasma analytes	Imaging
Core Biomarkers		
Core 1		
A (Aβ proteinopathy)	Aβ42	Amyloid PET
T_1: (phosphorylated and secreted AD tau)	p-tau 217, p-tau 181, p-tau 231	
Core 2		
T_2 (AD tau proteinopathy)	pT205, MTBR-243, non-phosphorylated tau fragments	Tau PET
Biomarkers of non-specific processes involved in AD pathophysiology		
N (injury, dysfunction, or degeneration of neuropil)	NfL	Anatomic MR or CT, FDG PET
I (inflammation) Astrocytic activation	GFAP	
Biomarkers of non-AD co-pathology		
V vascular brain injury		Anatomic infarction, WMH
S α-synuclein	αSyn-SAA*	

*Seed amplification assays

Biomarker profiles

- Full multimodal biomarker profile
  - ATNISV with +/- indicated as appropriate to each category
- Partial profiles
  - Possible in certain individuals
  - Useful conceptually and in clinical practice to characterize individuals

Treatment effects

SUPPORT FOR BIOLOGICAL DIAGNOSIS OF AD

- Anti Aβ immunotherapy, can reduce amyloid PET levels to below detection threshold
- Result in trends toward normalization of downstream biomarkers
- Anti Aβ immunotherapy, that reduces fibrillar amyloid levels measured on PET imaging, can slow the rate of cognitive decline in early symptomatic AD
- Consistency across both successful and failed immunotherapy agents that the amount of amyloid PET reduction is associated with the degree of clinical benefit

Impact on Clinical Trials and Clinical Practice

- The aims of the revision include
  - Improved fidelity in anchoring symptoms to pathology
  - Capture various biomarker features of AD including co-pathologies
  - Improved diagnostic prognostic accuracy
  - Improved prediction of treatment response and safety/tolerability
  - Standardized framework for earlier intervention
- Examples:
  - AHEAD implementation of plasma screening before PET
  - Trailblazer-ALZ-2 – ptau stratification/staging

NIA-AA Revised Criteria for Diagnosis and Staging of AD

Committee members

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Comments link: alz.org/nia-aa