NIA-AA Revised Criteria for Diagnosis and Staging of AD

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outline

- Background
- Biomarker categorization
- Diagnosis
- Biological disease staging
- Clinical staging
- Integrated biological and clinical staging
- Multi-modal biomarker profiles and identification of copathology
- Treatment effects
- Diversity and need for more representative cohorts
- Future Directions

Core principles from prior NIA AA work groups - 2011, 2012, 2018

- Separate syndrome (clinically identified impairment) from biology (etiology)
- AD is defined by its biology with the following implications:
  - The disease is first evident with appearance of β-amyloid plaques and tau tangles while people are asymptomatic. [caveat, early not well understood mechanisms]
  - Symptoms are a result of the disease process and are not necessary to diagnose AD
  - In living people the disease is diagnosed by disease specific biomarkers

Developments since 2018 that prompted this update

- Approved treatments that target core disease pathology. Importance of conceptual alignment between industry, academia and clinicians around biomarker classification, AD diagnosis, and staging.
- Development of plasma biomarkers, some (not all) with excellent diagnostic performance (ie equivalent to approved CSF assays)
  - Thus a new direction is to expand the 2018 framework from a research-only focus to one that provides diagnostic and staging criteria to inform both research and clinical care
- Recognition that imaging and fluid biomarkers within a category are not interchangeable for some intended uses

Changes from the draft presented at AAIC

- Clarified intent – to inform criteria for diagnosis and staging of AD that reflect current science and not to serve as clinical practise guidelines
- More nuanced biomarker classification: concepts of T1/ T2 & Core 1/Core 2
- Clarified minimum performance criteria for Core 1 biomarkers to be used to diagnose AD
- Separated CSF and plasma assays in description of intended uses
- Expanded discussion on the role of the clinician in medical decision making associated with biomarker testing
- Deemphasized discussion of research use only biomarkers

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Categorization of fluid analyte and imaging biomarkers – 4 criteria

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, FDG PET
I (inflammation) Astrocytic activation	GFAP	
Biomarkers of non-AD co-pathology		
V vascular brain injury		Infarction on MR or CT, WMH
S α-synuclein	αSyn-SAA*	

Core 1 vs Core 2: distinguished by timing onset and intended use. Classification of ptau

Intended uses for imaging, CSF and plasma biomarker assays

Intended Use	CSF	Plasma	Imaging
Diagnosis			
A: (Aβ proteinopathy)			Amyloid PET
T_1: (phosphorylated and secreted AD tau)		p-tau 217	
Hybrid ratios	p-tau181/Aβ42, t-tau/Aβ42, Aβ42/40	p-tau217/np-tau 217	
Staging, prognosis, as an indicator of biological treatment effect			
A: (Aβ proteinopathy)			Amyloid PET
T_1: (phosphorylated and secreted AD tau)		p-tau 217	
Hybrid ratios	p-tau181/Aβ42, t-tau/Aβ42, Aβ42/40	p-tau217/np-tau 217	
T_2: (AD tau proteinopathy)	pT205, MTBR-243, non-phosphorylated tau fragments	pT205	Tau PET
N (injury to or degeneration of neuropil)	NfL	NfL	Anatomic MR, FDG PET
I (inflammation) Astrocytic activation	GFAP	GFAP	
Identification of co-pathology			
N (injury, dysfunction, or degeneration of neuropil)	NfL	NfL	Anatomic MR, FDG PET
V vascular brain injury			Infarction on MR or CT, WMH
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Diagnosis of Alzheimer's disease: Core 1 and Core 2 AD Biomarkers

- Core 1 biomarkers: The diagnosis of Alzheimer's disease can be established by abnormality on specific Core 1 biomarkers – ie amyloid PET, CSF Aβ42/40, CSF p-tau181/Aβ42, CSF t-tau/Aβ42; or, "accurate" plasma assays
- Core 1 biomarkers are useful for: (1) the early detection of AD in people without symptoms (2) the confirmation that AD is an underlying pathology in someone with symptoms
- Core 2 biomarkers are those in the T_2 category: tau PET, pT205, MTBR-423 and non-phosphorylated tau
- Core 2 biomarkers not typically standalone tests for the diagnosis of AD but can be combined with Core 1 to stage biological disease severity and, (1) provide information on the likelihood that symptoms are associated with AD, 2) inform on risk of progression in people without symptoms, 3) inform on the likely rate of progression in symptomatic individuals

Diagnosis of Alzheimer's disease: minimum accuracy benchmark

- Only biomarkers that have been proven to be accurate with respect to an accepted reference standard should be used for clinical diagnostic purposes, and the same criteria apply for PET, CSF, or BB biomarkers
- Minimum requirement, an accuracy of 90% for the identification moderate/frequent neuritic plaques at autopsy (or an approved surrogate which at this point would be amyloid PET or CSF) in the intended use population.
- For BBB assays this translates to accuracy equivalent to that of approved CSF assays – at present only some plasms ptau 217 assays
- specification of accurate "in the intended use population" addresses positive and negative predictive value which depend on the prior probability of AD in the population of interest

Clinical application of biomarkers: clinical judgement is paramount

- when a biomarker test result seems discordant with the clinical presentation
- when assessing the likely contribution of AD vs other pathologies to clinical symptoms, particularly when the clinical presentation suggests copathology is present
- to assess potential effects of confounding medical conditions on biomarker results
- The committee strongly recommends that clinicians should not be restricted by payers in pursuing further testing when this is indicated in the judgement of the clinician
- we recommend that biomarkers testing should only be performed under the supervision of a physician

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Biological staging

- Staging of AD applies only to individuals in whom the disease has been diagnosed by an abnormal core biomarker
- Biological staging (biomarkers) vs clinical staging (clinical assessment)
- Based on natural history of biomarker events
- Core biomarkers only

Description of Initial, Early, Intermediate, and Advanced stage PET

	Initial stage biomarkers	Early stage biomarkers	Intermediate stage biomarkers	Advanced stage biomarkers
	(A)	**(B)**	**(C)**	**(D)**
PET	amyloid PET	tau PET medial temporal region	tau PET moderate neocortical uptake	tau PET high neocortical uptake
	A+T-	$A+T_{MTL}+$	$A+T_{MOD}+$	$A+T_{HIGH}+$
Core 1 fluid	CSF Aβ42/40, p-tau181/Aβ42, t-tau/Ab42, and accurate* plasma assays can establish that an individual is in biological stage A or higher, but cannot discriminate among PET stages A-D at present			

Staging may be accomplished by 1) a combination amyloid PET and tau PET, or 2) a combination of Core 1 fluid biomarkers (which would establish biological stage A or higher), plus tau PET (which would be used to discriminate among stages).

Conceptual Biological Staging with Fluid Biomarkers

	Initial stage biomarkers	Early stage biomarkers	Intermediate stage biomarkers	Advanced stage biomarkers
	(A)	(B)	(C)	(D)
Fluid staging	CSF Aβ42/40, p-tau181/Aβ42, t-tau/Aβ42, and accurate** plasma assays	pT205*	MTBR-243*	Non phosphorylated tau*

PET and fluid measures are not equivalent and hence stages A-D with PET are not equivalent to stages A-D for fluid biomarkers.

*Validation of pT205, MTBR-243 and non-phosphorylated tau as early, intermediate and advanced stage fluid markers respectively is conceptual for now, awaiting further studies.

** Accurate is defined in the text (section 3.2) and in text box 2

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Comments link: alz.org/nia-aa