Implementation of the Revised NIA-AA AD Criteria Across the ADRC Network: Overview of Considerations, Challenges and Opportunities

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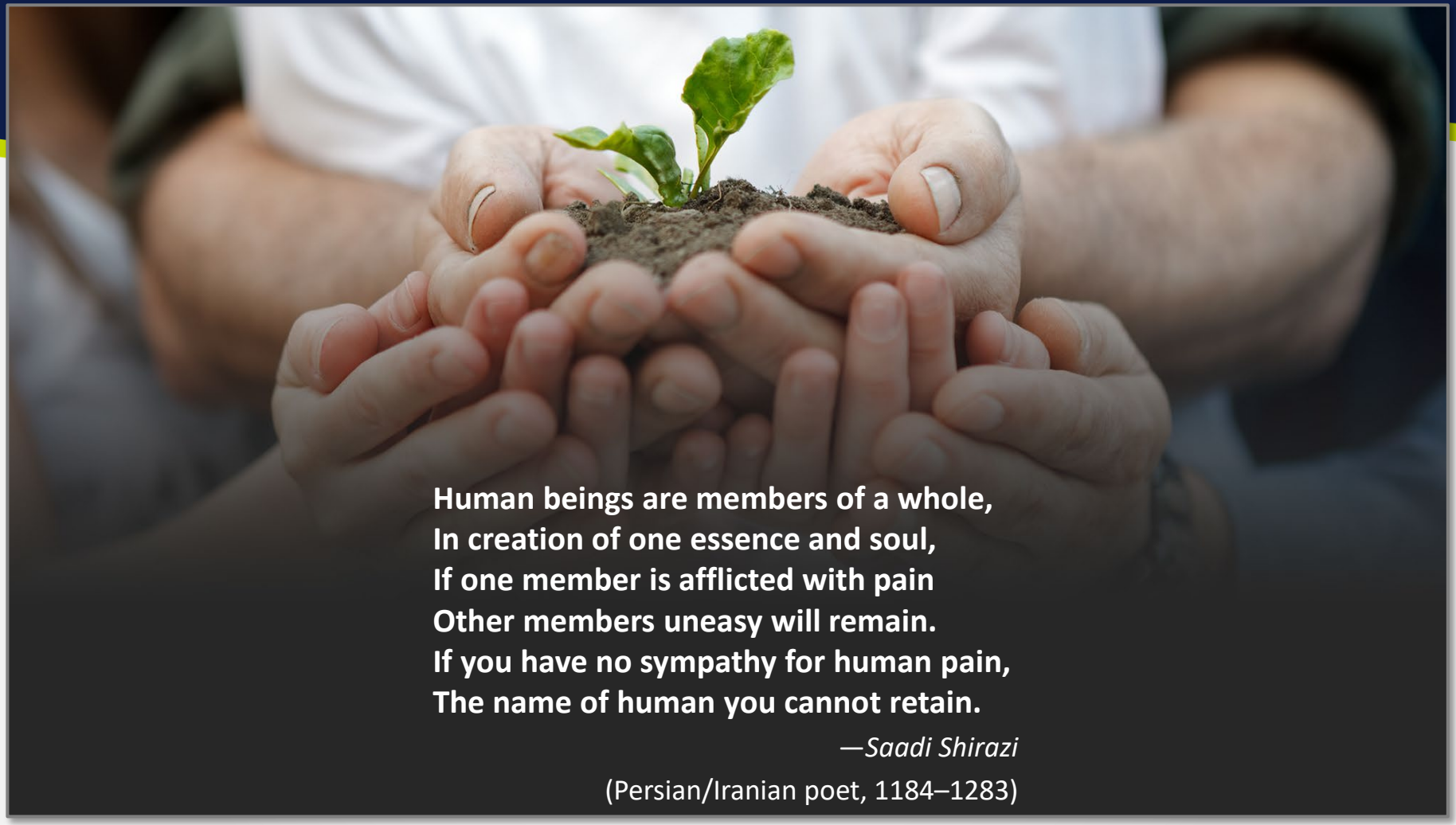
Human beings are members of a whole,
In creation of one essence and soul,
If one member is afflicted with pain
Other members uneasy will remain.
If you have no sympathy for human pain,
The name of human you cannot retain.
—Saadi Shirazi
(Persian/Iranian poet, 1184–1283)

20,000 foot view

- We are at the beginning of a new and transitional era in ADRD with an expected non-linear trajectory of advances spurred by biomarkers → potential for precision and personalized medicine aimed at pathobiology!
- With many strengths and resources ADRC's are well-positioned to be on the frontlines to implement, assess, validate and enhance the revised AD criteria
  - Proficiency and multi-disciplinary research and subspecialty expertise (critical for the scientific aspects and the "clinician judgment" and "care, consideration and compassion" pieces of our research endeavors involving participants)
  - Leveraging existing and developing new collaborations, consortia, projects and resources
- Transitions often involve challenges – but also present opportunities
- → will require **thoughtfulness**; innovation; methodical, rigorous and stepwise approach; and **collaborations**

Revised NIA-AA AD Criteria – "Important qualifiers around the biological diagnosis of AD"

- "A major new direction therefore 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"
- " It is necessary to separate syndrome (clinically identified impairment) from biology (etiology)"
- NACC UDS 4.0 approach:
  - Level of Impairment (CU, SCD, MCI, Cognitively Impaired not-MCI, MBI, Behaviorally Impaired not-MBI, dementia) --> domains impacted
  - Clinical Syndrome (amnestic predominant, dysexecutive predominant, primary visual syndrome, primary language/PPA syndromes, etc)
  - Biomarker evidence (fluid, imaging, genetic, other) --> patterns of biomarkers consistent with X
  - Etiological Diagnosis (primary/contributing) [with or without biomarker evidence – integrating full data available and using clinical judgment]

Revised NIA-AA AD Criteria – "Important qualifiers around the biological diagnosis of AD"

- "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"
- "We recommend as a minimum requirement, an accuracy of 90% for the identification of intermediate/high AD neuropathologic change at autopsy (or an approved surrogate which at this point would be amyloid PET or CSF) in the intended use population"
- "Clinical judgement is always required when employing or interpreting biomarker tests clinically. The judgement of the clinician is paramount:
  1) In situations where a biomarker test result seems discordant with the clinical presentation
  2) When assessing the likely contribution of AD vs other pathologies to clinical symptoms, particularly when the clinical presentation suggests co-pathology is present,
  3) To assess potential effects of confounding medical conditions on biomarker results"
- "In the absence of approved interventions for unimpaired individuals, we do not advocate AD biomarker testing in this population currently, although this may change in the future."

Revised NIA-AA AD Criteria – Differences, Challenges, Cautions and Considerations

- Diversity of biomarkers utilized at Centers without standardization and harmonization wrt measures, platforms, and well-established reference ranges
- More biomarker data utilized, more heterogeneity and variability --> Clinical Judgment
- Return of result considerations to participants – adoption and implementation in the context of the revised criteria will need to consider differences, interpretation and maturity of measures, and to be done very thoughtfully and methodically; including differences with NACC UDS guidance regarding etiological diagnosis:
  - "*using all the available data (i.e. clinical, cognitive, biomarker, etc) and "*" your Center's standards"
  - *For those with no biomarker data, enter a **presumed** etiological diagnosis*
  - **For unimpaired participants:** Indicate the presence of any etiological diagnosis by selecting "present".

Revised NIA-AA AD Criteria – Differences, Challenges, Cautions and Considerations

- Revised criteria are specific regarding Core 1 and 2 biomarkers (e.g. Core 1 biomarkers that can be diagnostic of AD: amyloid PET; CSF Aβ42/40, CSF p-tau181/Aβ42, CSF t-tau/Aβ42; or, “accurate” plasma assays
- NACC UDS 4.0 reporting:
  - Is more general for fluid biomarkers → “consistent (c/w) with AD” = no/yes/indeterminate
  - For amyloid/tau PET: elevated = no/yes/indeterminate
- NACC UDS 4.0 for non-core:
  - N: structural imaging or FDG PET (→ pattern c/w X = AD/FTLD/LBD)
  - V: structural imaging (→ pattern c/w X)
- UDS 4.0 does allow for “other biomarker” to be listed and pattern c/w X
- UDS 4.0 can facilitate AD diagnostic mapping more readily
  - Facilitation of clinical Staging (CU = C_1, SCD = C_2, MCI = C_3, Dementia = $C_{4\text{-}6}$)
  - Does not yet have level of specificity required for biological staging (other than Stage A vs Stages B-D if Tau PET data available and c/w AD pattern – in addition to Core 1 A data)

Revised NIA-AA AD Criteria – Differences, Challenges, Cautions and Considerations

Table 6. Integrated biological and clinical 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

Table 3a. Biological staging

	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).

Opportunities

- Harmonization and standardization
- NCRAD
  - Report utilization from ADC Fluid Biomarker Initiative
  - Plethora of plasma and CSF A and T1 core biomarker results, plasma Nfl and GFAP
  - Opportunities for collaborations, reference range development, harmonization between centers, and standardization
- SCAN, CLARiTI AD, Digital biomarkers
- CMS lifting of amyloid PET NCD → potential for more “standardized” Core 1 A data for symptomatic participants
- Utilization of Core 1+2 biomarkers to assign likelihood of impact of biology on symptoms (cause/contribution)
- Iterative development and harmonization of terminology (e.g. Clinical Stage, Biomarker Spectrum – A+/- → A_i i=0,1,2,3; $A_{3\rightarrow0}$ High amyloid removal to “negative”)
- Hierarchical decision rules to resolve discordant biomarkers within same category → to aid “clinical judgment”
- Work towards Biological Staging A-B-C-D in UDS4.1 and Integrated Biological and Clinical Staging?

Summary

- We are at the beginning of a new, hopeful and foundational era – revised AD criteria are forward thinking and reflect the transition we're in
  - As a result have experience some 1st world challenges
  - ADRC transitional implementation will be helpful on many levels to assess and refine criteria and approach (who – more inclusively, when, what, how)
  - Continue to build our ADRC infrastructure -- be thoughtful, innovative, methodical, rigorous, and collaborative

“Where there is no hope, there can be no endeavour.”
— *Samuel Johnson*

“The journey of a thousand miles begins with one step.”
— *Lau Tzu*

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THANK YOU!

…the glass is
more than half full!