

# **Update on NIA-AA Guidelines**

**ADC Directors Meeting**

**September 2015**

**Neuropathology Session**

# NIA-AA Guidelines

***National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease.***

Hyman BT, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Carrillo MC, Dickson DW, Duyckaerts C, Frosch MP, Masliah E, Mirra SS, Nelson PT, Schneider JA, Thal DR, Thies B, Trojanowski JQ, Vinters HV, Montine TJ. *Alzheimers Dement.* 2012 Jan;8(1):1-13.

**National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach.** Montine TJ, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Dickson DW, Duyckaerts C, Frosch MP, Masliah E, Mirra SS, Nelson PT, Schneider JA, Thal DR, Trojanowski JQ, Vinters HV, Hyman BT; National Institute on Aging; Alzheimer's Association. *Acta Neuropathol.* 2012 Jan;123(1):1-11

- NACC supplement (awarded in 2013) with goal of determining the extent, sources and potential approaches to mitigate variation in the neuropathologic assessment of AD using the 2012 NIA-AA scheme
- “Multisite assessment of NIA-AA guidelines for the neuropathologic evaluation of Alzheimer's disease.” Montine TJ, Monsell SE, Beach TG, Bigio EH, Bu Y, Cairns NJ, Frosch M, Henriksen J, Kofler J, Kukull WA, Lee EB, Nelson PT, Schantz AM, Schneider JA, Sonnen JA, Trojanowski JQ, Vinters HV, Zhou XH, Hyman BT, *Alzheimers Dement.* 2015 Aug 29. PMID: 26327235

# Design

- **14 cases total**
  - selected for varying levels of AD neuropathologic change
- **Evaluated**
  - Current practice (focus)
    - Local staining, local evaluation
  - Estimate potential sources of variance
    - By evaluator (central staining with local evaluation)
    - By staining protocols (consensus evaluation)
  - WSI vs. glass slides

|                                      | For "A" score <sup>^</sup> | For "B" score <sup>#</sup> | For "C" score <sup>*</sup> |
|--------------------------------------|----------------------------|----------------------------|----------------------------|
|                                      | A $\beta$ Stain            | NFT Stain                  | NP Stain                   |
| Middle frontal gyrus                 | X                          | X                          | X                          |
| Superior and middle temporal gyri    | X                          | X                          | X                          |
| Inferior parietal lobule             | X                          | X                          | X                          |
| Occipital Cortex (BA 17 & 18)        |                            | X                          |                            |
| Hippocampus and entorhinal cortex    | X                          | X                          |                            |
| Basal ganglia at anterior commissure | X                          |                            |                            |
| Midbrain including substantia nigra  | X                          |                            |                            |
| Cerebellar cortex                    | X                          |                            |                            |

Unstained sections (14 cases) sent to each center,  
stained and read locally with data and slides sent back

|                | Average weighted $\kappa$ | 95% CI      |
|----------------|---------------------------|-------------|
| Severity score | 0.88                      | (0.77-0.95) |
| A score        | 0.84                      | (0.68-0.92) |
| B score        | 0.70                      | (0.45-0.83) |
| C score        | 0.77                      | (0.58-0.88) |

High level of agreement, especially for *Severity*

# 8 cases used (part of the previously done local/local set)

Stained centrally  
Read locally

Stained locally  
Read locally

|                | Average           |             | Average           |             |
|----------------|-------------------|-------------|-------------------|-------------|
|                | weighted $\kappa$ | 95% CI      | weighted $\kappa$ | 95% CI      |
| Severity score | 0.70              | (0.31-0.84) | 0.84              | (0.56-0.91) |
| A score        | 0.67              | (0.33-0.84) | 0.81              | (0.50-0.90) |
| B score        | 0.68              | (0.37-0.81) | 0.83              | (0.61-0.92) |
| C score        | 0.71              | (0.42-0.88) | 0.73              | (0.52-0.83) |

Stained locally & read locally outperforms other approach (confidence intervals overlap)

Set of 6 cases which had been stained at 5 of the  
participating sites  
Consensus meeting read vs initial reads by the same  
neuropathologists

|                | Consensus evaluation |             | Independent evaluation |             |
|----------------|----------------------|-------------|------------------------|-------------|
|                | Average              |             | Average                |             |
|                | weighted $\kappa$    | 95% CI      | weighted $\kappa$      | 95% CI      |
| Severity score | 0.84                 | (0.48-0.96) | 0.67                   | (0.33-0.80) |
| A score        | 0.80                 | (0.67-0.87) | 0.64                   | (0.29-0.80) |
| B score        | 0.90                 | (0.43-1.00) | 0.75                   | (0.49-0.90) |
| C score        | 0.51                 | (0.26-0.79) | 0.49                   | (0.16-0.70) |



## Comparison of WSI vs Glass for set of 8 cases used in prior comparisons

|                | Whole slide imaging |             | Glass slides      |             |
|----------------|---------------------|-------------|-------------------|-------------|
|                | Average             |             | Average           |             |
|                | weighted $\kappa$   | 95% CI      | weighted $\kappa$ | 95% CI      |
| Severity score | 0.76                | (0.45-0.86) | 0.84              | (0.56-0.91) |
| A score        | 0.66                | (0.37-0.81) | 0.81              | (0.50-0.90) |
| B score        | 0.86                | (0.65-0.92) | 0.83              | (0.61-0.92) |
| C score        | 0.83                | (0.56-0.93) | 0.73              | (0.52-0.83) |

# Limitations

- **10 sites (limited by logistics of moving slides around)**
- **14 cases total -- estimates of sources of variance based on relatively few cases**
- **Focused on AD neuropathologic change (ABC scoring)**
  - LBD, VBI, HS, TDP-43 ...?

# Conclusions

- **Unique estimates of variance in evaluation of AD**
- **Current practice yields good (B & C) to excellent (severity & A) agreement**
  - Supports value of NACC dataset
- **Relevant additional observations:**
  - Central staining with local evaluation performed worst for all parameters
  - Consensus evaluation seemed to yield improved agreement for most parameters (except C scores)
  - WSI-based assessments approached traditional methods