Diagnostic Accuracy of the Clinical Diagnosis of Alzheimer's Disease at National Institute on Aging Alzheimer's Disease Centers, 2005-2010

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Background

- Literature review of 25 prior studies
- Neuropathological diagnosis as “gold standard”
- Very variable results
- Sensitivity between 41% and 100% (median of 87%)
- Specificity between 37% and 100% (median of 58%)

Why the Variability?

- Clinical diagnostic criteria did not change since 1984 (NINDS-ADRDA McKhann et al)
- Neuropathological “gold standard”changed several times.
- "Khachaturian criteria" of 1985
- "Tierney" criteria of 1988
- CERAD criteria in 1991
- NIA-Reagan criteria in 1997

Methods

- Utilized NACC data from between 2005 and 2010
- From more than 30 NIA AD Centers
- 1198 subjects with at least one UDS clinical visit and autopsy
- UDS represent most current clinical research protocol
- Excluded 271 because not demented or lacked critical data (differed from included in terms of age, gender and neuropath scores)
- Final subject number 919

Methods

- Sensitivity and specificity estimated for two levels of clinical confidence, “Probable” and “Possible” AD (NINDS-ADRDA criteria, McKhann et al 1984)
- Also stratified the gold standard for four levels of neuropathological severity, based on neuritic plaque density and Braak stage
- No adjustments for other subject characteristics.
- Groups were compared with t-tests and analysis of variance

Groups

Clinical Diagnosis	Age	Gender	Interval (mos)	NP Density (median)	Braak Stage (median)
Probable AD N = 526	**81.2**	**220F/306M**	**11.5**	**frequent**	**5**
Possible AD N = 122	**83.2**	**53F/69M**	**10.4**	**moderate**	**4**
Not AD N = 271	**72.8**	**95F/176M**	**9.8**	**sparse**	**2**

Not AD group significantly younger

Groups differed significantly in terms of NP Density and Braak stage

Sensitivity/Specificity

bottom row most relevant?
Or should npath be more stringent?

Neuropathological AD Definition	Clinically Probable AD N = 526	Clinically Probable or Possible AD N = 648
CERAD NP Freq Braak Stage V or VI N = 427	N = 327 Sensitivity 76.6% Specificity 59.5%	N = 373 Sensitivity 87.3% Specificity 44.3%
CERAD NP Mod or Freq Braak Stage V or VI N = 486	N = 366 Sensitivity = 75.3% Specificity = 63.0%	N = 418 Sensitivity = 85.9% Specificity = 47.0%
CERAD NP Freq Braak Stage III - VI N = 490	N = 370 Sensitivity = 75.5% Specificity = 63.6%	N = 421 Sensitivity = 85.9% Specificity = 47.1%
CERAD NP Mod or Freq Braak Stage III-VI N = 618	N = 438 Sensitivity = 70.9% Specificity = 70.8%	N = 511 Sensitivity = 82.7% Specificity = 54.5%

Sensitivity increased but specificity decreased with more permissive clinical criteria; reverse for neuropathological criteria

Positive Predictive Value

bottom row most relevant?

Neuropathological AD Definition	Clinically Probable AD N = 526	Clinically Probable or Possible AD N = 648	Dementia N = 919
CERAD NP Freq Braak Stage V or VI N = 427	N = 327 PPV = 62.2%	N = 373 PPV = 57.6%	N = 427 PPV = 46.0%
CERAD NP Mod or Freq Braak Stage III-VI N = 618	N = 438 PPV = 83.3%	N = 511 PPV = 78.8%	N = 618 PPV = 67.2%

Clinical Probable AD but found to have less than Minimal AD Histopathology 88 Cases

Primary Neuropathological Findings	# of Cases
Primary neuropathological diagnosis of AD despite low level of AD histopathology	17
Tangle-only dementia or argyrophilic grain disease (idiopathic?)	15
Frontotemporal lobar dementia (not subtyped)	15
Cerebrovascular disease	10
Lewy body disease, with or without AD	9
Hippocampal sclerosis, with or without AD	9
Progressive supranuclear palsy	3
Corticobasal degeneration	2
Neuroaxonal dystrophy/Hallervorden-Spatz-like condition	2
Miscellaneous	6

Clinically Not AD
Primary Neuropath DX
271 Cases

Primary Neuropathological Diagnosis	# of Cases
AD (with NIA-Reagan intermediate or high)	107
Frontotemporal lobar dementia	60
Lewy body disease, with or without AD	31
Creutzfeldt-Jakob disease and other prion encephalopathies	23
Progressive supranuclear palsy	18
Tangle-only dementia or argyrophilic grain disease	9
Corticobasal degeneration	8
Pick's disease	6
Cerebrovascular disease	6
Hippocampal sclerosis, with or without AD	2
Amyotrophic lateral sclerosis	2
Miscellaneous	3

Results Summary

- Sensitivity ranged from 70.9% to 87.3% while specificity ranged from 44.3% to 70.8%. Sensitivity was increased with more permissive clinical criteria and specificity was increased with more restrictive criteria while the opposite was true for neuropathological criteria.
- For common minimal histopath definition of AD (NIA-Reagan intermediate or high), sensitivity was 82.7%, specificity 54.5%, with permissive clinical definition (probable and possible AD)
- This is similar to prior NACC estimate from 1998 (Mayeux et al N Engl J 1998) and to overall median values for 25 reviewed studies

How to Use These Data?

- For clinical trials, where objective is to exclude as many non-AD dementias as possible (due to non-AD cases causing a lowering of effect size) more restrictive clinical criteria (probable AD) are probably desirable
- For epidemiological studies, where the objective might be to determine, as best as possible with clinical methods, the true prevalence of AD in the population, then less restrictive criteria (probable plus possible) are probably desirable

How to Use These Data?

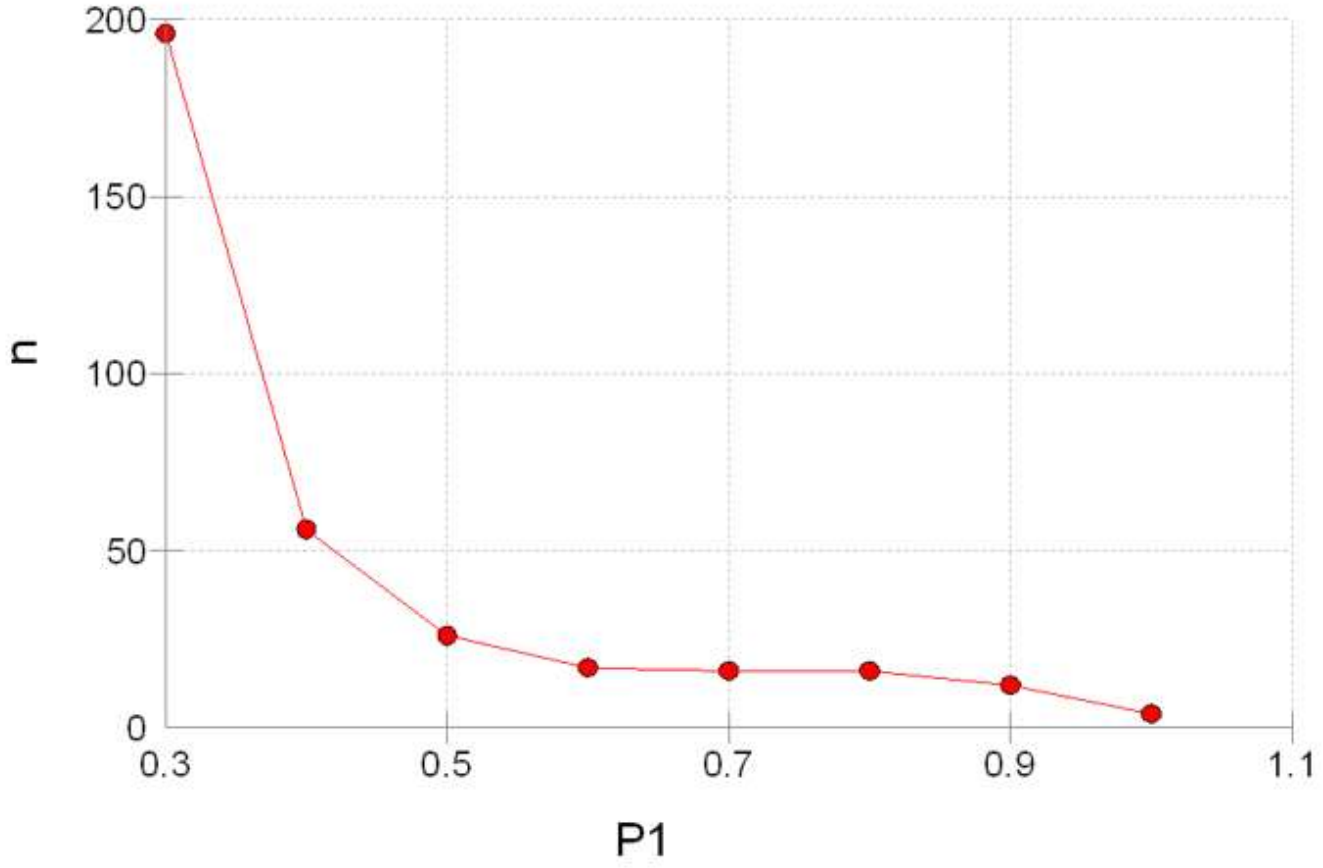
- For neuropathological criteria, if the objective is to define the level of pathology that is the best threshold for dementia, large multivariable logistic regression modeling, including all major contributing pathological lesions (not just AD lesions) is still needed (available studies have still not captured all relevant lesions in the same study)
- If the objective is to define AD biologically, any brain with any plaques and tangles might be the most unambiguous definition, analogously to any tiny focus of cancer is still cancer, a single atheroma is still coronary artery disease

How to Use These Data?

- If the objective is to separate “benign” AD from “malignant” AD (e.g. analogously to slow-growing and fast-growing prostate cancer), then a time component may be necessary; this might be provided by serial imaging
- Ultimately cortical biopsy and molecular profiling may be necessary, analogously to cancer histological subtyping, staging and molecular profiling

How relevant is a 20% clinical diagnostic error?

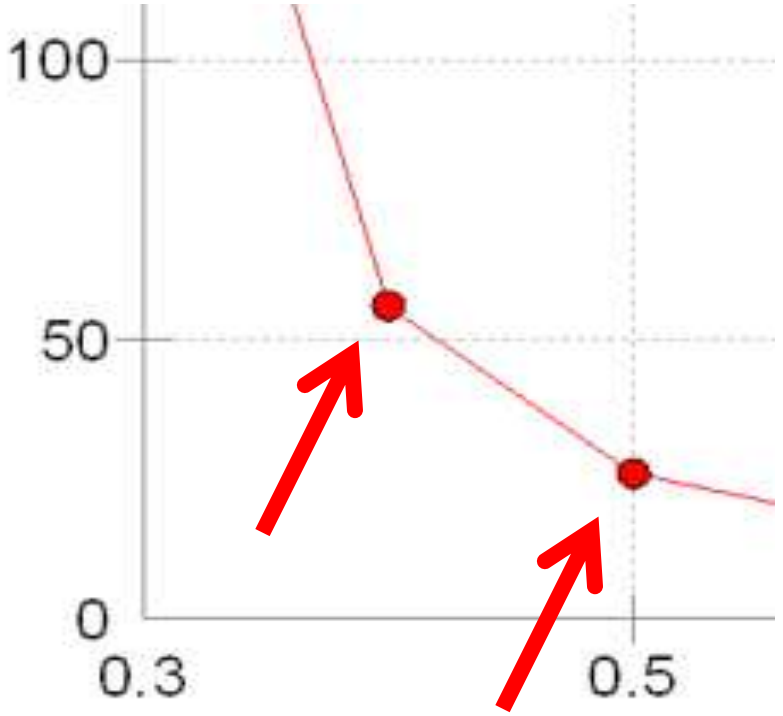
Effect Size, Required Subject Number and Statistical Power



For effect size > 50%, 20% diagnostic error not significant but for effect size under 50%, it probably is

Diagnostic Error Causes, for Drugs that Work only on AD, a decrease in the perceived effect size due to “dilution” of the subject test population with non-AD subjects

- Drug has true benefit for 50% of AD subjects
- Diagnostic error 20%
- Only 80% of trial subjects have AD
- 0.8 dx error x 50% effect size = 40%
- perceived effect = 40%
- Doubling of subject number required if true drug effect size 50%
- Exponentially more subjects needed for lower effect sizes



Still Unaddressed

- The effect of Braak stage
- Those in Braak V and VI probably less likely to respond to medication than those in Braak III & IV
- The effect of comorbid diagnoses
- Perhaps 50% of AD subjects have a second major neuropath dx
- AD/DLB, ADLB, AD/VaD, AD/PSP, AD/HS, AD/FTLD-TDP, etc
- What if these “variants” have varying responses to medication?

Results Summary and Conclusion

- Neurologists of the NIA-ADCs have higher predictive accuracy when they diagnose AD in demented subjects but have lower predictive accuracy when they diagnose demented persons with diseases other than AD – many of those diagnosed with another dementia actually have AD.
- Sensitivity and specificity vary with level of clinical stringency and different stringencies might be considered depending on what needs to be accomplished
- The misdiagnosis rate should be considered when estimating subject numbers for AD clinical trials and epidemiological studies.

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