A Biomarker Approach to the Diagnosis of Dementia

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How do we currently diagnose dementia?
MAJOR NEUROCOGNITIVE DISORDER (DEMENTIA)

• A. Evidence of significant cognitive decline from a previous level of performance in one or more of the domains outlined above based on:
  1. Concerns of the patient, a knowledgeable informant or the clinician that there has been a significant decline in cognitive function; AND
  2. A clear impairment in cognitive performance preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

• B. The cognitive deficits are sufficient to interfere with independence (i.e., requiring assistance at a minimum with instrumental activities of daily living [i.e., more complex tasks such as paying bills or managing medications]).

• C. The cognitive deficits do not occur exclusively in the context of a Delirium.

• D. The cognitive deficits are not primarily attributable to another mental disorder (e.g., Major Depressive Disorder, Schizophrenia).
Mild Neurocognitive Disorder (MCI)

A. Evidence of modest cognitive decline from a previous level of performance in one or more of the domains outlined above based on:
   1. Concerns of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and
   2. A modest impairment in cognitive performance preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

• B. The cognitive deficits are insufficient to interfere with capacity for independence in everyday activities, i.e., complex instrumental activities of daily living such as paying bills or managing medications are preserved. However, greater effort, compensatory strategies, or accommodation may be required to maintain independence.

• C. The cognitive deficits do not occur exclusively in the context of a Delirium.

• D. The cognitive deficits are not primarily attributable to another mental disorder (e.g., Major Depressive Disorder, Schizophrenia)
What is a biomarker?

- A biomarker is a characteristic that is **objectively measured** and evaluated as an indicator of normal biological processes, **pathogenic processes** or pharmacological responses to a **therapeutic intervention** (Biomarkers Definition Working Group. Clin. Pharmacol. Ther. 69, 89–95 (2001)).

- Many uses:
  1. For diagnosis
  2. To predict natural outcome in an individual
  3. To predict response to treatment
  4. To use as surrogate markers of response
  5. To serve as endophenotypes
Etiology

- Second step in diagnostic process
- Specific criteria
- Major / minor can have same etiology
- Etiology for minor less definite
- Multiple etiologies common

**Big four**
- Alzheimer’s disease
- Vascular cognitive impairment
- Cortical Lewy Body disease
- Frontotemporal lobar atrophy

**Other**
- Huntington’s disease
- Infectious diseases (including prion, HIV, HSV)
- PD (including PSP, MSA, CBD)
- Traumatic brain injury
- Alcohol and other substances
- Metabolic/Endocrine
- Storage diseases
- Drugs and toxins
- Deficiencies

**Establishing etiology:**
- History
- Physical exam
- Laboratory investigations
- Neuroimaging
- Biomarkers
MAJOR AND MILD NEUROCOGNITIVE DISORDER DUE TO ALZHEIMER’S DISEASE

A. The individual meets criteria for Major or Mild Neurocognitive Disorder.
B. There is insidious onset and gradual progression of impairment in one or more cognitive domains (for Major Neurocognitive Disorder, two domains must be impaired).
C. The syndrome as a whole is not better attributed to:
   1. Cerebrovascular disease (i.e., there is no history of stroke temporally related to the onset of cognitive impairment; and any infarcts or white matter hyperintensities are judged insufficient to account for the clinical picture)
   2. Lewy body disease (i.e., core features of Lewy body disease are absent)
   3. Parkinson’s disease (i.e., spontaneous parkinsonism with onset well before the cognitive decline)
   4. Fronto-temporal lobar degeneration (i.e., core features of fronto-temporal lobar degeneration are absent)
   5. Other concurrent, active neurologic or systemic illness (i.e., there is no other condition with an appropriate temporal relationship and severity to account for the clinical picture).
D. A level of certainty must be specified.
Major NCD due to AD
(Alzheimer’s Dementia)

- Probable AD is diagnosed if one of the following is present, otherwise Possible Alzheimer’s disease should be diagnosed.

A. Biomarker evidence of an Alzheimer’s disease pathophysiological process.

B. Evidence of a causative Alzheimer’s disease genetic mutation, from either family history or genetic testing such as those for amyloid precursor protein (APP), presenilin 1 (PSEN1), presenilin 2 (PSEN2).

C. Typical clinical course with all three of the following
   1. Clear evidence of decline in memory and at least one other cognitive domain (based on detailed history or serial neurocognitive testing)
   2. Steadily progressive, gradual decline in cognition, with no extended plateaus
   3. No evidence of mixed etiology (i.e., absence of concomitant cerebrovascular disease, Lewy Body disease, Parkinson’s disease, other neurological or systemic disease or condition that could be contributing to cognitive decline).
The neuropathological basis of dementia is heterogeneous
Person-Specific Contribution of Neuropathologies to Cognitive Loss in Old Age

- Data from two longitudinal clinico-pathological studies (*Religious Order* and *Memory and Aging*)
- Neuropathology was ubiquitous, with 94% of participants having 11, 78% having 21, 58% having 31, and 35% having 41.
- AD was most frequent (65%) but rarely occurred in isolation (9%).
- Remarkably, >230 different neuropathologic combinations were observed, each of which occurred in <6% of the cohort.
Pathologies in older brains

1. Amyloid plaques – diffuse and neuritic
2. Neurofibrillary tangles
3. Lewy bodies – brain stem; limbic (transitional); neocortical; amygdala-predominant
4. Primary tauopathy – 3R, 4R and mixed
5. Age-related tauopathy – PART and ARTAG (Age-related tau astrogliopathy)
6. TDP-43 (transactive response DNA binding protein 43 kDa)
7. Hippocampal sclerosis
8. VBI (vascular brain injury) from Large vessel disease – large infarcts
9. VBI from Small vessel disease – lacunes, white matter hyperintensities, microbleeds, dilated perivascular spaces, microinfarcts, reduced cerebral blood flow
10. Cerebral amyloid angiopathy (CAA)
11. Dendritic and synaptic loss
12. Neuroinflammation
<table>
<thead>
<tr>
<th>Neuropathological findings</th>
<th>Age &lt;80 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No dementia</td>
</tr>
<tr>
<td></td>
<td>(n=36)</td>
</tr>
<tr>
<td>Neuritic plaques in neocortex</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>20 (56%)</td>
</tr>
<tr>
<td>Mild</td>
<td>6 (17%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>8 (22%)</td>
</tr>
<tr>
<td>Severe</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Diffuse plaques in neocortex</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>14 (39%)</td>
</tr>
<tr>
<td>Mild</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>13 (36%)</td>
</tr>
<tr>
<td>Severe</td>
<td>5 (14%)</td>
</tr>
<tr>
<td>Tangles in hippocampus/entorhinal cortex</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>9 (26%)</td>
</tr>
<tr>
<td>Mild</td>
<td>9 (26%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>9 (26%)</td>
</tr>
<tr>
<td>Severe</td>
<td>7 (21%)</td>
</tr>
<tr>
<td>Tangles in neocortex</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>28 (80%)</td>
</tr>
<tr>
<td>Mild</td>
<td>6 (17%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
</tr>
<tr>
<td>Vascular disease</td>
<td></td>
</tr>
<tr>
<td>Any vascular disease</td>
<td></td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>0</td>
</tr>
<tr>
<td>Infarct</td>
<td>10 (28%)</td>
</tr>
<tr>
<td>Lacune</td>
<td>10 (28%)</td>
</tr>
<tr>
<td>Small-vessel disease</td>
<td>20 (59%)</td>
</tr>
<tr>
<td>Overall vascular pathology</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>8 (24%)</td>
</tr>
<tr>
<td>Infarct or lacune only</td>
<td>5 (15%)</td>
</tr>
<tr>
<td>Small-vessel disease</td>
<td>12 (35%)</td>
</tr>
<tr>
<td>Multiple</td>
<td>9 (26%)</td>
</tr>
<tr>
<td>Severe congophilic angiopathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Brain weight (kg) *</td>
<td>1.24</td>
</tr>
</tbody>
</table>

Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS)*

Lancet 2001; 257:169-75
In this dataset, of the 35% of persons who did not meet criteria for pathologic AD, 21% had clinical AD dementia; furthermore, of the 44% who had clinical AD dementia proximate to death, 17% did not meet pathologic criteria for AD.
Dementia

Preclinical states

CU

MCI

First symptoms

3–5 yrs

Biomarkers

Specific cognitive disorders

Dementia

Current point of diagnosis

to be earlier with a higher specificity?
The case of AD
NIA-AA Diagnostic criteria for MCI

1. Hippocampal atrophy
2. FDG-PET
3. Amyloid PET

Albert M et al, 2011
PET imaging

- **PET-FDG.** Pooled sensitivities and specificities (9 studies) of 86% for temporo-parietal hypometabolism (*Patwardhan, 2004*)

- **PET-PiB.** Increased radioligand retention in AD compared to control subjects (*Klunk, 2004*)
The pattern of PiB retention replicates the sequence of Amyloid deposition described from postmortem studies.

Stages of Amyloid deposition in the human brain (Braak and Braak)

Regional distribution of 11C-PIB

PiB– HC  PiB+ HC  MCI  AD
PiB PET Images of normal control, MCI, and AD subjects showing a range of amyloid-β deposition

Cold Spring Harb Perspect Med 2012;2:a006213
Tau pathology in AD

Tau imaging

rSUV (target/cerebellum) Images 80-100 min post inj
CSF biomarkers of AD

Total Aβ
Aβ1-40
Aβ1-42
Aβ42/40 ratio

Diagram showing the structure of APP, β-sAPP, and the β-secretase and γ-secretase pathways involved in the production of Aβ. The diagram illustrates the intracellular and extracellular regions of APP and the cleavage sites for β-secretase and γ-secretase.
CSF Aβ42 levels are tightly coupled with cortical amyloid load in the earliest stages of preclinical AD, and begin to decrease dramatically prior to the point when an abnormal threshold of cortical accumulation is detected with amyloid imaging.

Figure 5A. Sensitivity and specificity for cerebrospinal fluid β-amyloid-42 to differentiate Alzheimer’s disease from controls in prospective studies on consecutive patients. In the six studies, the mean sensitivity was 89% at a specificity of 90%.

Aβ 1-42

Blenno K, 2005
Total tau
Mean sensitivity 84%
specificity 91%

CSF biomarkers of AD

Figure 5C. Sensitivity and specificity for cerebrospinal fluid P-tau to differentiate Alzheimer's disease from controls. Three of the studies were prospective, on consecutive patients. The mean sensitivity was 81% at a specificity of 92%.

P-tau

P-tau

P-tau181

P-tau231

P-tau199

P-tau 396 + 404

P-tau 231 + 235

P-tau 181 + 231
Brain atrophy in MCI

In AD, difference in rates reaches the voxelwise significance level of 0.05 in most regions of the brain, and remains significant after corrected for multiple comparisons in ROIs including the temporal lobes, parietal lobes, occipital lobes, and frontal lobes.

For MCI versus Controls, only the parietal and temporal lobes reach ROI significance.

Hippocampal atrophy from memory complaints to AD diagnosis

Rate of hippocampal atrophy:
- Early AD: 3-6% /year
- Normal ageing: 0.3-2.2% /year

SD: 2.5-3.3% for 1 year study

Rate of atrophy is not linear; accelerates from Normal to MCI to AD and then decelerates.

Rate of hip atrophy correlates with CSF pTau
AD Progression: ADNI model

Primary Prevention

Secondary Prevention

Early Treatment

Abnormal

Normal

Presymptomatic

eMCI

LMCI

Dementia

Time

FDG-PET

MRI hippocampal volume

CSF Aβ42

Amyloid imaging

Cognitive performance

CSF Tau

Function (ADL)

AD biomarker grouping  AT (N)

- Aggregated Aβ or associated pathologic state (A)
  - CSF $A\beta_{42}$, or $A\beta_{42}/A\beta_{40}$ ratio
  - Amyloid PET
- Aggregated tau (NFT) or associated pathologic state (T)
  - CSF pTau
  - Tau PET
- Neurodegeneration or neuronal injury (N)
  - Anatomic MRI
  - FDG PET
  - CSF total tau
Alzheimer’s disease with dementia. A 75-year-old woman with amnestic multidomain dementia.

- Abnormal amyloid PET with Pittsburgh compound B (top left),
- tau PET with flortaucipir (top right and bottom left), and
- atrophy on MRI (bottom right).

Biomarker profile A+T+(N)+

Participant in the Mayo Alzheimer’s Disease Research Center.
Preclinical Alzheimer’s pathologic change. A cognitively unimpaired 67-year-old man. Abnormal amyloid PET (Pittsburgh compound B, top row), no uptake on tau PET (with flortaucipir, middle row), no atrophy on MRI (bottom row).

Does this patient have Alzheimer’s disease?

A+ T- (N)-
A 91-year-old male with severe amnestic dementia.  
- Abnormal amyloid PET with Pittsburgh compound B (top row),  
- Normal tau PET (flortaucipir, middle row), and  
- Severe medial temporal atrophy on MRI (bottom row).  

The biomarker profile (A+T-(N)+) suggests the patient has Alzheimer’s pathologic change (A+T-) plus an additional degenerative condition [(N)+], likely hippocampal sclerosis.

Participant in the Mayo Alzheimer’s Disease Research Center
<table>
<thead>
<tr>
<th>AT(N) profiles</th>
<th>Biomarker category</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-T-(N)-</td>
<td>Normal AD biomarkers</td>
</tr>
<tr>
<td>A+T-(N)-</td>
<td>Alzheimer’s pathologic change</td>
</tr>
<tr>
<td>A+T+(N)-</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>A+T+(N)+</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>A+T-(N)+</td>
<td>Alzheimer’s and concomitant suspected non Alzheimer’s pathologic change</td>
</tr>
<tr>
<td>A-T+(N)-</td>
<td>Non-AD pathologic change</td>
</tr>
<tr>
<td>A-T-(N)+</td>
<td>Non-AD pathologic change</td>
</tr>
<tr>
<td>A-T+(N)+</td>
<td>Non-AD pathologic change</td>
</tr>
</tbody>
</table>

**Severity**
- 0 normal
- 1 intermediate
- 2 clearly abnormal

**Cognitive staging**
- 0 Unimpaired
- 1 Subjective concern
- 2 Mild impairment

NIA-AA Research Framework

Jack CR et al, 2018
Adding genetics
Alzheimer’s disease causal and contributory mutations

Presenilin 2
Presenilin 1
Apolipoprotein E
Amyloid Precursor Protein
Apo E genotyping in the diagnosis of AD

- N=2188 referred patients
- AD in 1833, confirmed pathologically in 1770.
- Apo E4 +ve; 62% clinical AD & 65% pathol AD

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical diagnosis</td>
<td>93%</td>
<td>55%</td>
</tr>
<tr>
<td>Apo E4 +ve</td>
<td>65%</td>
<td>68%</td>
</tr>
<tr>
<td>Clinical diag + E4</td>
<td>61%</td>
<td>84%</td>
</tr>
<tr>
<td>Apo E4/4</td>
<td>14%</td>
<td>95%</td>
</tr>
</tbody>
</table>

The best prediction accuracy AUC = 78.2% (95% confidence interval 77–80%) was achieved by a logistic regression model with APOE, the polygenic score, sex and age as predictors.

Dataset comprising 17,008 cases and 37,154 controls obtained from the International Genomics of Alzheimer’s Project (IGAP).

ROC curves for predictive models with different predictors for risk of Alzheimer’s disease

BRAIN 2015: 138; 3673–3684
Adding other pathologies
Vascular pathology

- Large infarct
- Perivasculare space
- Perfusion
- Microbleeds
- WMLs
- Perivascular space
- Microinfarct
Vascular +/- Amyloid

A PIB negative

B PIB positive

Lee J et al, Neurology 2011
Lewy Bodies
Hypothetical model of prodromal DLB

Neuroimaging in DLB and AD

FDG-PET

DLB

AD

FP-CIT SPECT

DLB

AD

Lancet 2015; 386: 1683–97
FTD genetics

1. Approximately 40% have a family history of early-onset dementia, and approximately 10% show an autosomal dominant pattern.

2. Mutations linked with FTD
   - microtubule associated protein tau (MAPT) gene
   - granulin gene (GRN)
   - C9ORF72 gene
   - transactive response DNA-binding protein of 43 kDa (TDP-43, or TARDBP)
   - valosin-containing protein (VCP)
   - chromatin modifying protein 2B (CHMP2B)
   - Fused in sarcoma protein (FUS).

3. Many individuals with known familial transmission do not have a known mutation.
**bvFTD**

**Behavioural-variant frontotemporal dementia (bvFTD)**

Patient shows marked atrophy throughout the medial and lateral frontal cortex and the temporal poles, with striking relative preservation of the posterior brain regions on a sagittal view.
Semantic dementia

Patient shows asymmetric degeneration of the temporal poles (left > right)

CNS Drugs 2010; 24 (5): 375-398

Progressive nonfluent aphasia (PNFA)

Patient shows atrophy in the left inferolateral and dorsomedial frontal cortex and anterior insula.
FDG PET for FTD
## Biomarker approach to diagnosis

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Severity of pathology</th>
<th>Severity of Cognitive Syndrome (C)</th>
<th>Genetics (G)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A amyloid</td>
<td>0,1,2</td>
<td>0,1,2,3</td>
<td>0,1,2</td>
</tr>
<tr>
<td>T tau</td>
<td>0,1,2</td>
<td>0,1,2,3</td>
<td>0,1,2</td>
</tr>
<tr>
<td>V Large Vessel</td>
<td>0,1,2</td>
<td>0,1,2,3</td>
<td>0,1,2</td>
</tr>
<tr>
<td>Vs Small Vessel</td>
<td>0,1,2</td>
<td>0,1,2,3</td>
<td>0,1,2</td>
</tr>
<tr>
<td>L Lewy Body</td>
<td>0,1,2</td>
<td>0,1,2,3</td>
<td>0,1,2</td>
</tr>
<tr>
<td>D DNA-binding</td>
<td>0,1,2</td>
<td>0,1,2,3</td>
<td>0,1,2</td>
</tr>
<tr>
<td>protein</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>X other</td>
<td>0,1,2</td>
<td>0,1,2,3</td>
<td>0,1,2</td>
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</table>

Uncertain 7; Unknown 9