Advances in fluid biomarker tests: from CSF to blood tests

Douglas Galasko, MD
Department of Neurosciences
Shiley-Marcos Alzheimer’s Disease Research Center
University of California, San Diego
What is a biomarker?

**FDA:** a defined characteristic that is measured as a characteristic of normal biological processes, pathologic processes, or responses to an exposure or intervention, including therapeutic interventions.

**Examples:**
Molecular: blood glucose; Hgb A1c
Radiographic: tumor size
Physiologic: blood pressure
Brain pathology in Alzheimer’s

<table>
<thead>
<tr>
<th>Co-Pathology</th>
<th>Vascular changes: 60% e.g. micro-infarcts, strokes, amyloid ...</th>
<th>Lewy bodies: $\alpha$-synuclein 20%</th>
<th>Hippocampal sclerosis 5-10%</th>
</tr>
</thead>
</table>

- Tangles - tau
- Plaques – amyloid beta protein (Aβ) deposits
Biomarkers can detect Alzheimer brain pathology

**Structure:**
- MRI: atrophy, pathways

**Function:**
- PET: glucose use
- fcMRI: networks

**Pathology:**
- PET imaging:
  - Plaques: amyloid PET
  - Tangles: tau PET
- CSF:
  - Aβ42, tau, P-tau

Brain atrophy and neuron loss

Amyloid plaques

Neurofibrillary tangles
Brain amyloid PET imaging

Amyloid PET scans detect amyloid plaques deposited in the brain. Amyloid scans become positive >10 years before people develop symptoms. About 30% of people over 70 have positive scans.
Brain Tau PET imaging

<table>
<thead>
<tr>
<th>Age</th>
<th>MMSE</th>
<th>PiB (DVR)</th>
<th>Dx</th>
</tr>
</thead>
<tbody>
<tr>
<td>71</td>
<td>30</td>
<td>Low (1.0)</td>
<td>CN</td>
</tr>
<tr>
<td>74</td>
<td>30</td>
<td>High (1.2)</td>
<td>CN</td>
</tr>
<tr>
<td>79</td>
<td>29</td>
<td>High (1.8)</td>
<td>CN</td>
</tr>
<tr>
<td>70</td>
<td>27</td>
<td>High (1.5)</td>
<td>MCI</td>
</tr>
<tr>
<td>59</td>
<td>26</td>
<td>High (1.7)</td>
<td>MCI</td>
</tr>
<tr>
<td>71</td>
<td>23</td>
<td>High (1.5)</td>
<td>AD</td>
</tr>
<tr>
<td>52</td>
<td>11</td>
<td>High (1.5)</td>
<td>AD</td>
</tr>
</tbody>
</table>
Evolution of Alzheimer imaging biomarkers

Amyloid PET  Glucose use  MRI cortical thickness

Estimated years to onset
-3  -6  -15  -22

Gordon, Lancet Neurology 2018

DIAN study – autosomal dominant AD,
Gordon, Lancet Neurology 2018
CSF A-beta42 and amyloid PET imaging correlate

Lower CSF Aβ42 is associated with a higher fibrillar amyloid burden

AUC values:
- p-tau/Aβ_{1-42} 0.944
- t-tau/Aβ_{1-42} 0.940
- Aβ_{1-42} 0.889
- p-tau_{181} 0.845
- t-tau 0.803

Cutpoint values:
- p-tau/Aβ_{1-42} 0.021
- t-tau/Aβ_{1-42} 0.222
- Aβ_{1-42} 980 pg/mL
- p-tau_{181} 21.8 pg/mL
- t-tau 245 pg/mL

2017 ADNI dataset included in collaboration with the Swedish BioFINDER study

_Hansson et al, 2018_
CSF biomarkers in MCI predict AD

Pathological CSF = cutoffs chosen by a mixture model analysis of AD vs NC, and used either Aβ42/P-tau or Aβ42/total tau

Buchhave et al, 2012
Predicting progression from MCI to AD

Hazard ratios:

- Ab42- / t-tau+ 1.68
- Ab42+ / t-tau- 2.80
- Ab42+ / t-tau+ 9.23

Cox proportional hazards models adjusted for gender, age, education and APOE e4 allele #.
CSF Aβ42 and tau in preclinical AD

CSF biomarkers of amyloid and tau in an aging cohort

The highest risk of developing MCI or dementia was for people with abnormal amyloid AND tau

Vos et al, 2013
Developing a more detailed biomarker picture?

- **Neurogranin** - dendritic Ca++ regulation / damage
- **P-tau** - tangle pathways
- **Tau** - neuronal or axonal damage
- **SNAP25** - presynaptic
- **NPTX2**
- **YKL40, S100b** - astrocytes
- **NFL** - axonal integrity
- **Aβ42**, **sAPP**
- **Aβ38, 40**
- **sTREM2** - microglia
- **BBB**: albumin ratio, MMPs

**-omics**
New biomarkers – synaptic damage

Loss of synaptic markers at autopsy correlates strongly with cognitive measures in AD

Mechanisms of damage related to Aβ and tau may involve synapses

Synapses have complex and diverse protein components, especially in the hippocampus
Neuronal pentraxin 2, a novel synaptic biomarker, relates to cognition (stage)
The challenge of blood tests

Can proteins originating in the brain be detected in blood despite major dilution and removal by the liver and kidneys?

Plasma Aβ levels are about 1/30 of those in CSF

Short half-life, cleared by hepatic and renal pathways
Ultrasensitive assays

> 100x more sensitive than ELISA

Quanterix SiMOA (single molecule analysis)

Singulex Erenna

Immuno-PCR
Plasma tau in TBI

Concussed Professional ice hockey players
Plasma tau in AD

Levels are slightly increased in AD, but do not correlate with CSF tau

Zetterberg et al, 2013
Plasma neurofilament light

Mattsson, 2017 (ADNI)
Plasma Neurofilament light in neurological disorders
Plasma Amyloid-β-protein 42/40

Ovod, 2017

Yanagisawa, 2018
Summary

Brain imaging and CSF biofluid biomarkers provide complementary information about Alzheimer’s

Core CSF biomarkers have diagnostic value for Alzheimer’s independent of stages of disease

Novel biomarker discovery can detect different aspects of neurodegeneration relevant to Alzheimer’s.

Translation from biomarkers to laboratory tests is well under way

Plasma or serum biomarkers are detectable and have value at least as screening tests
ADRC initiatives

Continue CSF collection – repeat lumbar punctures at intervals of 2-3 years

many local investigators use ADRC CSF data

Expand blood collection – beginning a large-scale bank of blood products across ALL of the NIH ADRC’s

Develop and discover new biomarker tests, and compare CSF, blood, MRI and retinal imaging