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- Integrated Diagnostics

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None

Clinical Trials

None

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Stock Equity

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Speaker’s Bureau

None

Editorial Boards

None

I own no stocks or equity in any biotech or pharmaceutical company
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The Knight Alzheimer’s Disease Research Center at Washington University in St. Louis

- Randy Bateman (Wash U)
- Cliff Jack (Mayo Clinic)
- Bill Klunk (U Pitt)

*Our research participants*
Outline

- “Re”-Defining AD
- Role of biomarkers
- CSF biomarkers in AD
- Potential use of CSF markers in clinical trials
- Current and future challenges
Alzheimer’s Disease (AD) is a progressive neurodegenerative disorder that culminates in end-organ (brain) failure which manifests as dementia.

...thus, AD refers to the neurodegenerative brain disorder regardless of clinical status.

AD can be conceptualized as having two major stages:
1) Preclinical (pre-symptomatic)
2) Symptomatic - Prodromal (incipient/MCI)
   - Dementia of the Alzheimer type

- Amyloid plaques (amyloid-β)
- Neurofibrillary Tangles (tau)
Prevalence of plaques compared to DAT suggests a “preclinical” stage of AD. 

Amyloid Plaques at Autopsy

Prevalence of AD Dementia

DAT=dementia of the Alzheimer type

Sperling et al., 2011, Alzheimers Dement 7:280-92

(figure courtesy of Mark Mintun and John Morris)
Clinicopathologic features of normal aging, “preclinical AD” and early stage DAT

<table>
<thead>
<tr>
<th></th>
<th>Normal Aging</th>
<th>Preclinical AD</th>
<th>Very Mild AD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plaques in neocortex</strong></td>
<td>None or a few diffuse plaques</td>
<td>Many plaques</td>
<td>Many plaques</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(diffuse &gt; neuritic)</td>
<td>(diffuse &gt; neuritic)</td>
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<tr>
<td><strong>Tangles in entorhinal cortex &amp; hippocampus/CA1</strong></td>
<td>Few to many (increases w/age)</td>
<td>Many</td>
<td>Many</td>
</tr>
<tr>
<td><strong>Cell loss in entorhinal cortex &amp; hippocampus/CA1</strong></td>
<td>None</td>
<td>Little to none</td>
<td>Substantial (30%-60%)</td>
</tr>
<tr>
<td><strong>Clinical diagnosis</strong></td>
<td>Normal, CDR 0</td>
<td>Normal, CDR 0</td>
<td>Very mild dementia or MCI, CDR 0.5</td>
</tr>
<tr>
<td><strong>Pathological diagnosis</strong></td>
<td>Normal</td>
<td>AD</td>
<td>AD</td>
</tr>
</tbody>
</table>

### Clinicopathologic features of normal aging, “preclinical AD” and early stage DAT

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<tr>
<td>cortex &amp;</td>
<td></td>
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<td></td>
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<tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td>Normal, CDR 0</td>
<td>Normal, CDR 0</td>
<td>Very mild dementia or MCI, CDR 0.5</td>
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<tr>
<td>diagnosis</td>
<td></td>
<td></td>
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<tr>
<td><strong>Pathological</strong></td>
<td>Normal</td>
<td>AD</td>
<td>AD</td>
</tr>
<tr>
<td>diagnosis</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Why is preclinical diagnosis and treatment important?

The overarching therapeutic objective of “preclinical” treatment is to treat early pathologic processes (e.g., lower amyloid-β burden) in order to prevent subsequent neurodegeneration and eventual cognitive decline and dementia.
Late treatment... uncertain effect on dementia
Early treatment...halt or delay established cognitive decline

Cognitive Function

- Normal
- Cognitively Normal
- Mildly Impaired
- Demented

TIME

EARLY TREATMENT

- Normal aging
- "Halt Progression"
- "Delay Progression"

Mildly impaired
Preclinical treatment...prevent cognitive decline

A PRECLINICAL TREATMENT

NORMAL

Cognitive Function

PRECLINICAL Treatment

SEVERELY IMPAIRED

Cognitively Normal

Mildly Impaired

Demented

TIME

Normal aging “Prevention”

PREVENT

Cognitively normal
Potential Roles of CSF Biomarkers in the Clinical Setting*

**Diagnostic**: increase diagnostic certainty

Q? Who has dementia due to AD pathology?

**Prognostic**: predict cognitive decline

Q? Who, when, how fast?

**Theragnostic**: detect biochemical effects of treatment

Q? Target engagement?

*Research setting: understanding disease pathophysicsology
Established CSF biomarkers of AD

Published $A\beta_{42}$: sensitivity, 70-100%; specificity, 40-90%

Published Tau: sensitivity, 40-85%; specificity, 65-85%

*Sunderland et al., 2003, JAMA 289:2094-103*
Established CSF biomarkers of AD

- **Aβ42**
  - Published: sensitivity, 70-100%
  - Specificity, 40-90%

- **Tau**
  - Published: sensitivity, 40-85%
  - Specificity, 65-85%

Sunderland et al., 2003, JAMA 289:2094-103

- Plaques
- Tangles
Do CSF biomarkers reflect underlying AD pathology?
Amyloid PET imaging agents as candidate biomarkers of AD

$[^{11}C]-PIB$

Klunk et al., 2004, Ann Neurol 55:306-19

$[^{18}F]-AV-45$

Wong et al., 2010, J Nucl Med 51:913-20

<table>
<thead>
<tr>
<th>Compound name</th>
<th>$K_i$ (nM, n=3)</th>
<th>Compound name</th>
<th>$K_i$ (nM, n=3)</th>
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<tbody>
<tr>
<td>BAY 94-9172 (AV-1)</td>
<td>2.22 ± 0.54</td>
<td>AV-45</td>
<td>2.87 ± 0.17</td>
</tr>
<tr>
<td>AV-136</td>
<td>6.37 ± 3.75</td>
<td>AV-137</td>
<td>&gt;1,000</td>
</tr>
<tr>
<td>PIB</td>
<td>0.87 ± 0.18</td>
<td>BTA-1</td>
<td>1.28 ± 0.46</td>
</tr>
<tr>
<td>GE-067 (3'-F-PIB)</td>
<td>0.74 ± 0.38</td>
<td>AZD2184</td>
<td>1.70 ± 0.54</td>
</tr>
<tr>
<td>BF-170</td>
<td>428 ± 57</td>
<td>IMPY</td>
<td>1.29 ± 0.46</td>
</tr>
<tr>
<td>Thioflavin T</td>
<td>&gt;1,000</td>
<td>FDDNP</td>
<td>172 ± 18</td>
</tr>
<tr>
<td>IMSB</td>
<td>&gt;1,000</td>
<td>K-114</td>
<td>&gt;1,000</td>
</tr>
<tr>
<td>SB-13</td>
<td>3.18 ± 1.04</td>
<td>CG</td>
<td>&gt;1,000</td>
</tr>
</tbody>
</table>

Choi et al., 2009, J Nucl Med 50:1887-94
N=24

Slide animation courtesy of Bill Klunk

Fagan et al., 2006, Ann Neurol 59:512-19
Low CSF $\beta_42$ is a marker of cortical amyloid as detected by PET PIB, even in the absence of cognitive symptoms (CDR 0)

Mixed Cognitive States

Cognitively Normal (CDR 0)

Fagan et al., 2006, Ann Neurol 59:512-19
Forsberg et al., 2008, Neurobiol Aging, 29:1456-65
Grimmer et al., 2009, Biol Psychiatry, 65:927-34
Jagust et al., 2009, Neurology 73:1193-99
Tolboom et al., 2009, J Nucl Med, 50:1464-70
Forsberg et al., 2010, Curr Alz Res, 7:56-66

O CDR 0 (cognitively normal)

N=189 CDR 0
Mean age 64 years
Fagan et al., 2009, EMBO Mol Med 1:317-80

MCBP = 0.03
MCBP = 0.36
MCBP = 0.82
Plasma levels of Aβ_{40} and Aβ_{42} are not related to cortical amyloid load as detected by PET PIB.

Fagan et al., 2009, EMBO Mol Med 1:317-80

N=189 CDR 0
Mean age 64 years
Medial temporal lobe atrophy in AD


Vemuri et al., 2009, Neurology 73:287-93

*Atrophy measure = STAND
Lower CSF Aβ42 is associated with smaller brain volume in cognitively normal (CDR 0) individuals but not those with very mild/mild AD dementia (CDR 0.5/1)

N=69 CDR 0
N=29 CDR 0.5/1
Mean age 72 years

Fagan et al., 2009, Ann Neurol 65:176-83
Higher CSF tau is associated with smaller brain volume in individuals with very mild/mild AD dementia (CDR 0.5/1) but not in cognitively normal individuals (CDR 0).

Fagan et al., 2009, Ann Neurol 65:176-83

CDR 0

\[ \text{Normalized whole brain volume} \]

\[ \text{CSF } A\beta_{42} \text{ in Non-Demented} \]

\[ r=0.3004 \]

\[ p=0.0128 \]

\[ \text{N=69 CDR 0} \]

\[ \text{N=29 CDR 0.5/1} \]

\[ \text{Mean age 72 years} \]

CDR >0

\[ \text{Normalized whole brain volume} \]

\[ \text{CSF } A\beta_{42} \text{ in Very Mild/Mild DAT} \]

\[ r=0.0510 \]

\[ p=0.7970 \]

\[ \text{CSF tau in Non-Demented} \]

\[ r=-0.0606 \]

\[ p=0.6237 \]

\[ \text{CSF tau in Very Mild/Mild DAT} \]

\[ r=-0.4440 \]

\[ p=0.0180 \]

Fagan et al., 2009, Ann Neurol 65:176-83
Low levels of CSF $A\beta_{42}$ are correlated with volumetric reductions (over 1 year) in multiple brain regions in cognitively normal older individuals

N=71 CDR 0
Mean age 76 years

Fjell et al., 2010, Cereb Cortex 20:2069-79
Do CSF biomarkers reflect underlying AD pathology?

YES, EVEN WHEN INDIVIDUALS ARE COGNITIVELY NORMAL
Do CSF biomarkers reflect underlying AD pathology?

Do CSF biomarkers predict future cognitive decline?
The CSF tau(s)/Aβ42 ratio predicts progression (yes vs. no) from MCI to AD dementia over 5 years

Hansson et al., 2006, Lancet Neurol 5:228-34

N=134 MCI
Median age at LP ~72 years

Low CSF tau/Aβ42

High CSF tau/Aβ42

<table>
<thead>
<tr>
<th>Numbers at risk</th>
<th>Time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>134</td>
</tr>
<tr>
<td>Normal CSF</td>
<td>67</td>
</tr>
<tr>
<td>Pathological CSF</td>
<td>67</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal CSF</td>
<td>134</td>
<td>131</td>
<td>111</td>
<td>87</td>
<td>74</td>
<td>55</td>
<td>31</td>
</tr>
<tr>
<td>Pathological CSF</td>
<td>67</td>
<td>66</td>
<td>62</td>
<td>56</td>
<td>47</td>
<td>40</td>
<td>28</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pathological CSF (T-tau and Aβ42)</th>
<th>Unadjusted hazard ratio (95% CI)</th>
<th>Adjusted hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30.0 (9.32 – 96.8)†</td>
<td>17.7 (5.33 – 58.9)†</td>
</tr>
<tr>
<td>Pathological CSF (P-tau and Aβ42)</td>
<td>26.3 (8.16 – 84.5)†</td>
<td>16.8 (5.02 – 56.5)†</td>
</tr>
</tbody>
</table>

Hansson et al., 2006, Lancet Neurol 5:228-34
CSF Aβ42 predicts rate of cognitive decline (CDR-SB*) in individuals with very mild dementia/MCI (CDR 0.5)

Of 49 very mild DAT/MCI subjects, the 10 with the lowest CSF Aβ42 progressed, whereas the 10 with the highest Aβ42 generally did not.

N=49 CDR 0.5
*Higher CDR-SB = worse performance

Abnormal CSF $A\beta_{42}$ and tau(s) predict increased rate of cognitive decline (CDR-SB*) in individuals with very mild AD/MCI (CDR 0.5).


*Higher CDR-SB = worse performance
The CSF tau/Aβ$_{42}$ ratio predicts progression (yes vs. no) from cognitively normal to MCI or AD dementia

Cognitively normal (CDR 0) → MCI/AD (CDR>0)

N=164 CDR 0
Mean age at LP = 75 years

Fagan et al., 2007, Arch Neurol, 64:343-49
Li et al., 2007, Neurology, 69:631-39
Craig-Schapiro et al., 2010 , Biol Psychiatry, 68:903-12
Tarawneh et al., 2011, Ann Neurol, 70:274-85
The ratio of CSF VILIP-1/Aβ42 predicts progression (yes vs. no) from cognitively normal (CDR 0) to MCI/very mild or mild AD dementia (CDR>0)

- VILIP-1 is a calcium-signaling protein produced by neurons. Levels in the CSF are elevated in response to acute stroke in animal models and in AD. Thus, VILIP-1 may be a marker of neurodegeneration.

Cognitively normal → MCI/AD

Upper 15% vs. lower 85% of values
(HR 13.00; 95% CI: 4.38-30.90, p<0.0001)

N=164 CDR 0
Mean age at LP = 72 years

Lee et al., 2008, Clin Chem 54:1617-23
Tarawneh et al., 2011, Ann Neurol, 70:274-85
The ratio of CSF YKL-40/Aβ42 predicts progression (yes vs. no) from cognitively normal (CDR 0) to MCI/very mild or mild AD dementia (CDR>0)

- In the brain, YKL-40 (aka, chitinase 3 like 1) is an astrocyte-derived glycoprotein that may play a role in neuroinflammation and/or remodeling. Mean levels in the CSF are increased in early stage AD.

N=174 CDR 0
Mean age at LP = 71 years

Craig-Schapiro et al., 2010, Biol Psychiatry, 68:903-12
Low levels of CSF Aβ42 are associated with more subtle cognitive decline in cognitively normal older individuals

- Baseline CSF Aβ42 levels correlate with reductions in MMSE over 8 year follow-up in cognitively normal elderly women (n=55)
  
  *Gustafson et al., 2007, J Neurol Neurosurg Psychiatry 78:461-64*

- Low levels of CSF Aβ42 at baseline are associated with future (3 yr) development of subjective memory impairment affecting quality of life (memQoL) in cognitively normal elders (n=57)
  
  *Stomrud et al., 2007, Dement Geriatr Cogn Disord 24:118-24*

- Low levels of CSF Aβ42 at follow-up (3-4 yrs) are associated with worse performance on ADAS-cog delayed recall and slower cognitive speed in cognitively normal elders (n=37)
  
  *Stomrud et al., 2010, Arch Neurol 67:217-23*

- BUT...Baseline CSF Aβ42 levels are not associated with rate of cognitive decline (CDR-SB) over 2 years in cognitively normal individuals (ADNI) (n=109)
  
  *Vemuri et al., 2009, Neurology 73:294-301*
Do CSF biomarkers reflect underlying AD pathology? 
YES

Do CSF biomarkers predict future cognitive decline?
*Do CSF biomarkers reflect underlying AD pathology?*

**YES**

*Do CSF biomarkers predict future cognitive decline?*

**YES...EVEN WHEN INDIVIDUALS ARE COGNITIVELY NORMAL**
In sum, converging evidence demonstrates...

- There exists a “preclinical” stage of AD that likely spans ~10-15 years prior to dementia onset.

- The AD biomarker “signature” in CSF includes reductions in the level of $A\beta_{42}$ and increases in total tau and phosphorylated tau ($p$-tau).

- Changes in CSF measures are reflective of underlying disease pathologies (e.g., amyloid plaque load [amyloid imaging], neurodegeneration [MRI]).

- Certain biomarker changes can be detected in the preclinical (pre-symptomatic) stage (e.g., reduced $A\beta_{42}$, increased tau/$A\beta_{42}$).

- Presence of these pathologies and their biomarkers in the preclinical stage are not clinically benign, i.e., they are predictive of future cognitive decline.
Hypothetical model of dynamic biomarkers of AD with emphasis on the preclinical period

- Amyloid
- CSF/PET
- FDG PET/fMRI
- Tau
- MRI
- Cognition
- Clinical function

Sperling et al., 2011, Alzheimers Dement 7:280-92
(Modified from Jack et al., 2009, Brain 132:1355-65)
What are the “real world” clinical implications?

1) Proposed revisions of NINCDS/ADRDA criteria for AD diagnosis
   a) expand the scope of AD (pre-symptomatic → MCI (AD) → AD dementia)
   b) include biomarkers
   c) distinguish between research criteria and clinical criteria
      Preclinical: Sperling et al., 2011, Alzheimers Dement 7:280-92
      MCI: Albert et al., 2011, Alzheimers Dement 7:270-79
      AD: McKhann et al., 2011, Alzheimers Dement 7:263-69

2) Paradigm shift from “cure” to “prevention”:
   *Intervene in cognitively normal individuals with preclinical AD to prevent neurodegeneration and symptomatic AD*

3) Potential use of biomarkers in design/evaluation of clinical trials
   a) target engagement
   b) inclusion criteria (confirm and enrich for presence of therapeutic target)
   c) surrogate outcome measures
      - amyloid = CSF Aβ42, amyloid imaging
      - neurodegeneration = CSF tau(s), CSF VILIP-1, brain atrophy (MRI)
Current approach to Alzheimer’s disease (AD) clinical trials (a) and an alternative approach based on segmenting the population using biomarkers (b).

Adapted from Cummings, 2011, Curr Psychiatry Rep 13:437-42
# Potential use(s) of biomarkers in AD clinical trials

<table>
<thead>
<tr>
<th>BM TYPE</th>
<th>GOAL</th>
<th>PRACTICALITY</th>
<th>EXAMPLES</th>
</tr>
</thead>
</table>
| Theragnostic| Prove target engagement                   | Drug choice  | Secretase inhibitor: CSF Aβ synthesis/clearance (SILK)  
Secretase modulator: CSF Aβ isoform synthesis (SILK)  
Anti-amyloid (e.g., antibody): CSF Aβ(42), amyloid imaging  
Tau kinase inhibitor: CSF ptau |
| Diagnostic  | Ensure AD pathology in subjects           | Reduce subject number and heterogeneity | Amyloid: CSF Aβ_{42}, amyloid imaging  
Neurofibrillary tangles/ neurodegeneration: CSF tau, CSF ptau, CSF VILIP-1, MRI |
| Prognostic  | Define disease stage                      | Reduce trial duration | Proximity to clinical progression: CSF tau/Aβ_{42}, CSF VILIP-1/Aβ_{42}, combination of CSF, amyloid, MRI |
| Surrogate Outcome | Prove effect on downstream targets         | Potentially reduce trial duration | Neurodegeneration: CSF tau, CSF VILIP-1, MRI (e.g., in response to anti-amyloid therapies) |
Stable-Isotope-Labeling Kinetics (SILK) method to assess the effect of a γ-secretase inhibitor on central Aβ production in humans

1. Infusion of $^{13}$C$_6$-leucine

2. In vivo labeling of new CNS proteins

3. CSF collection and quantification of labeled Aβ species over time

Adapted from Bateman et al., 2009, Ann Neurol 66:48-54
Production inhibitor model
The γ-secretase inhibitor LY 450139 enters then exits the brain rapidly (within 12 hrs) and reduces production (but not clearance) of CNS Aβ.

Blue = placebo (100%)
Orange = 100 mg (47%)
Green = 140 mg (52%)
Red = 280 mg (84%)

Production of new Aβ 1-12 hours

Bateman et al., 2009, Ann Neurol 66:48-54
Proposed stages of AD with potential prevention and treatment targets

Abnormal

1° Primary Prevention
Delay onset of AD pathology
- Decrease Aβ42 production
- Prevent tangle formation

2° Secondary prevention
Delay onset of cognitive impairment in individuals with evidence of pathology
- Decrease accumulated Aβ burden
- Decrease neurodegeneration with anti-tau or neuroprotective agents

3° Tertiary prevention and treatment
Delay onset or progression of dementia
- Neuroprotection-prevent neuronal loss
- Enhance function of remaining neurons
- Neurotransmitter repletion

Normal

No pathology Preclinical MCI Dementia

Clinical disease stage

Adapted from Sperling et al., 2011, Sci Transl Med 3:111cm33-111cm33
Current challenges and potential future directions

• Establish the reliability and validity of biomarkers (individual and panels) for diagnostic (sensitivity/specificity) and prognostic purposes

• Define biomarker cut-off values (standardization efforts)

• Better define the sequence of biomarker changes and the extent to which they predict subsequent cognitive decline

• Need for novel biomarker development (esp. Aβ oligomers, imaging for intra-neuronal pathologies, e.g., tangles, α-synuclein inclusions)

• Need more sensitive biomarkers that can detect early synaptic dysfunction and neural network disruption (e.g., BOLD imaging)

• Begin/continue large longitudinal studies with existing markers ASAP, including planning for prevention trials in preclinical populations, e.g., Dominantly Inherited Alzheimer Network [DIAN], Alzheimer Prevention Initiative [API], Anti-Amyloid Treatment in Asymptomatic AD [A4])
Quality control and standardization efforts for AD fluid biomarkers

<table>
<thead>
<tr>
<th>PRE-ANALYTIC FACTORS</th>
<th>ANALYTIC PERFORMANCE</th>
<th>CLINICAL DIAGNOSTIC PERFORMANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Define and control</td>
<td>Assure stability and reproducibility</td>
<td>Analyte validation between studies</td>
</tr>
<tr>
<td></td>
<td>Assay platform</td>
<td>Sensitivity/specificity (autopsy confirmed)</td>
</tr>
<tr>
<td>❑ Time of sample collection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>❑ Fasting state (Y/N)</td>
<td>Assay QC</td>
<td>Define cut-off values</td>
</tr>
<tr>
<td>❑ LP needle type</td>
<td>Reagent lot-to-lot variability</td>
<td>Longitudinal change in biomarkers within individuals over time</td>
</tr>
<tr>
<td>(atraumatic Sprotte vs cutting)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>❑ Plastic tubes</td>
<td>Laboratory expertise</td>
<td></td>
</tr>
<tr>
<td>(propylene vs polystyrene)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>❑ # freeze/thaw cycles</td>
<td>Within-run/ between-run reliability</td>
<td></td>
</tr>
<tr>
<td>❑ Interval between sample collection/freezing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>❑ Centrifugation (Y/N)</td>
<td>Within-lab/ between lab reliability</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Equipment QC</td>
<td></td>
</tr>
</tbody>
</table>
INNOTEST CSF values are ~2-5-fold higher than INNO-BIA (xMAP) values.

Fagan et al., 2011, Arch Neurol 68:1137-44
The CSF tau(s)/$A\beta_{42}$ ratios are better indicators of PIB-positivity than the individual markers alone.
Recent data from the QC Program for AD CSF Biomarkers

**INNOTEST ELISA**

**Aβ42**
- CV = 24%

**Tau**
- CV = 20%

**P-tau181**
- CV = 12%

**AlzBio3 (xMAP)**

**Aβ42**
- CV = 24%

**Tau**
- CV = 22%

**P-tau181**
- CV = 28%

Mattsson et al., unpublished observations
Q & A