Can Alzheimer’s Disease be Diagnosed with a Blood Test?

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Disclosures

- Multiple Commercial Methods developed
  - Blood test for Alzheimer’s disease
  - Blood-based screening tool for neurodegenerative diseases
  - Personalized medicine approach for treating neurocognitive loss

- Funding:
  - National Institute on Aging – R01AG039389 (O’Bryant), P30AG12300 (Rosenberg, UTSW ADC)
  - Centers for Medicare & Medicaid Services
  - Multiple private sources
How this Journey Began

&

2 Fundamental Questions
Alzheimer’s Disease
Prevalence and Impact on Health Care and Families
The facts

1. Elderly segment of the U.S. is growing at a rapid rate
2. 40 million Americans age 65+
3. Nearly 90m Americans 65+ by 2050
The facts

- Currently, ~5.2 million people suffer from Alzheimer’s disease
- Estimated that a new case of Alzheimer’s disease emerges every 69 seconds!
- Financial burden
  - $200 billion dollars annually
  - ~$1.1 TRILLION dollars by 2050
How Common is Alzheimer’s Disease?

• 13% of those 65+
• Approximately $\frac{1}{2}$ of those over 85

• Age 65-74 = 2%
• Age 75-84 = 19%
• Age 85+ = 42%

• Estimated that over 300,000 Texans suffer from AD
Mild Cognitive Impairment

- “prodromal” category to AD or other dementias
- Cognitive decline but maintain daily function
- Approx. 15% annual conversion rate from MCI to AD
- Estimated 10-30% of those 65+ meet criteria for MCI
How is Alzheimer’s disease diagnosed?

• Current state-of-the-art diagnosis comes from specialty clinics and includes:
  • Medical exam by specialist
  • Neuropsychological testing (testing of thinking abilities)
  • Blood work
  • Brain imaging

• Confirmation at autopsy
  • Looking for the “hallmarks” of AD (plaques and tangles)
Symptoms of AD

• Difficulties learning and remembering information
  • Remote memory intact
• Misplacing things
• Repeating questions
• Disorientation in once familiar places
• Difficulty finding words
• Mood changes
  • Become withdrawn and isolated
• Do these changes:
  1. Reflect a change from prior levels?
  2. Impact daily activities?
QUESTION 1:

DIAGNOSING ALZHEIMER’S DISEASE
Current state-of-the-art diagnosis

PCP Referral → Specialist Exam → Brain MRI → Memory Testing → Blood Work
Current state-of-the-art diagnosis

PCP Referral → Specialist Exam → Brain MRI → Memory Testing → Blood Work → Diagnosis

$$$$$
How is Alzheimer’s disease diagnosed?

Screen Positive?

Yes

No

Screen again next year

How to screen 40 million Americans?
How is Alzheimer’s disease diagnosed?

How to screen 40 million Americans?

Screen Positive?

Yes

No

Screen again next year
Summary of Prior Work

1. Discovery of algorithm
   - Luminex platform
   - N=400 (AD n=197, NC n=203)
   - 108 proteins

2. Refinement of algorithm
   - Luminex platform
   - N=400 (AD n=197, NC n=203)
   - Top 30 markers

3. Cross-validation in ADNI
   - Luminex platform
   - TARCC = training set (serum)
   - ADNI = test set (plasma)

4. Cross-validation on independent assay platform
   - ECL (Meso Scale Discovery) platform
   - AD n=150, NC n=150
   - 21 proteins
## Summary of Prior Work

<table>
<thead>
<tr>
<th>Diagnostic Accuracy of Blood Markers of AD</th>
<th>AUC</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tbody>
<tr>
<td>108 protein algorithm</td>
<td>0.95</td>
<td>0.94</td>
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<tr>
<td>30-protein algorithm</td>
<td>0.94</td>
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<tr>
<td>Serum-Plasma algorithm</td>
<td>0.89</td>
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<tr>
<td>CSF biomarker accuracy</td>
<td>0.92</td>
<td>0.84</td>
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<tr>
<td>21-protein version</td>
<td>0.98</td>
<td>0.90</td>
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</table>

Summary of Prior Work

5. Cross-validation Among Mexican Americans
   - Luminex platform – AUC = 0.88 (TARCC)
   - ECL platform – AUC = 0.88 (HABLE)
   - MCI using ECL platform – AUC = 0.90 (HABLE)

6. Cross-validation among Choctaw, African American And Panamanians

Cross-validation across additional cohorts

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<th>AUC</th>
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<tr>
<td>HABLE</td>
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<td>Panama</td>
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<tr>
<td>UTSW ADC</td>
<td>.84</td>
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<tr>
<td>All Merged N=1,500</td>
<td>.90</td>
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</table>
Discriminating AD from non-AD dementias

• 2 separate studies:
  • Collaboration with UTSW:
    • 13 serum-proteins from 203 patients
    • AD n=51, PD n=49, DS n=11, FTD n=19, DLB n=11, NC n=61
    • >98% accurate
  • Collaboration with Mayo Clinic, Jacksonville
    (data presented last week at DLB conference)
    • DLB n=35, AD n=39, control n=48 (PD n=40 being added)
    • >98% accurate
Biomarkers – discovery to clinic

Institute of Medicine Report (IOM)
Next Step: Trial

Institute of Medicine Report (IOM)
Fit-For-Purpose Validation Approach

1. Identify Fit-for-Purpose of potential biomarker
2. Identify methods
3. Examine fitness for purpose
4. Examine in clinical context
5. Clinical use with continual quality improvement
## Purpose: Primacy Care Screen for Alzheimer’s

<table>
<thead>
<tr>
<th>Test</th>
<th>Discovery</th>
<th>Validate across platforms</th>
<th>Validate across cohorts</th>
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<th>Validate across ethnicities</th>
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</table>

*Discovery Phase*
*Test Validation Phase*
*Pro/Retro study with archived samples*
*Clinical Trial – test does NOT direct patient care*
Clinical Trial Application?

• Many trials require PET scan or lumbar puncture positive findings for amyloid presence

• Can our blood test be the first line in the screening process for such trials?
  • Combined data >1,500 people
  • Can accurately screen out 95% of those who should not be scanned
  • Can rule in 76% accurate
  • Would cut cost of screening by 88% into the trial
QUESTION 2:

FINDING BETTER TREATMENTS
A Lesson from Heart Disease
Heart Disease

- Rheumatic heart disease
- Hypertensive heart disease
- Ischemic heart disease
- Inflammatory heart disease
Heart Disease

Hypertensive heart disease

- Aneurysm
- Atherosclerosis
- Hypertension
- Peripheral arterial disease
Atherosclerosis

- Total cholesterol
- Triglycerides
- LDL
- HDL
Atherosclerosis

- Total cholesterol
- Triglycerides
- LDL
- HDL

Treat at this level
Applying this to Alzheimer’s disease?
Prior Trials!

- Neurodegenerative Disease
  - Alzheimer’s Disease
  - Parkinson’s Disease
  - Multiple Sclerosis
  - DLB, FTD, ALS, TBI, etc.
Prior Trials!

- Neurodegenerative Disease
  - Alzheimer’s Disease
  - Parkinson’s Disease
  - Multiple Sclerosis
  - DLB, FTD, ALS, TBI, etc.

Treat at this level
Targeted clinical trial based on underlying biology
New Concept

Neurodegenerative Disease
- Alzheimer’s Disease
- Parkinson’s Disease
- Multiple Sclerosis
- DLB, FTD, ALS, TBI, etc.

APOE4
- Inflammation
- Metabolic dysfunction
- Amyloid
- Oxidative Stress
- Depression

Treat at this level

New Model

Neurodegenerative Disease
- Alzheimer’s Disease
- Parkinson’s Disease
- Multiple Sclerosis
- DLB, FTD, ALS, TBI, etc.

- APOE4
- Inflammation
- Metabolic dysfunction
- Amyloid
- Oxidative Stress
- Depression

NSAIDs

Treat at this level

References:
Demographic characteristics of the sample cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>Naproxen (n=51)</th>
<th>Rofecoxib (n=55)</th>
<th>Placebo (n=51)</th>
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<tbody>
<tr>
<td>Age</td>
<td>74.0 (7.8)</td>
<td>73.8 (7.3)</td>
<td>73.8 (7.8)</td>
</tr>
<tr>
<td>Education</td>
<td>13.9 (3.2)</td>
<td>13.9 (3.2)</td>
<td>14.4 (3.2)</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>48%</td>
<td>54%</td>
<td>55%</td>
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<tr>
<td>ApoE4 positive</td>
<td>71%</td>
<td>69%</td>
<td>68%</td>
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• 22% patients improved on MMSE
• 12% remained stable
• 19% declined 1-2 points
• 47% declined >2 points
# ADCS Trial Results

<table>
<thead>
<tr>
<th></th>
<th>Biomarker Predicted Adverse Responder</th>
<th>Biomarker Predicted Non-Responder</th>
<th>Biomarker Predicted Stable</th>
<th>Biomarker Predicted Responder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Sample (93% accurate)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Adverse Responder</td>
<td>65 (89%)</td>
<td>2</td>
<td>2</td>
<td>4</td>
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<tr>
<td>Non-Responder</td>
<td>0 (100%)</td>
<td>30 (100%)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Stable</td>
<td>1 (89%)</td>
<td>1</td>
<td>17 (89%)</td>
<td>0</td>
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<tr>
<td>Responder</td>
<td>3 (89%)</td>
<td>2</td>
<td>0</td>
<td>29 (89%)</td>
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</table>
AD Precision Medicine

AD Blood Screen Positive?

Yes

Targeted treatment to particular profile
What about precision medicine for preventing AD?
Precision Medicine For Preventing Memory Loss?

Cognitively Normal Elders

- Depression
  - DepE positive? ≈15-20%
    - Anti-Depressant Therapy
- Amyloid
  - Pre-Alzheimer's disease ≈5-150%
- Inflammation
  - Inflammatory subgroup Positive? ≈10-15%
  - NSAIDs
- Neurotrophic dysfunction
  - Neurotrophic subgroup positive? ≈15-20%
- Diabetes
  - Metabolic subgroup positive? ≈15-20%
  - Exercise
  - Diabetic medications
AD Precision Medicine

Screen Positive?

Yes

Targeted treatment to particular profile
• Projects pending to apply these methods to...
  • 2 ongoing trials (Phase 2 and Phase 3)
  • 7 previously conducted trials (Phase 2 and 3)
    • Including 1 prevention trial
Precision Medicine for Preventing AD

AD Blood Screen Positive?

No

Yes
Begin Preventative Treatment

Positive for Subgroup?

No
Screen again next year

AD Risk Subgroup Screen

Depression
Inflammation
Neurotrophic dysfunction
Metabolic dysfunction
Oxidative stress
Summary

• **UNTHSC** in on the verge of bringing to Texas...
  
  • The *first-ever* clinical trial of an Alzheimer’s blood test
  
  • A precision medicine approach to treating Alzheimer’s
  
  • A personalized approach to preventing Alzheimer’s
Special Thanks

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Questions?