Blood Tests for Alzheimer’s Disease – Close but Still not There

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Disclosures

- Funding:
  - R01AG058533, R01AG058537, R01AG054073, R01AG051848, R01AG058252
  - Alzheimer’s Association, Michael J Fox Foundation
  - Multiple Commercial Methods developed

- Biotechnology
  - Cx Precision Medicine, Inc., founding scientist
THANK YOU!!!

**Clinical Core**
- Leigh Johnson, Ph.D. (Director)
- Judy O’Jile, Ph.D.
- Long Wong, MD, PhD
- Stephanie Large, NP-C
- Kim Brown
- Daisy Ruiz
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- Marcela Davila

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- Erin Donoho
- Kelly Berry
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- Kellie Johnson “KJ”

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- Rocky Vig

**IT Core**
- Chris Conger
- Sean Davidson

**Outreach Core**
- Haydee Izurieta Munoz

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- Robert Rissman (UCSD)
- Kristine Yaffe (UCSF)
- Arthur Toga (USC)
- Meredith Braskie (USC)
- HABS-HD Team
- Neill Graff-Radford (Mayo)
- Nicole Schupf (Columbia)
- ABC-DS Consortium
Recent Advances in Blood Based Biomarkers
Lots of Excitement
ORIGINAL PAPER

Plasma p-tau231: a new biomarker for incipient Alzheimer's disease pathology

Nicholas J. Ashton1,2,3,4,5, Tharick A. Pascoal6,7, Thomas K. Karikari1, Andréa L. Benedet8,9, Juan Lantero-Rodriguez1, Gunnar Brinkmalm1, Annina Snellman1, Michael Schöll10,11, Claire Troakes14, Abdulkadir Hashim4,5, Sanaa Castelain8, Runia Vanmarckalan2,3,4, Henrik Zetterberg1,2,3,4, Bartolomeu Massioli12,13.

JAMA | Original Investigation

Discriminative Accuracy of Plasma Phospho-tau217 for Alzheimer Disease vs Other Neurodegenerative Disorders

Sebastian Palmqvist, MD, PhD; Shenerima Janelidze, PhD; Yakeel T. Quiroz, PhD; Henrik Zetterberg, MD, PhD; Francisco Lopeza, MD; Erik Stomrud, MD, PhD; Yi Lin; Yinghua Chen, MSc; Geidy E. Serrano, PhD; Antoine Leuzy, PhD; Niklas Mattsson-Carlgren, MD, PhD; Olaf Strandberg, PhD; Ruben Smith, MD, PhD; Andres Villegas, MD; Diego Sepulveda-Falla, MD; Xiyan Chai, MD; Nicholas K. Proctor, BSc; Thomas G. Beach, MD, PhD; Kaj Blennow, MD, PhD; Jeffrey L. Dage, PhD; Eric M. Reiman, MD; Oskar Hansson, MD, PhD.

RESEARCH ARTICLE

A blood screening tool for detecting mild cognitive impairment and Alzheimer's disease among community-dwelling Mexican Americans and non-Hispanic Whites: A method for increasing representation of diverse populations in clinical research

Sid E. O'Bryant1,2, Fan Zhang1,3, Melissa Petersen1,3, James R. Hall1,2, Leigh A. Johnson1,2, Kristine Yaffe4,5, David Mason2, Meredith Braskie6, Robert A. Barber1,2, Robert A. Rissman7,8, Mark Mapstone9, Michelle M. Mielke10,11, Arthur W. Toga6, for the HABLE Study Team1

Article

Tau PET correlates with different Alzheimer’s disease-related features compared to CSF and plasma p-tau biomarkers

Rik Ossenkoppele1,2,3, Oo. Juhan Reimand13,4, Ruben Smith1,5, Antoine Leuzy1, Olof Strandberg1, Sebastien Palmqvist1,5,6, Erik Stomrud1, Henrik Zetterberg1,2,3,4,5, the Alzheimer's Disease.

FEATURED ARTICLE

Detecting amyloid positivity in early Alzheimer’s disease using combinations of plasma Aβ42/Aβ40 and p-tau

Shenerima Janelidze1,2, Sebastian Palmqvist1,2, Antoine Leuzy1, Erik Stomrud1,2, Inge M.W. Verberk3, Henrik Zetterberg4,5,6,7, Nicholas J. Ashton8,9,10, Pedro Pesini11, Leticia Sarasa11, José Antonio Allué11, Charlotte E. Teunissen3, Jeffrey L. Dage12, Kaj Blennow4,5, Niklas Mattsson-Carlgren1,12,14, Oskar Hansson1,2.

FEATURED ARTICLE

Plasma p-tau181, p-tau217, and other blood-based Alzheimer’s disease biomarkers in a multi-ethnic, community study

Adam M. Brickman1,2,3, Jennifer J. Manly1,2,3, Lawrence S. Honig1,3, Danury Sanchez1,2, Dolly Reyes-Dumeyer1,2, Rafael A. Lantigua1,4, Patrick J. Lao1,2, Yaakov Stern1,2, Jean Paul Vonsattel1,5, Andrew F. Teich1,3,5, David C. Airey6, Nicholas Kyle Proctor6, Jeffrey L. Dage6, Richard Mayeux1,2,3.
Ashton 2021 (ptau231)

Profile of AD
AUC=0.91
SN=0.76
SP=0.99

Profile of MCI
AUC=0.91
SN=0.88
SP=0.96

O'Bryant 2021 (proteomic profile)

Schindler 2019 C2N Ab profile
<table>
<thead>
<tr>
<th>COU=detecting cerebral amyloid (PET/CSF)</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>West et al C2N biomarker 2021</td>
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</tr>
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</tr>
<tr>
<td>Grothe 2021 (ptau181)</td>
<td>0.94</td>
</tr>
</tbody>
</table>
What’s Changed?

• Technological advances have yielded better assays with lower detection levels as well as better performance parameters
  • E.g., ITR Biomarker Core – has run n>20,000 Simoa assays and CVs <=5%

• Technological advances in automation systems combined with the assay advances have drastically improved the field
  • E.g., ITR Biomarker Core can run n approx. 50,000 samples annually across 3 platforms (Simoa, Luminex, ECL)
Why Blood Based Biomarkers?

• Less invasive and most cost effective
• Scalable – depending on platform, company, etc.
• Increase access to clinical research and trials
• Increase access to confirmatory diagnostic methods

• Will they replace CSF and/or PET methods?
Potential roles and advantages of blood-based biomarkers

- Blood Biomarkers have multiple advantages
  - Non-invasive, simple, inexpensive
  - Can be utilized to reach large scale populations
  - Can be incorporated into existing medical model and paradigm

- Blood-based markers **should** be utilized to complement imaging and CSF biomarkers and **should not** be considered replacements for these markers
  - Multi-stage process for detecting AD/ADRDs in primary care clinics
  - Multi-stage process for screening possible subjects into trials
  - Identification of subgroups for targeted therapy

Watching The Pendulum Swing

Blood Biomarkers Have No Use In AD

Blood Biomarkers Will Replace CSF and PET Methods

Blood Biomarkers Used as Part of Comprehensive Set of Tools
Watching The Pendulum Swing

When I started

Blood Biomarkers Have No Use In AD

Blood Biomarkers Used as Part of Comprehensive Set of Tools

Today

Blood Biomarkers Will Replace CSF and PET Methods

Where We Need To Be
How to Move towards Clinic?

Perspective

Blood-based biomarkers in Alzheimer disease: Current state of the science and a novel collaborative paradigm for advancing from discovery to clinic

Sid E. O’Bryant\textsuperscript{a,\ast}, Michelle M. Mielke\textsuperscript{b,c}, Robert A. Rissman\textsuperscript{d}, Simone Lista\textsuperscript{e,f}, Hugo Vanderstichele\textsuperscript{g}, Henrik Zetterberg\textsuperscript{h,i}, Piotr Lewczuk\textsuperscript{j,k}, Holly Posner\textsuperscript{l}, James Hall\textsuperscript{a}, Leigh Johnson\textsuperscript{a}, Yiu-Lian Fong\textsuperscript{m}, Johan Luthman\textsuperscript{n}, Andreas Jeromin\textsuperscript{o}, Richard Batrla-Utermann\textsuperscript{p}, Alcibiades Villarreal\textsuperscript{q}, Gabrielle Britton\textsuperscript{q}, Peter J. Snyder\textsuperscript{r}, Kim Henriksen\textsuperscript{s}, Paula Grammas\textsuperscript{t}, Veer Gupta\textsuperscript{u}, Ralph Martins\textsuperscript{u}, Harald Hampel\textsuperscript{e,f}, and the Biofluid Based Biomarker Professional Interest Area
Still the “Wild West”

• Many assays are conducted in single labs without cross-validation
• Many cross-validations fail and go unpublished
• Very few present the relevant statistics to assess the biomarker as a “diagnostic” biomarker
  • AUC and correlations do not get you there
  • Journal editors forgot about STARD guidelines
  • Need to publish the sensitivity and specificity statistics for diagnostic accuracy to be assessed
Methodological Considerations

• VERY few consider fit-for-purpose biomarker validation methods
• Few studies have been formulated from the beginning to directly address a specific context of use (COU)
• Most studies identify “biomarkers” in search of a COU
• Are our study designs correct?
  • Are we using the correct outcome measures
  • Are the prospective studies:
    • At appropriate intervals?
Are We Asking the Correct Questions?

Academic Model
- Create case-control cohort
- Discover biomarker correlated with disease status
- Examine correlation with relevant clinical endpoints
- Define Fit-for-Purpose of new biomarker?

Industry Model
- Identify Fit-for-Purpose of potential biomarker
- Identify methods
- Examine fitness for purpose
- Examine in clinical context
- Clinical use with continual quality improvement

Context of use
<table>
<thead>
<tr>
<th>Study Description</th>
<th>AUC</th>
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Context of use
Reframing the Context and Study Designs targeted to COUs

Fig. 2. Public-private partnership model for moving from biomarker discovery to clinical use. Abbreviation: COU, context of use.
## COU – Blood as Surrogate for PET/CSF for Prevention Trial

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<thead>
<tr>
<th>COU=detecting cerebral amyloid (PET/CSF)</th>
<th>AUC (SN, SP)</th>
<th>PPV/NPV</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>BR=10%</td>
<td>BR=20%</td>
<td>BR=30%</td>
</tr>
<tr>
<td>West et al C2N biomarker 2021</td>
<td>0.90 (0.9,0.75)</td>
<td>0.29/0.99</td>
<td>0.47/0.97</td>
<td>0.61/0.95</td>
</tr>
<tr>
<td>Schindler 2019 C2N</td>
<td>0.94 (0.95,0.75)</td>
<td>0.30/0.99</td>
<td>0.49/0.98</td>
<td>0.62/0.97</td>
</tr>
<tr>
<td>Janelidze 2021- MCI (ptau217+Ab42/Ab40 + NFL)</td>
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</tr>
<tr>
<td>Janelidze 2021 - Control (ptau217)</td>
<td>0.81 (0.75, 0.75)</td>
<td>0.25/0.96</td>
<td>0.43/0.92</td>
<td>0.56/0.88</td>
</tr>
<tr>
<td>Janelidze 2020 (ptau217)</td>
<td>0.83 (0.8,0.75)</td>
<td>0.26/0.97</td>
<td>0.44/0.94</td>
<td>0.58/0.90</td>
</tr>
<tr>
<td>Grothe 2021 (ptau181)</td>
<td>0.94 (0.85,0.7)</td>
<td>0.24/0.98</td>
<td>0.41/0.95</td>
<td>0.55/0.92</td>
</tr>
</tbody>
</table>
COU – Blood as Surrogate for PET/CSF for Clinical Diagnosis

<table>
<thead>
<tr>
<th>COU=Detecting Cerebral Alzheimer’s disease (clinical)</th>
<th>AUC (SN, SP)</th>
<th>PPV/NPV</th>
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<th>PPV/NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BR=10%</td>
<td>BR=20%</td>
<td>BR=30%</td>
<td></td>
</tr>
<tr>
<td>Ashton 2021 (ptau231) – primary care</td>
<td>0.75 (0.6,0.7)</td>
<td>0.18/0.94</td>
<td>0.33/0.88</td>
<td>0.46/0.80</td>
</tr>
<tr>
<td>Brickman 2021 (ptau217)</td>
<td>0.84 (0.8,0.7)</td>
<td>0.23/0.97</td>
<td>0.40/0.93</td>
<td>0.53/0.89</td>
</tr>
<tr>
<td>Palmqvist 2021 (ptau217), neuropathology defined</td>
<td>0.89 (0.80,0.80)</td>
<td>0.31/0.97</td>
<td>0.5/0.94</td>
<td>0.63/0.90</td>
</tr>
<tr>
<td>O’Bryant 2021 (proteomic profile)</td>
<td>0.91 (0.76,0.99)</td>
<td>0.89/0.97</td>
<td>0.95/0.94</td>
<td>0.97/0.91</td>
</tr>
<tr>
<td></td>
<td>BR=60%</td>
<td>BR=70%</td>
<td>BR=80%</td>
<td></td>
</tr>
<tr>
<td>Putting Into Different COU</td>
<td>0.95/0.75</td>
<td>0.85/0.91</td>
<td>0.90/0.87</td>
<td>0.94/0.79</td>
</tr>
<tr>
<td></td>
<td>0.90/0.75</td>
<td>0.84/0.83</td>
<td>0.89/0.76</td>
<td>0.94/0.65</td>
</tr>
<tr>
<td></td>
<td>0.85/0.75</td>
<td>0.84/0.77</td>
<td>0.89/0.68</td>
<td>0.93/0.56</td>
</tr>
<tr>
<td></td>
<td>0.80/0.75</td>
<td>0.83/0.71</td>
<td>0.88/0.62</td>
<td>0.93/0.48</td>
</tr>
<tr>
<td></td>
<td>0.8/0.70</td>
<td>0.80/0.70</td>
<td>0.86/0.60</td>
<td>0.91/0.47</td>
</tr>
<tr>
<td></td>
<td>0.76/0.99</td>
<td>0.99/0.73</td>
<td>0.99/0.64</td>
<td>1.00/0.51</td>
</tr>
</tbody>
</table>

Neurology Clinic or AD Trial NHW
COU: Blood As Surrogate for CSF or PET

• Are Blood-Based Biomarkers Surrogates for PET and/or CSF Confirmatory Diagnostics?

NO

• See Morgan et al 2021 – Accuracy of Practitioner Estimates of Probability of Diagnosis Before and After Testing (pneumonia, cardiac ischemia, breast cancer, urinary tract infection)

• “practitioners overestimate the probability of disease before and after testing”… “widespread overestimates of the probability of disease likely contribute to overdiagnosis and overuse
FDA Overview of Biomarker Context of Use (COU) – **Focusing the Questions**

**Biomarker Categories**

- **Diagnostic**
- **Predictive**
- **Response**

**Context of Use Examples**

- **Patient Selection (COU1)**
  - Identify individuals on the basis of effect from a specific intervention or exposure (COU2)
- **Efficacy biomarker or Surrogate endpoints (COU3)**
COU-1: Screening

1. Screen for AD (MCI) within primary care settings.
2. Screen for amyloid positivity for enrollment into novel clinical trial.
3. Screen for amyloid negativity for enrollment for non-amyloid trial.

Blood Based Screening Tools
MRI, Cognitive Testing
PET, CSF

1. Therapy
2. Trial Enrollment
Detecting AD in Primary Care: Current state-of-the-art diagnosis

PCP Referral → Specialist Exam → Brain MRI → Memory Testing → Blood Work
Current state-of-the-art diagnosis
How is Alzheimer’s disease diagnosed?

Screen Positive?

Yes

No

How to screen 40 million Americans?

Screen again next year
How is Alzheimer’s disease diagnosed?

How to screen 40 million Americans?

Screen Positive?

Yes

No

Screen again next year
ADPC Study

- 1st study of AD Blood Test for primary care (300 of 500 participants already enrolled)
- Preclinical (brain amyloid + normal cognition); Prodromal (brain amyloid + MCI) and AD
- Can our AD Blood Test accurately determine which patients should and should not undergo additional examinations
- Study designed specifically for COU 1
COU 2: Patient selection for Novel Trials

Blood Based Screening Tools

MRI, Cognitive Testing

PET, CSF

Trial Enrollment

- Blood is ideal for large-scale screening
- Multi-tiered biomarker screening
- Initial biomarkers should screen OUT those who should undergo additional testing

O’Bryant et al 2016, 2017
### Blood Screen
- Increase Access and Potential Patient Pool
- Rule OUT 70%

### Phone Interview
- Eligibility questions
- Rule OUT

### MRI
- Rule Out

### Specialty Clinic Visit

- **Can be implemented in primary care settings**
- **Can increase access to thousands of potential patients**
- **Increased access AND LOWER costs**
COU2: Trial Targeting AD among Adults with Down Syndrome

Detecting Prevalent MCI
N=398 adults with DS

AUC=0.92

Detecting MCI in ABC-DS
N=336

AUC=0.95
AUC=0.98

ABC-DS AD – AUC=0.96

Petersen et al 2020; O’Bryant et al 2020; Petersen et al 2021
Plasma t-tau and NfL Only

MCI - Plasma tau and NfL with age and gender

ABC-DS

AUC=0.86

AD - Plasma tau and NfL with age and gender

ABC-DS

AUC=0.93
Putting data into practical example – using only tau and NfL with age and gender

• Screen n=5,000 adults with DS from primary care settings
• N=4,320 would be ruled OUT with blood test alone
• N=540 would be referred for additional screening
• At $50/test
  • $250,000 to screen n=5,000 potential patients
COU3: Predictive Biomarker

- AD (in DS and general population) is not “one pathology or disease” but has many subgroups

Think: cancer model
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

Rosiglitazone

Duloxetine

Treat at this level

Targeted therapeutics

A Precision Medicine Model for Targeted NSAID Therapy in Alzheimer’s Disease

Sid E. O’Bryant\textsuperscript{a,*}, Fan Zhang\textsuperscript{b}, Leigh A. Johnson\textsuperscript{a}, James Hall\textsuperscript{a}, Melissa Edwards\textsuperscript{c}, Paula Grammas\textsuperscript{d}, Esther Oh\textsuperscript{e,f}, Constantine G. Lyketsos\textsuperscript{f} and Robert A. Rissman\textsuperscript{g,h}

Table 1
Demographic characteristics of the sample cohort

<table>
<thead>
<tr>
<th></th>
<th>Naproxen ($n = 68$)</th>
<th>Rofecoxib ($n = 55$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>74.0 (7.8)</td>
<td>73.8 (7.3)</td>
</tr>
<tr>
<td>Education</td>
<td>13.9 (3.2)</td>
<td>13.9 (3.2)</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>48%</td>
<td>54%</td>
</tr>
<tr>
<td>ApoE4 positive</td>
<td>71%</td>
<td>69%</td>
</tr>
</tbody>
</table>
### Table 2
Treatment response prediction using proteomic profiling analyses

<table>
<thead>
<tr>
<th></th>
<th>SVM Predicted Decliner</th>
<th>SVM Predicted Non-Responder</th>
<th>SVM Predicted Responder</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Sample</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actual Rapid Decliner</td>
<td>41</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Actual Non-Responder</td>
<td>1</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Actual Responder</td>
<td>7</td>
<td>1</td>
<td>46</td>
</tr>
<tr>
<td><strong>Naproxen Arm</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Actual Rapid Decliner</td>
<td>26</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Actual Non-Responder</td>
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<td>10</td>
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<tr>
<td>Actual Responder</td>
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<td>0</td>
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<tr>
<td><strong>Rofecoxib Arm</strong></td>
<td></td>
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<td>Actual Rapid Decliner</td>
<td>23</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Actual Non-Responder</td>
<td>0</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Actual Responder</td>
<td>0</td>
<td>0</td>
<td>17</td>
</tr>
</tbody>
</table>

### Table 3
Inflammatory profile variable importance By NSAID

<table>
<thead>
<tr>
<th>Marker Rank</th>
<th>NSAID-general</th>
<th>Naproxen</th>
<th>Rofecoxib</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>CRP</td>
<td>CRP</td>
<td>IL6</td>
</tr>
<tr>
<td>2</td>
<td>IL6</td>
<td>IL6</td>
<td>CRP</td>
</tr>
<tr>
<td>3</td>
<td>IL10</td>
<td>TNFα</td>
<td>IL10</td>
</tr>
<tr>
<td>4</td>
<td>TNFα</td>
<td>IL10</td>
<td>TNFα</td>
</tr>
</tbody>
</table>
A Precision Medicine Approach to Treating Alzheimer’s Disease Using Rosiglitazone Therapy: A Biomarker Analysis of the REFLECT Trials

Sid E. O’Bryant, Fan Zhang, Melissa Petersen, Leigh Johnson, James Hall, and Robert A. Rissman

Fig. 6. Predictive biomarker accuracy in identifying responders versus non-responders in across 2mg XR and 8mg XR arms across trials.

<table>
<thead>
<tr>
<th>Actual</th>
<th>Predicted response</th>
<th>Nonresponse</th>
</tr>
</thead>
<tbody>
<tr>
<td>response</td>
<td>170</td>
<td>4</td>
</tr>
<tr>
<td>nonresponse</td>
<td>3</td>
<td>183</td>
</tr>
<tr>
<td>Precision/PPV</td>
<td>97.70%</td>
<td></td>
</tr>
<tr>
<td>Accuracy</td>
<td>98.06%</td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>98.27%</td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>97.86%</td>
<td></td>
</tr>
<tr>
<td>NPV</td>
<td>98.39%</td>
<td></td>
</tr>
<tr>
<td>AUC</td>
<td>99.10%</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 7. Predictive accuracy in identifying responders versus non-responders dosages.
COU4: Surrogate endpoints

1. Therapeutic intervention
2. Clinical trial
3. Completed trial

Prior to treatment

Biomarker (baseline value)

Surrogate end point (affected value)
- Benefit (efficacy)
- Harm (safety)

Measured change

Substituted for

6-month change

24-month treatment
Questions?