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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
- Kamiah Moss
- Jennifer Loya
- Miguel Reyes
- Jill Rhodes
- Raul Vintimilla
- Lily Cacho
- Elly Gardea
- Denise Duarte

Gemomics Core

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- Nicole Philips, Ph.D.

Biomarker Core

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- Tori Como
- David Julovich
- Melissa Pierce, PhD

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- Fan Zhang, PhD
- Marcela Davila

Administrative Core

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- David Mason, DO (Medical Director)
- Erin Donoho
- Kelly Berry
- La Shundra Marshall
- Kellie Johnson "KJ"

Imaging Core

- 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

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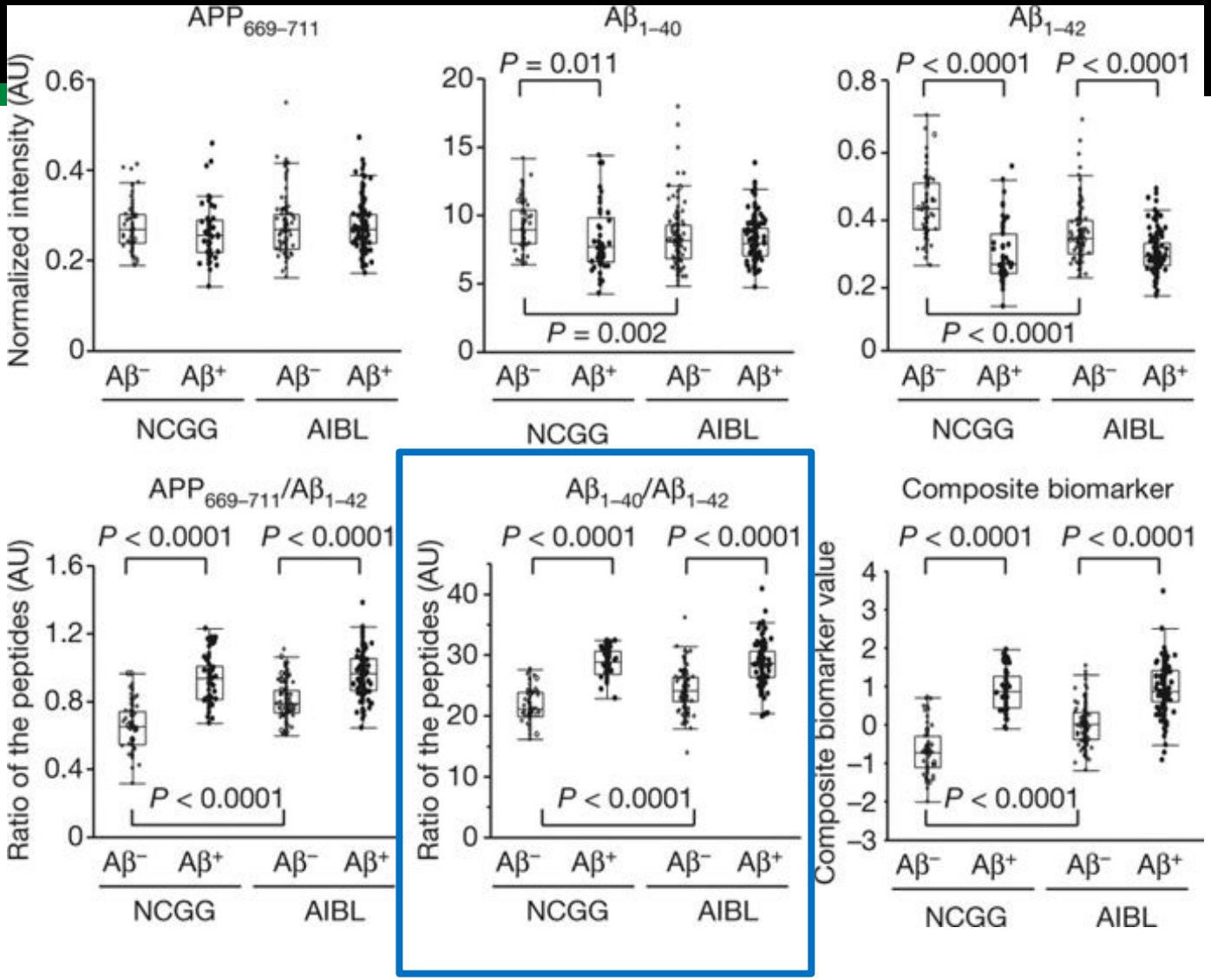
Recent Advances in Blood Based Biomarkers

Lots of Excitement

Nakamura – Nature, 2018



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Acta Neuropathologica (2021) 141:709–724
https://doi.org/10.1007/s00401-021-02275-6

ORIGINAL PAPER

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

Nicholas J. Ashton[1,2,3,4] · Tharick A. Pascoal[5,6] · Thomas K. Karikari[1] · Andréa L. Benedet[1,5] · Juan Lantero-Rodriguez[1] · Gunnar Brinkmalm[1] · Anniina Snellman[1] · Michael Schöll[1,2,10] · Claire Troakes[14] · Abdul Hye[3,4] · Serge Gauthier[7] · Eugeen Vanmechelen[8] · Henrik Zetterberg[1,9,10,11] · Pedro Rosa-Neto[1,12,13] ·

JAMA | Original Investigation

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

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

Received: 18 December 2020 | Revised: 13 April 2021 | Accepted: 22 April 2021
DOI: 10.1002/alz.12382

RESEARCH ARTICLE

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

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'Bryant[1,2] | Fan Zhang[1,3] | Melissa Petersen[1,3] | James R. Hall[1,2] | Leigh A. Johnson[1,2] | Kristine Yaffe[4,5] | David Mason[2] | Meredith Braskie[6] | Robert A. Barber[1,2] | Robert A. Rissman[7,8] | Mark Mapstone[9] | Michelle M. Mielke[10,11] | Arthur W. Toga[6] | for the HABLE Study Team[1]

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Article

TRANSPARENT PROCESS OPEN ACCESS

EMBO Molecular Medicine

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

Rik Ossenkoppele[1,2,*], Juhan Reimand[2,3,4], Ruben Smith[1,5], Antoine Leuzy[1], Olof Strandberg[1], Sebastian Palmqvist[1,6], Erik Stomrud[1,6], Henrik Zetterberg[7,8,9,10], the Alzheimer's Disease

Received: 29 December 2020 | Revised: 7 May 2021 | Accepted: 7 May 2021
DOI: 10.1002/alz.12395

FEATURED ARTICLE

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

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

Shorena Janelidze[1] | Sebastian Palmqvist[1,2] | Antoine Leuzy[1] | Erik Stomrud[1,2] | Inge M.W. Verberk[3] | Henrik Zetterberg[4,5,6,7] | Nicholas J. Ashton[4,8,9,10] | Pedro Pesini[11] | Leticia Sarasa[11] | José Antonio Allué[11] | Charlotte E. Teunissen[3] | Jeffrey L. Dage[12] | Kaj Blennow[4,5] | Niklas Mattsson-Carlgren[1,13,14] | Oskar Hansson[1,2]

Received: 10 September 2020 | Revised: 8 December 2020 | Accepted: 2 January 2021
DOI: 10.1002/alz.12301

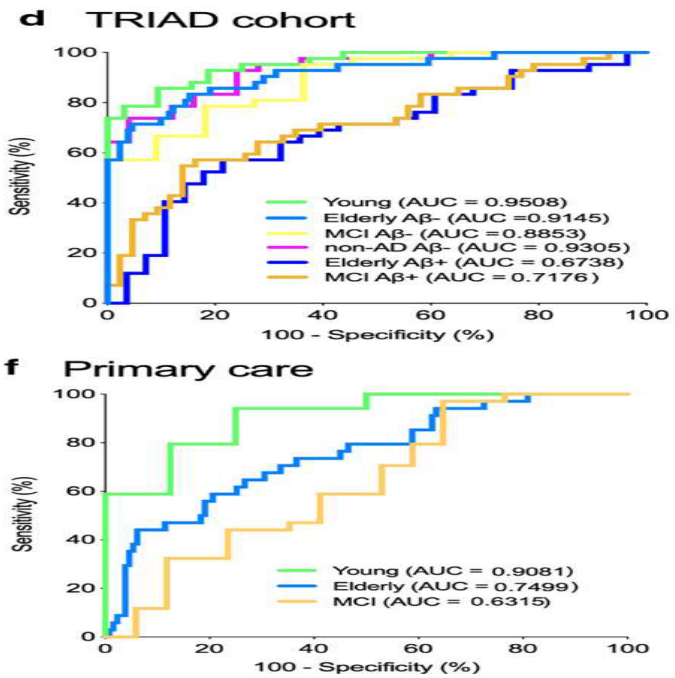
FEATURED ARTICLE

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

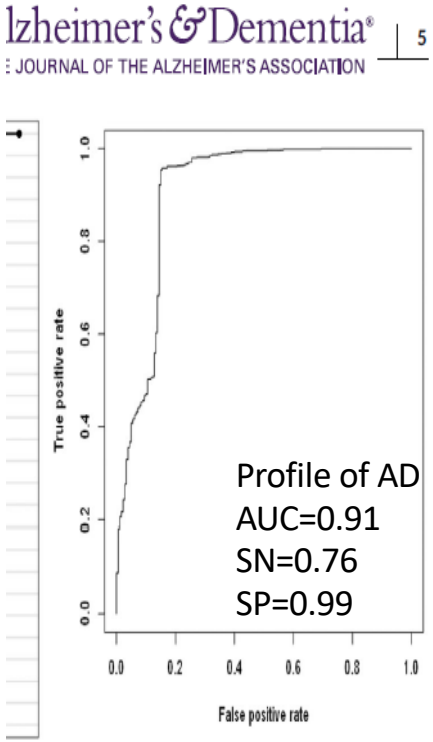
Plasma p-tau181, p-tau217, and other blood-based Alzheimer's disease biomarkers in a multi-ethnic, community study

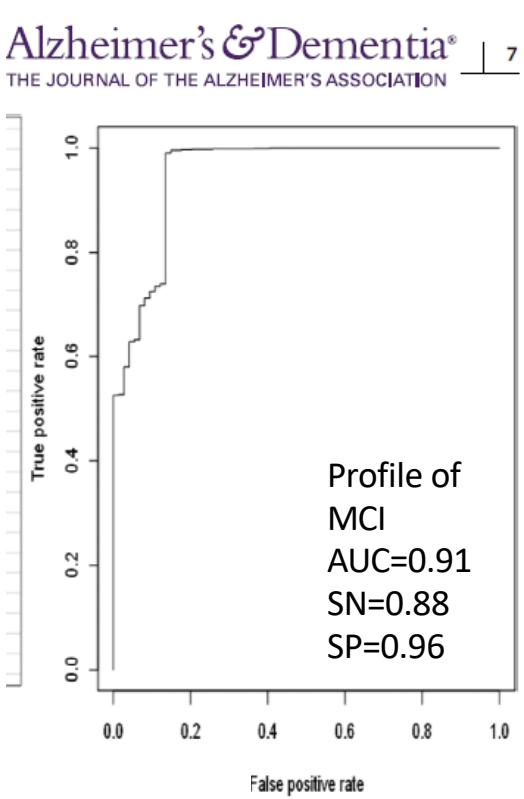
Adam M. Brickman[1,2,3] | Jennifer J. Manly[1,2,3] | Lawrence S. Honig[1,3] | Danurys Sanchez[1,2] | Dolly Reyes-Dumeyer[1,2] | Rafael A. Lantigua[1,4] | Patrick J. Lao[1,2,3] | Yaakov Stern[1,2,3] | Jean Paul Vonsattel[1,5] | Andrew F. Teich[1,3,5] | David C. Airey[6] | Nicholas Kyle Proctor[6] | Jeffrey L. Dage[6] | Richard Mayeux[1,2,3]

Ashton 2021 (ptau231)

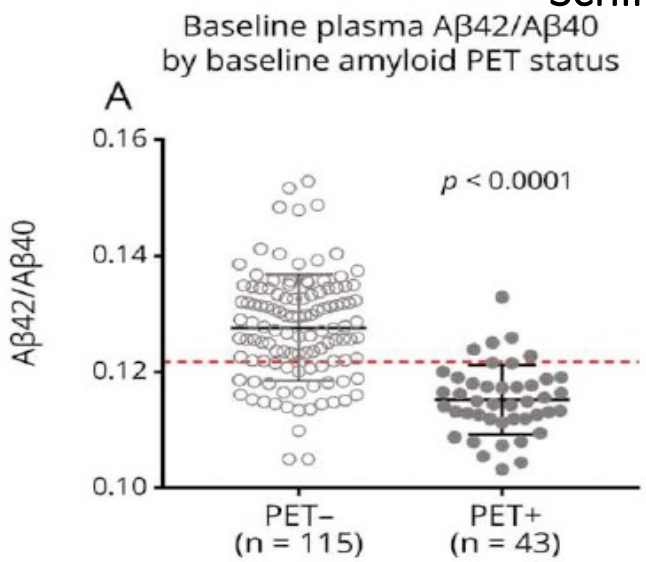


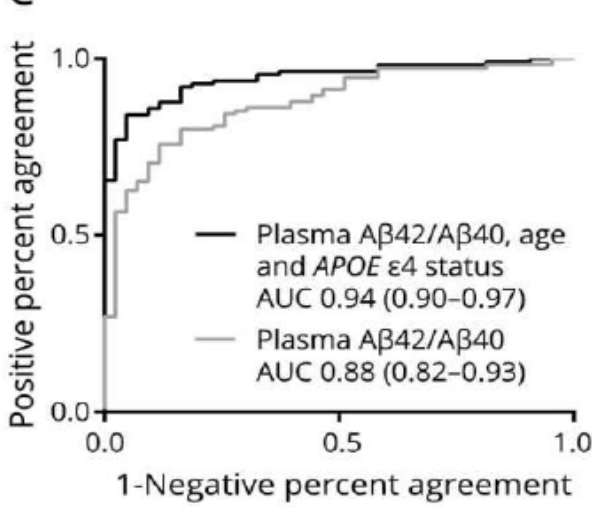
O'Bryant 2021 (proteomic profile)

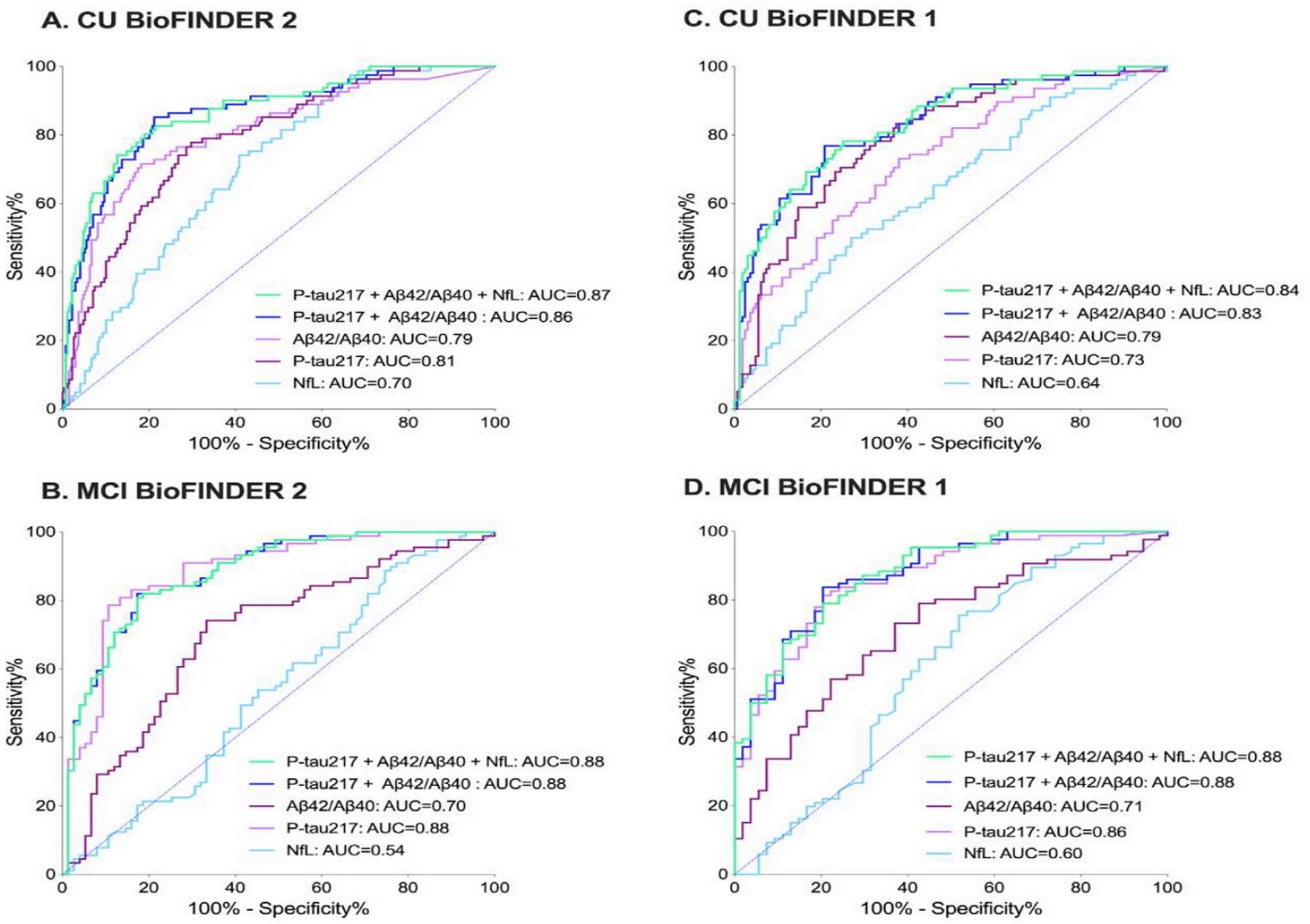




Schindler 2019 C2N Ab profile






A. CU BioFINDER 2
Sensitivity%
100% - Specificity%
P-tau217 + Aβ42/Aβ40 + NfL: AUC=0.87
P-tau217 + Aβ42/Aβ40 : AUC=0.86
Aβ42/Aβ40: AUC=0.79
P-tau217: AUC=0.81
NfL: AUC=0.70
C. CU BioFINDER 1
Sensitivity%
100% - Specificity%
P-tau217 + Aβ42/Aβ40 + NfL: AUC=0.84
P-tau217 + Aβ42/Aβ40 : AUC=0.83
Aβ42/Aβ40: AUC=0.79
P-tau217: AUC=0.73
NfL: AUC=0.64
B. MCI BioFINDER 2
Sensitivity%
100% - Specificity%
P-tau217 + Aβ42/Aβ40 + NfL: AUC=0.88
P-tau217 + Aβ42/Aβ40 : AUC=0.88
Aβ42/Aβ40: AUC=0.70
P-tau217: AUC=0.88
NfL: AUC=0.54
D. MCI BioFINDER 1
Sensitivity%
100% - Specificity%
P-tau217 + Aβ42/Aβ40 + NfL: AUC=0.88
P-tau217 + Aβ42/Aβ40: AUC=0.88
Aβ42/Aβ40: AUC=0.71
P-tau217: AUC=0.86
NfL: AUC=0.60

COU=detecting cerebral amyloid (PET/CSF)	AUC
West et al C2N biomarker 2021	0.90
Schindler 2019 C2N	0.94
Janelidze 2021- MCI (ptau217+Ab42/Ab40 + NFL)	0.88
Janelidze 2021 - MCI (ptau217)	0.88
Janelidze – Control (ptau217+Ab42/40+NFL)	0.87
Janelidze 2021 - Control (ptau217)	0.81
Janelidze 2020 (ptau217)	0.83
Grothe 2021 (ptau181)	0.94

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?

????

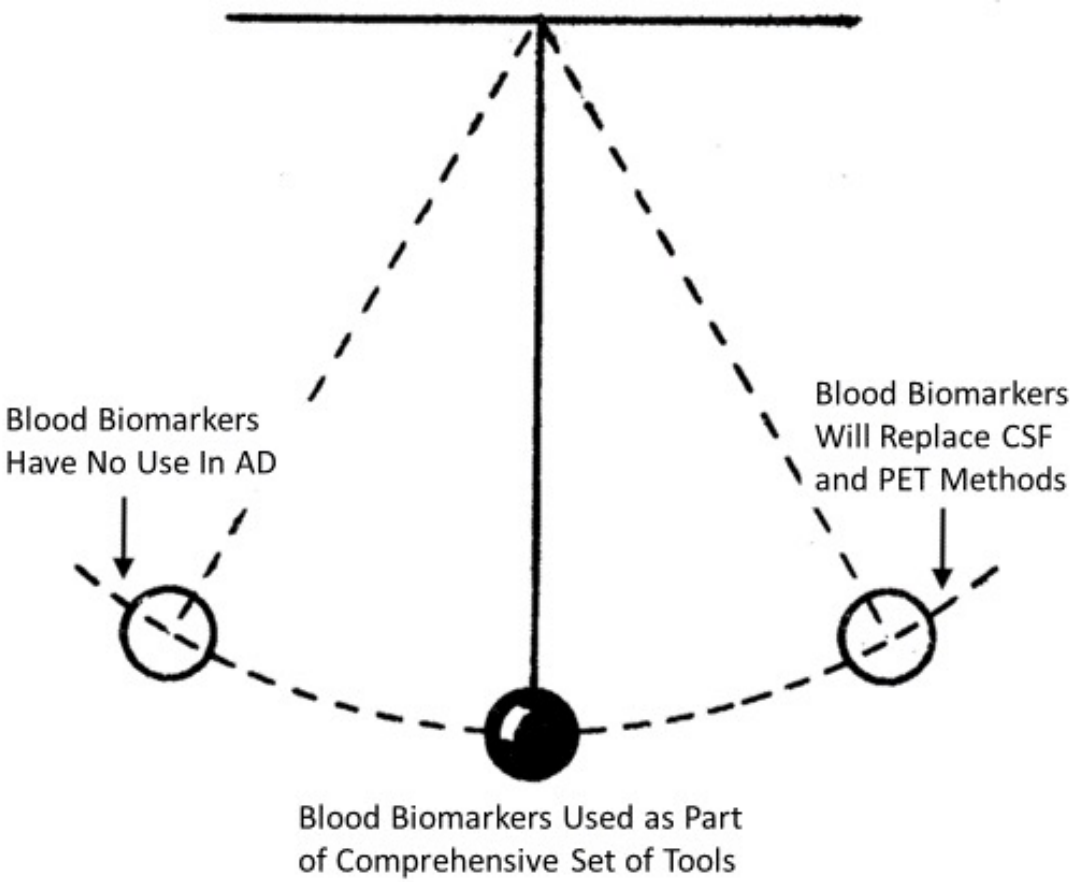
alzheimer's association AAIC 17

Potential roles and advantages of blood-based biomarkers

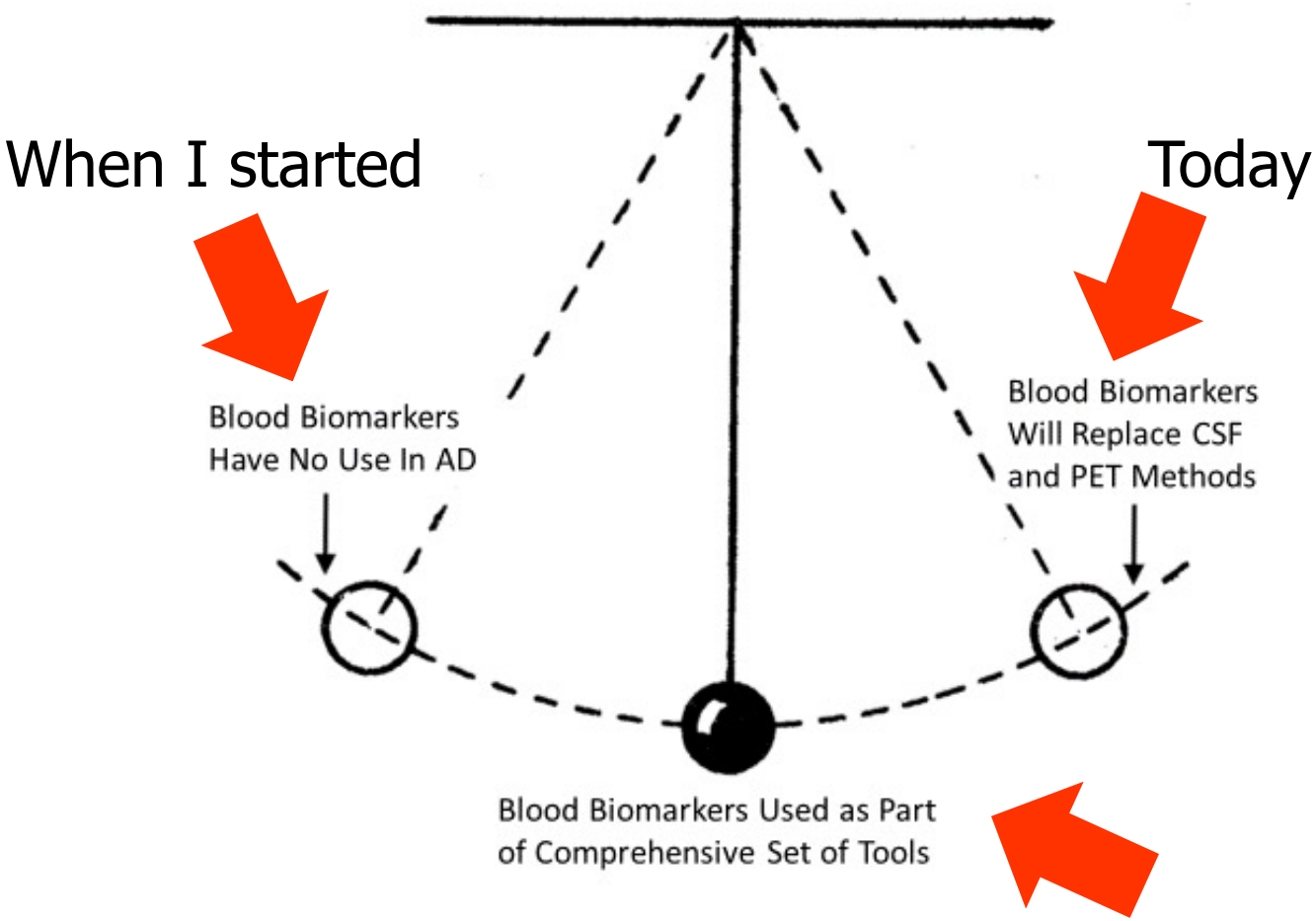
- Blood Biomarkers have multiple advantages
  - Non-invasive, simple, inexpensive
  - Can be utilized to reach large scale populations
  - Can be incorporated into existing medical model and paradigm
- Blood-based markers **should** be utilized to complement imaging and CSF biomarkers and **should not** 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

Anonymous, 1998; Henriksen 2014, Snyder 2014, Doecke et al 2012; Graff-Radford et al 2007; O'Bryant and colleagues 2014, 2015, 2016

Watching The Pendulum Swing



Watching The Pendulum Swing



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How to Move towards Clinic?

Alzheimer's & Dementia 13 (2017) 45-58

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[a,*], Michelle M. Mielke[b,c], Robert A. Rissman[d], Simone Lista[e,f], Hugo Vanderstichele[g], Henrik Zetterberg[h,i], Piotr Lewczuk[j,k], Holly Posner[l], James Hall[a], Leigh Johnson[a], Yiu-Lian Fong[m], Johan Luthman[n], Andreas Jeromin[o], Richard Batrla-Utermann[p], Alcibiades Villarreal[q], Gabrielle Britton[q], Peter J. Snyder[r], Kim Henriksen[s], Paula Grammas[t], Veer Gupta[u], Ralph Martins[u], Harald Hampel[e,f], and the Biofluid Based Biomarker Professional Interest Area

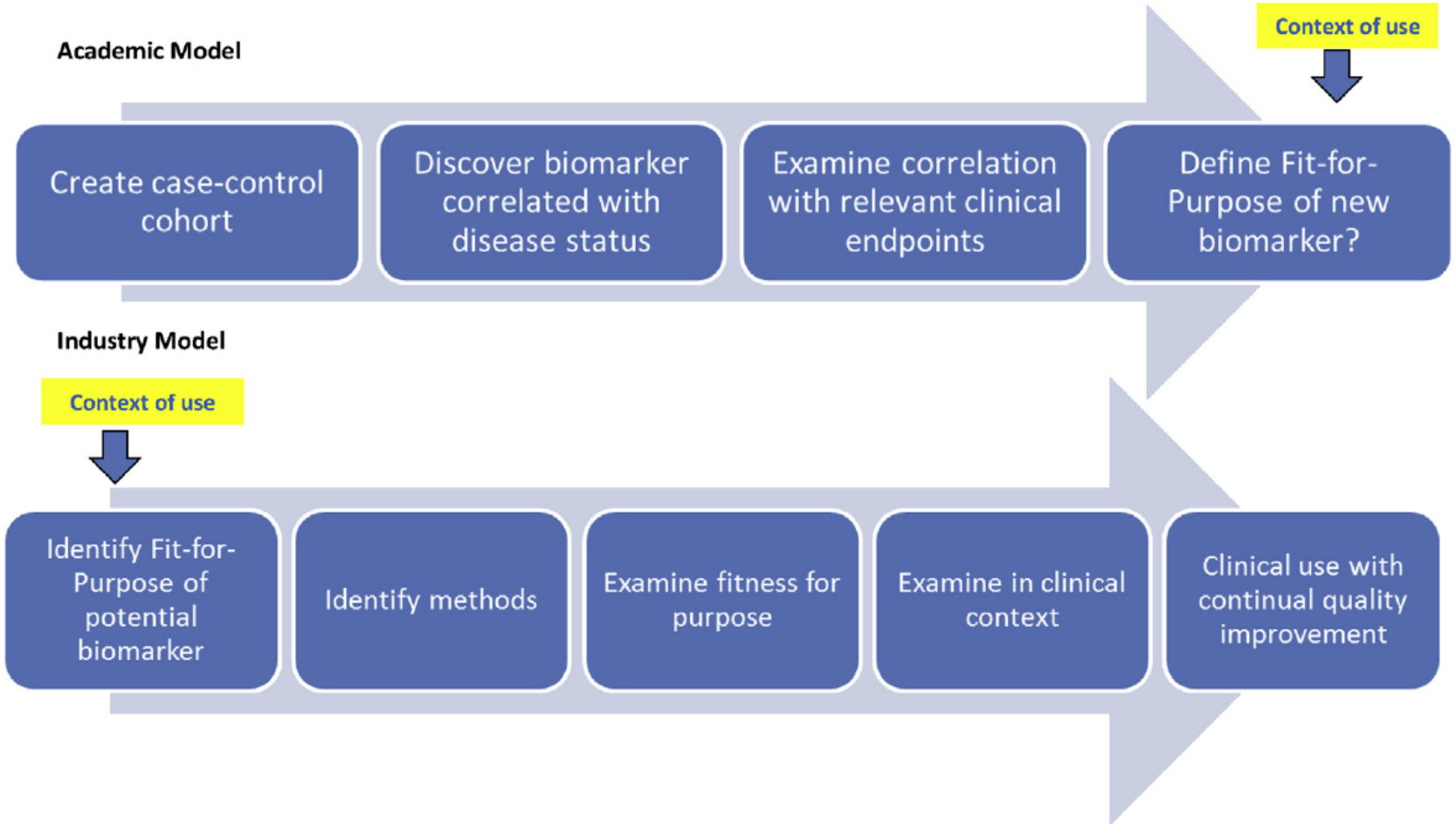
Still the "Wild West"

- 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?



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O'Bryant 2017

COU=detecting cerebral amyloid (PET/CSF)	AUC
West et al C2N biomarker 2021	0.90
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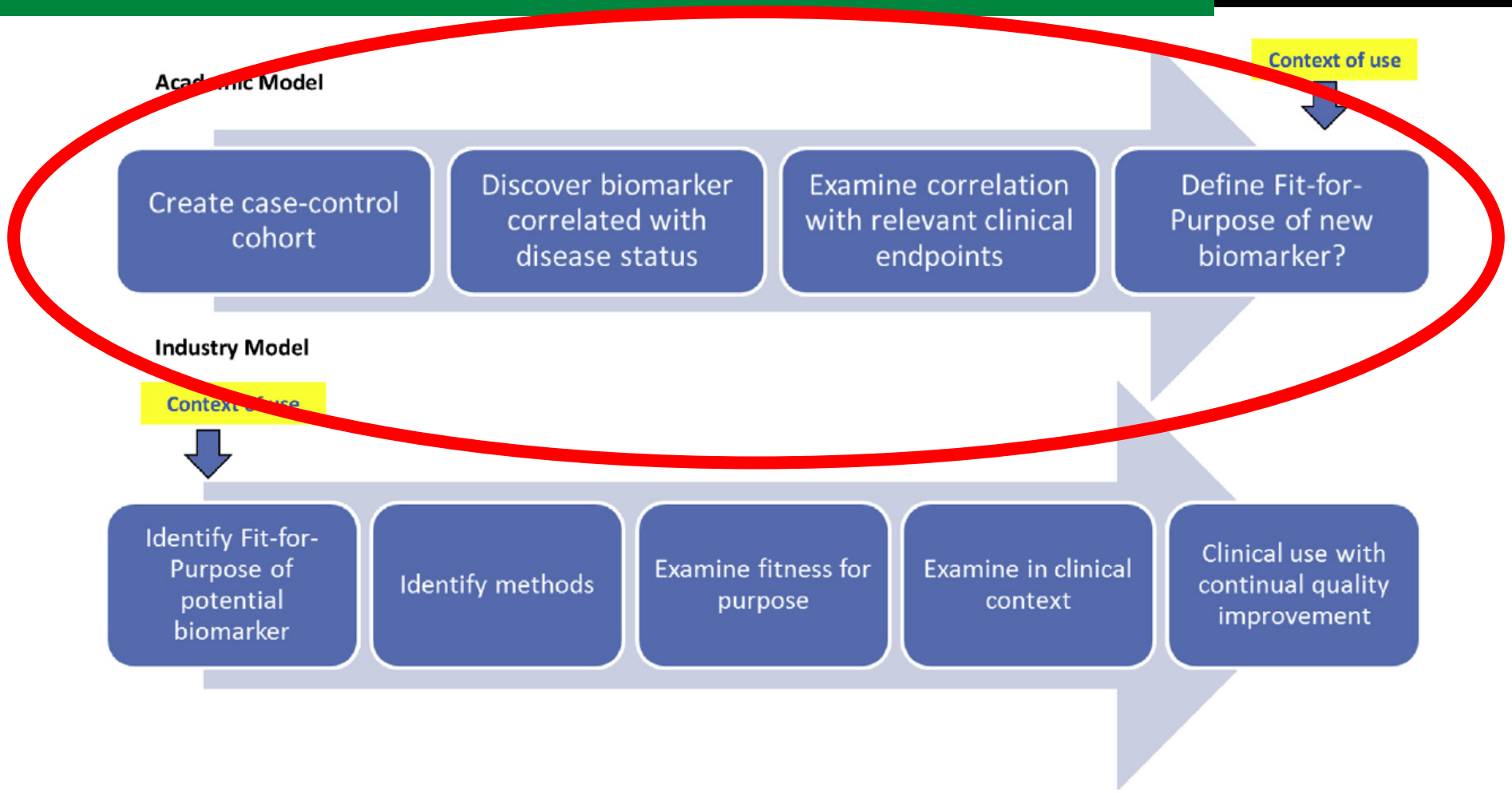
Grothe 2021 (ptau181)	0.94

Are We Asking the Correct Questions?



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O'Bryant 2017

Reframing the Context and Study Designs targeted to COUs

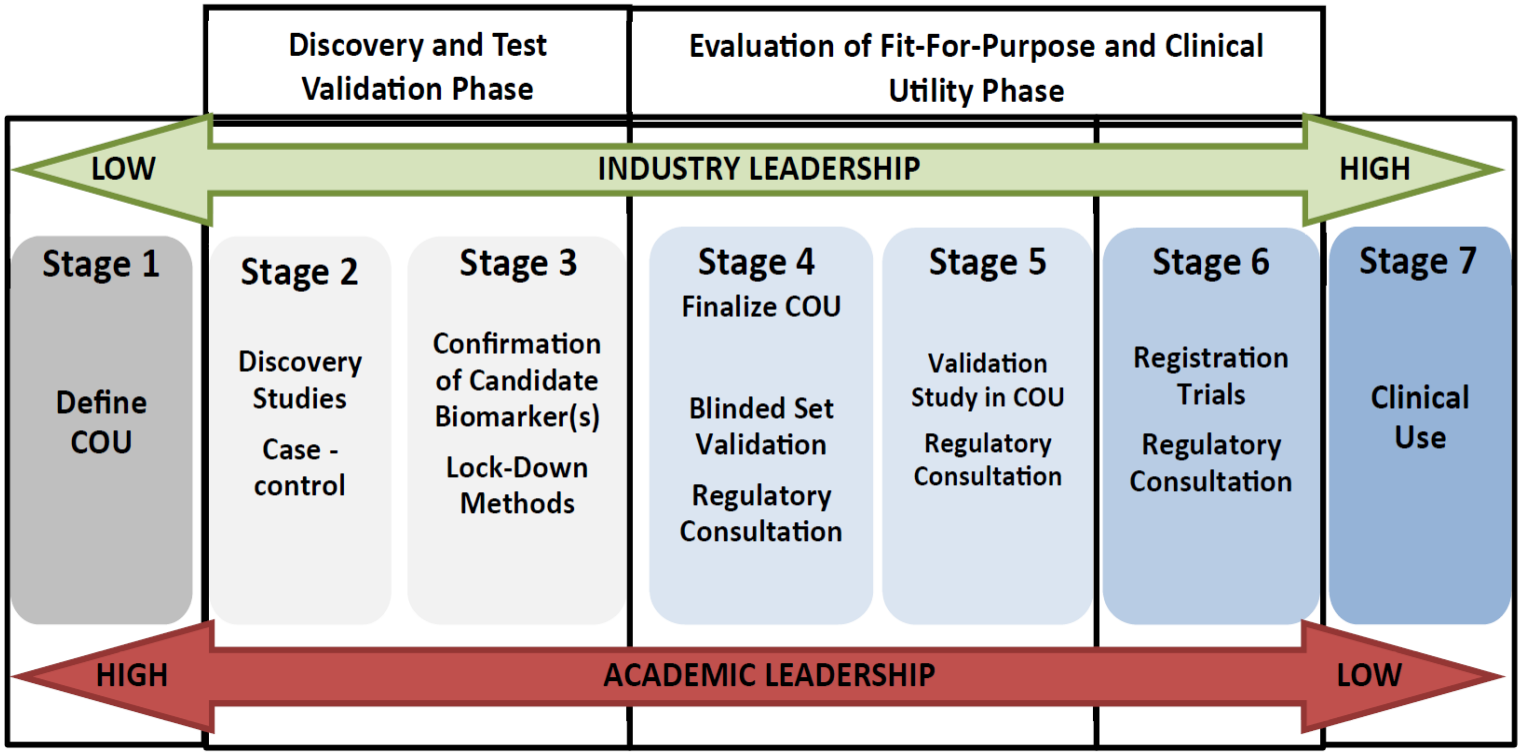


Fig. 2. Public-private partnership model for moving from biomarker discovery to clinical use. Abbreviation: COU, context of use.

COU – Blood as Surrogate for PET/CSF for Prevention Trial

COU=detecting cerebral amyloid (PET/CSF)	AUC (SN, SP)	PPV/NPV	PPV/NPV	PPV/NPV
		BR=10%	**BR=20%**	**BR=30%**
West et al C2N biomarker 2021	0.90 (0.9,0.75)	0.29/0.99	0.47/0.97	0.61/0.95
Schindler 2019 C2N	0.94 (0.95,0.75)	0.30/0.99	0.49/0.98	0.62/0.97
Janelidze 2021- MCI (ptau217+Ab42/Ab40 + NFL)	0.88 (0.85, 0.75)	0.27/0.98	0.46/0.95	0.59/0.92
Janelidze 2021 - MCI (ptau217)	0.88 (0.85,0.75)	0.27/0.98	0.46/0.95	0.59/0.92
Janelidze – Control (ptau217+Ab42/40+NFL)	0.87 (0.85,0.75)	0.27/0.98	0.46/0.95	0.59/0.92
Janelidze 2021 - Control (ptau217)	0.81 (0.75, 0.75)	0.25/0.96	0.43/0.92	0.56/0.88
Janelidze 2020 (ptau217)	0.83 (0.8,0.75)	0.26/0.97	0.44/0.94	0.58/0.90
Grothe 2021 (ptau181)	0.94 (0.85,0.7)	0.24/0.98	0.41/0.95	0.55/0.92

COU – Blood as Surrogate for PET/CSF for Clinical Diagnosis

COU=Detecting Cerebral Alzheimer's disease (clinical)	AUC (SN, SP)	PPV/NPV	PPV/NPV	PPV/NPV
		BR=10%	**BR=20%**	**BR=30%**
Ashton 2021 (ptau231) – primary care	0.75 (0.6,0.7)	0.18/0.94	0.33/0.88	0.46/0.80
Brickman 2021 (ptau217)	0.84 (0.8,0.7)	0.23/0.97	0.40/0.93	0.53/0.89
Palmqvist 2021 (ptau217), neuropathology defined	0.89 (0.80,0.80)	0.31/0.97	0.5/0.94	0.63/0.90
O'Bryant 2021 (proteomic profile)	0.91 (0.76,0.99)	0.89/0.97	0.95/0.94	0.97/0.91
		BR=60%	**BR=70%**	**BR=80%**
Putting Into Different COU	0.95/0.75	0.85/0.91	0.90/0.87	0.94/0.79
Neurology Clinic	0.90/.075	0.84/0.83	0.89/0.76	0.94/0.65
or AD Trial NHW	0.85/0.75	0.84/0.77	0.89/0.68	0.93/0.56
	0.80/0.75	0.83/0.71	0.88/0.62	0.93/0.48
	0.8/0.70	0.80/0.70	0.86/0.60	0.91/0.47
	0.76/0.99	0.99/0.73	0.99/0.64	1.00/0.51

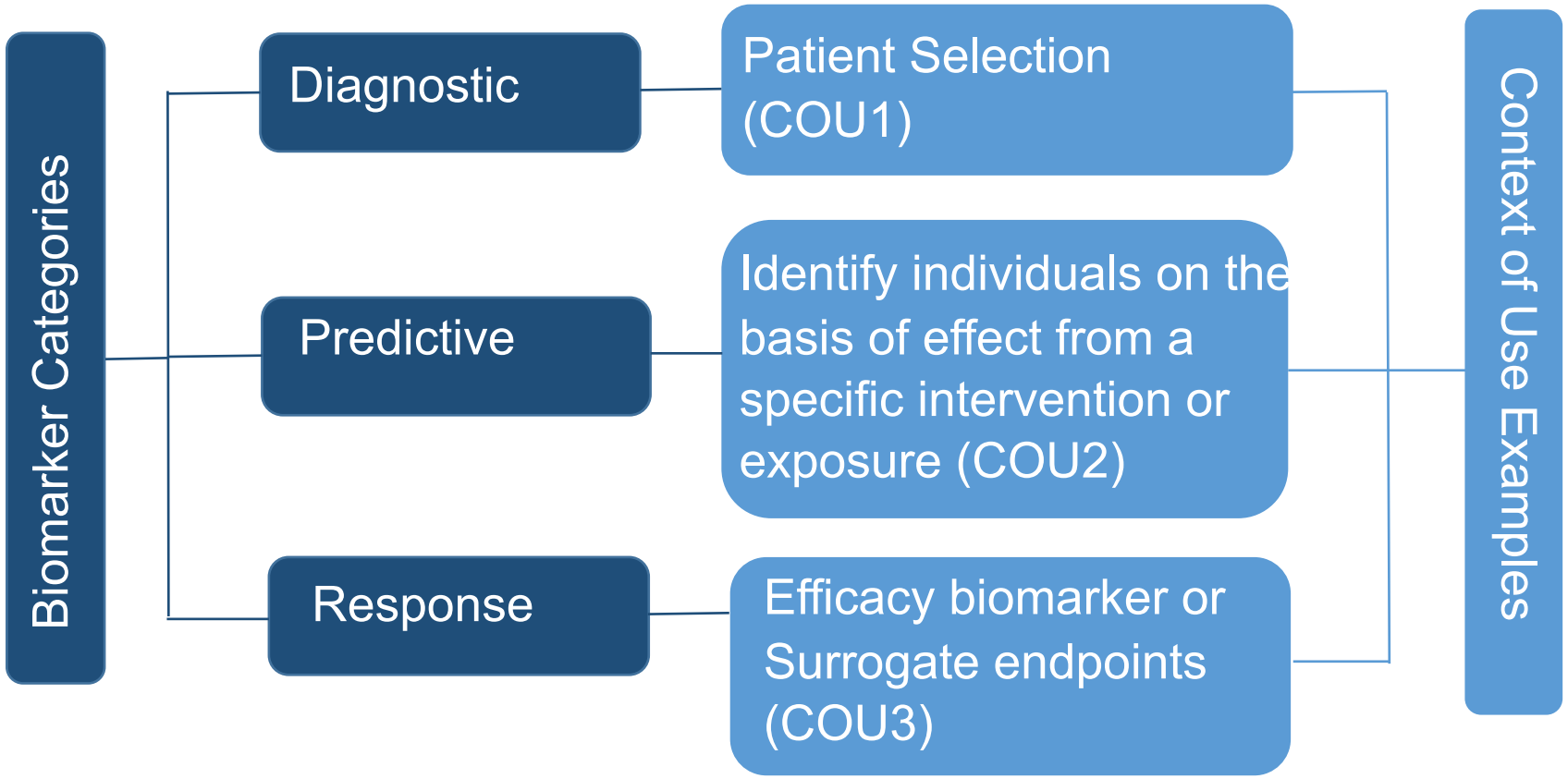
COU: Blood As Surrogate for CSF or PET

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

NO

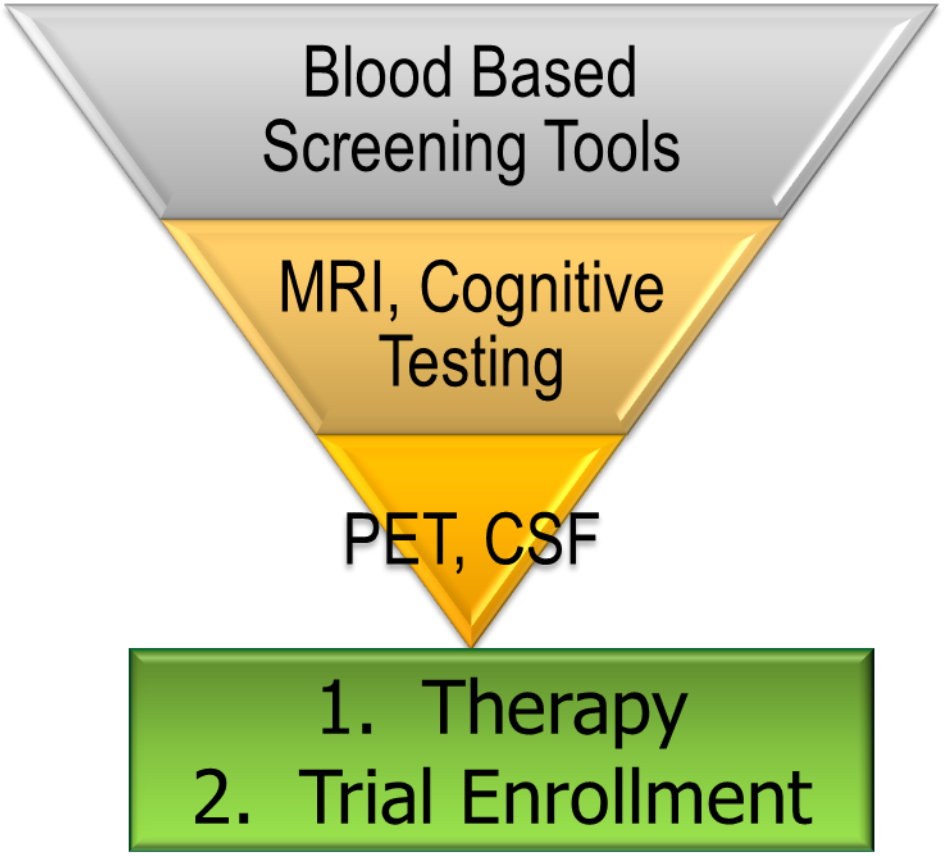
- See Morgan et al 2021 – Accuracy of Practitioner Estimates of Probability of Diagnosis Before and After Testing (pneumonia, cardiac ischemia, breast cancer, urinary tract infection)
- “practitioners overestimate the probability of disease before and after testing”… “widespread overestimates of the probability of disease likely contribute to overdiagnosis and overuse

FDA Overview of Biomarker Context of Use (COU) – Focusing the Questions



COU-1: Screening

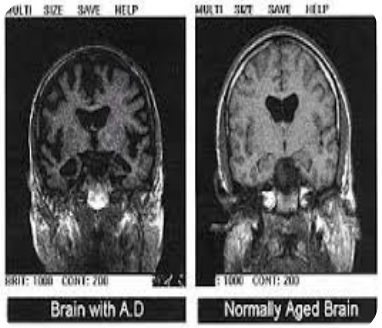
1. Screen for AD (MCI) within primary care settings.
2. Screen for amyloid positivity for enrollment into novel clinical trial.
3. Screen for amyloid negativity for enrollment for non-amyloid trial.



Detecting AD in Primary Care: Current state-of-the-art diagnosis

PCP Referral

Specialist Exam



Brain MRI

Blood Work

Memory Testing

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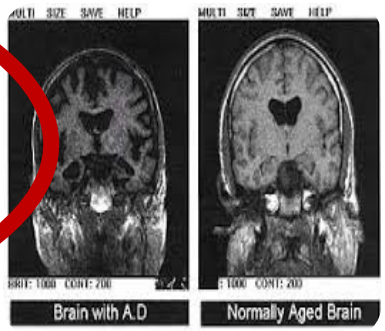
Current state-of-the-art diagnosis

PCP Referral

Specialist Exam



Brain MRI

Blood Work

Memory Testing

$$$$

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How is Alzheimer's disease diagnosed?

How to screen 40 million Americans?

Screen Positive?

Yes

No

Screen again next year

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How is Alzheimer's disease diagnosed?

How to screen 40 million Americans?

Screen Positive?

Yes

No

Screen again next year

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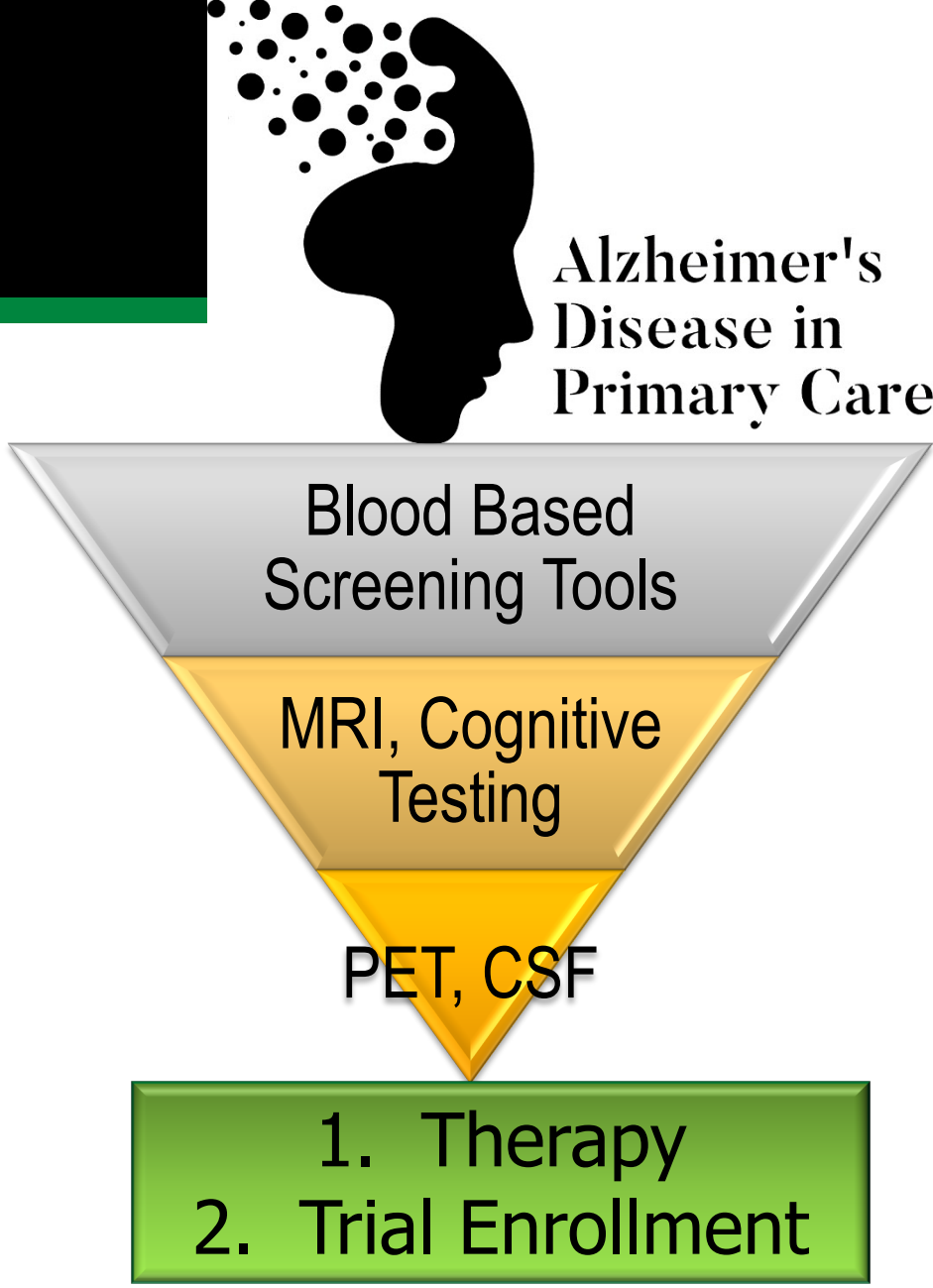
ADPC Study

- 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**



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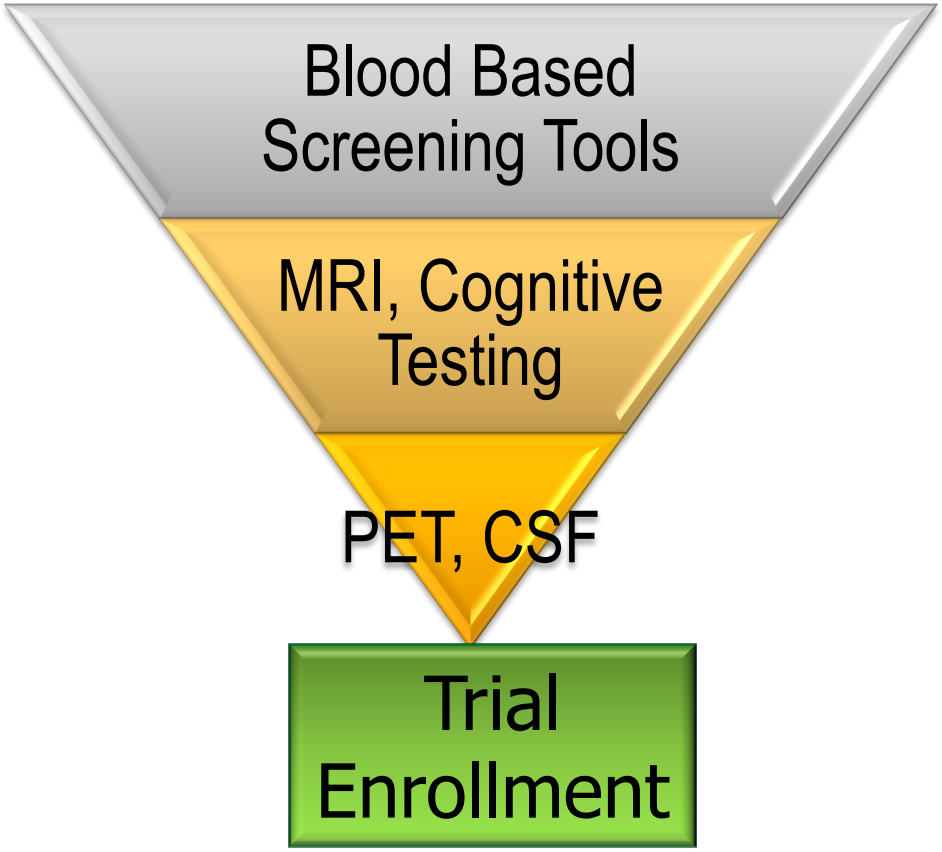
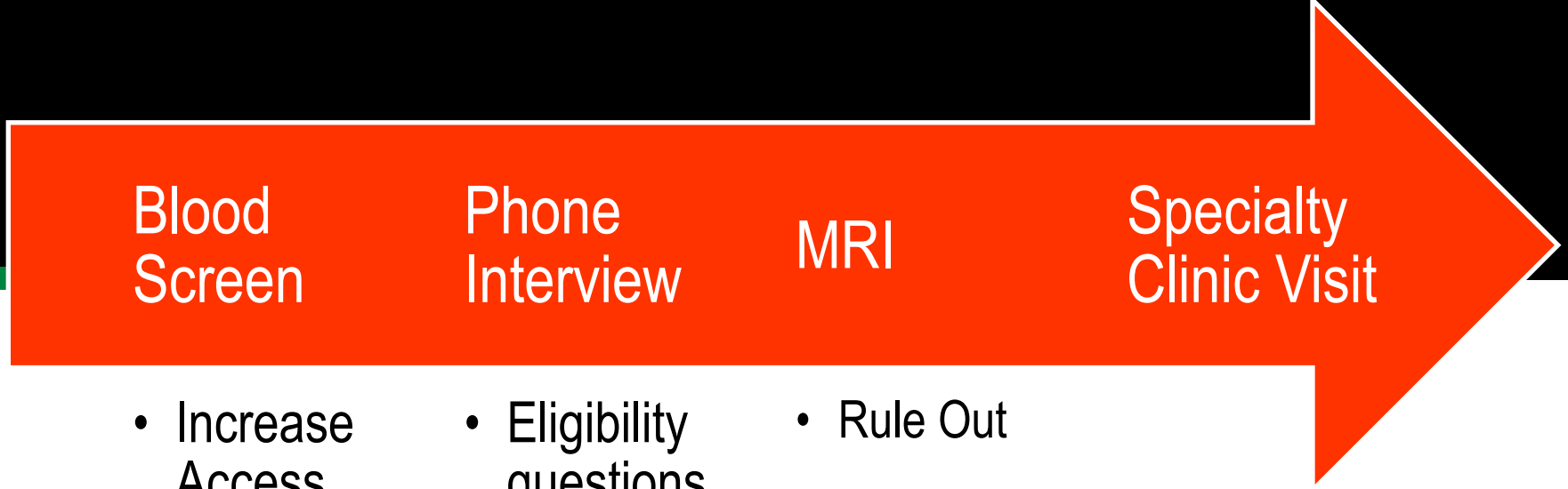
COU 2: Patient selection for Novel Trials



- 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



- Increase Access and Potential Patient Pool
- Rule OUT 70%

- Eligibility questions
- Rule OUT

- Rule Out

- **Can be implemented in primary care settings**
- **Can increase access to thousands of potential patients**
- **Increased access AND LOWER costs**

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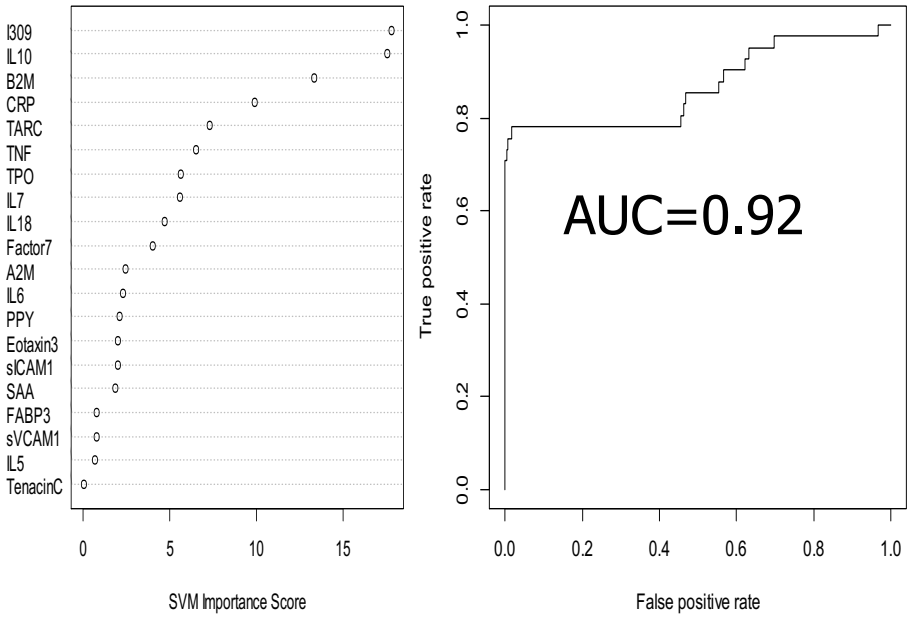
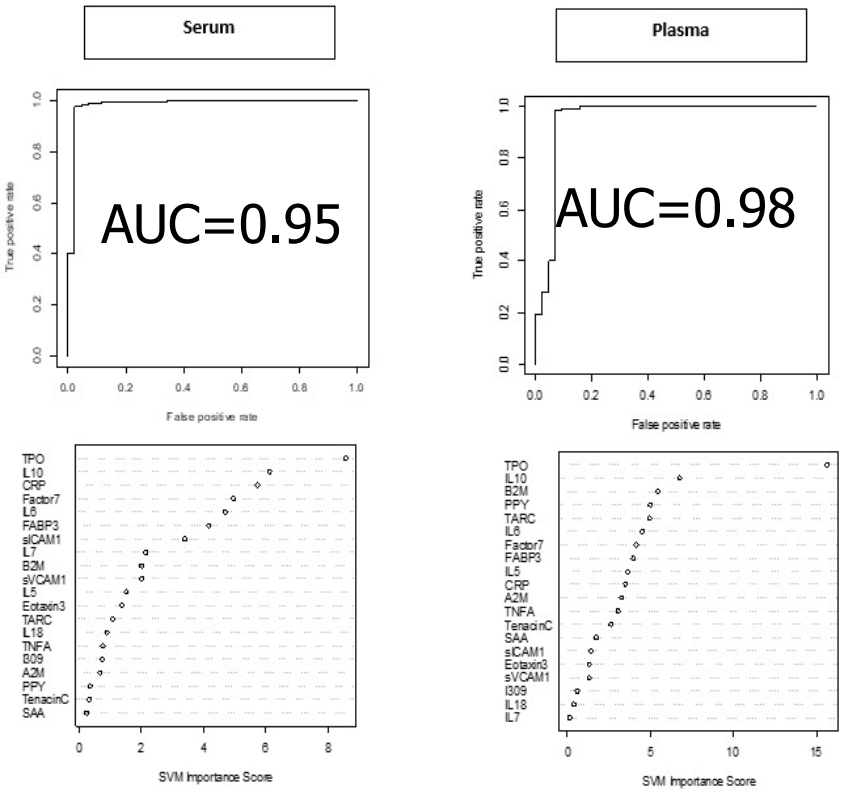
COU2: Trial Targeting AD among Adults with Down Syndrome

Detecting Prevalent MCI
N=398 adults with DS



ABC-DS AD – AUC=0.96

Detecting MCI in ABC-DS
N=336



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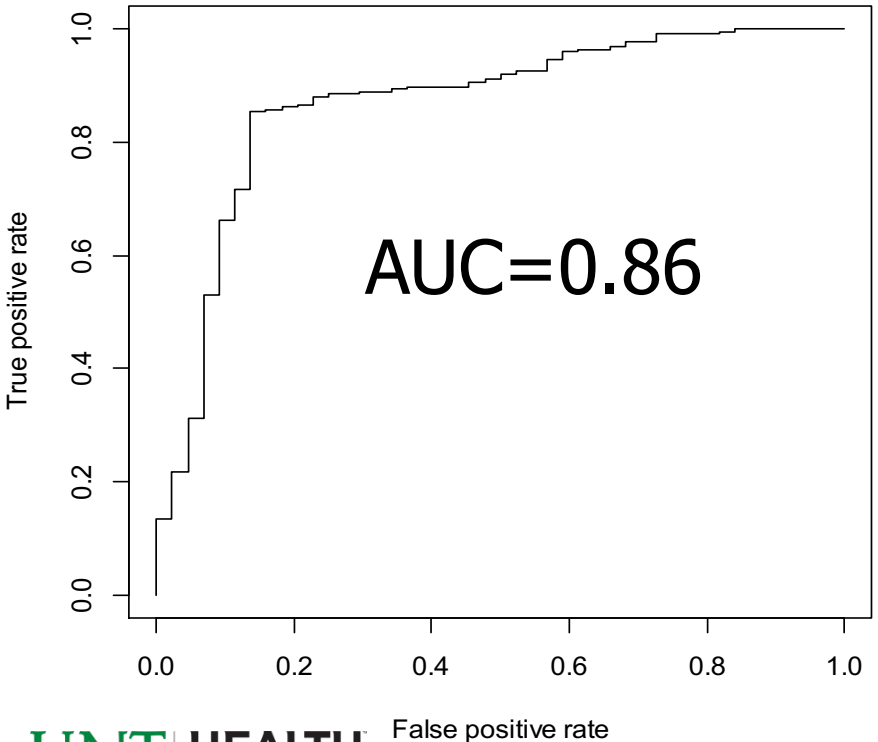
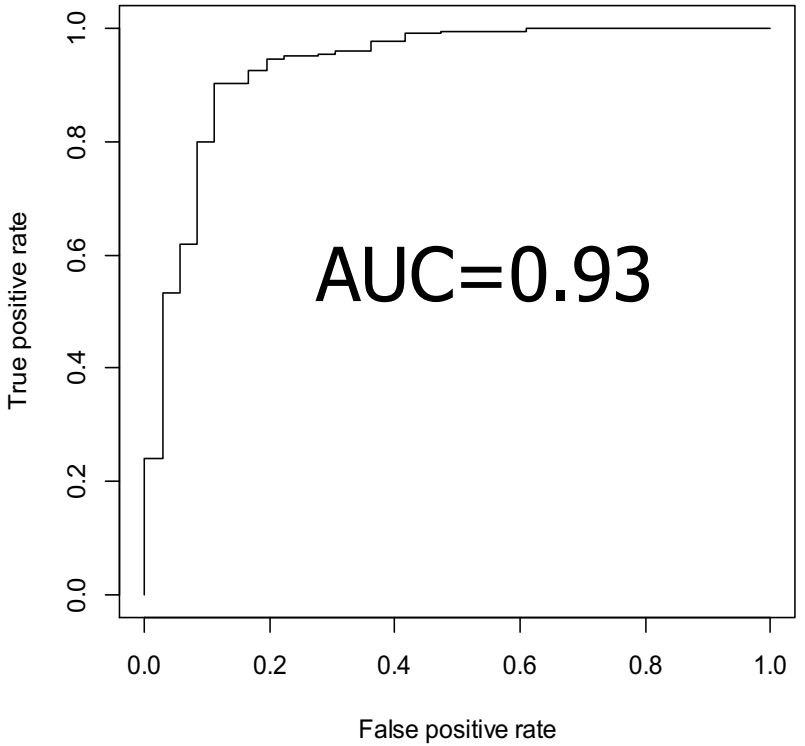
Petersen et al 2020; O'Bryant et al 2020; Petersen et al 2021

Plasma t-tau and NfL Only

MCI - Plasma tau and NfL with age and gender ABC-DS



AD - Plasma tau and NfL with age and gender ABC-DS



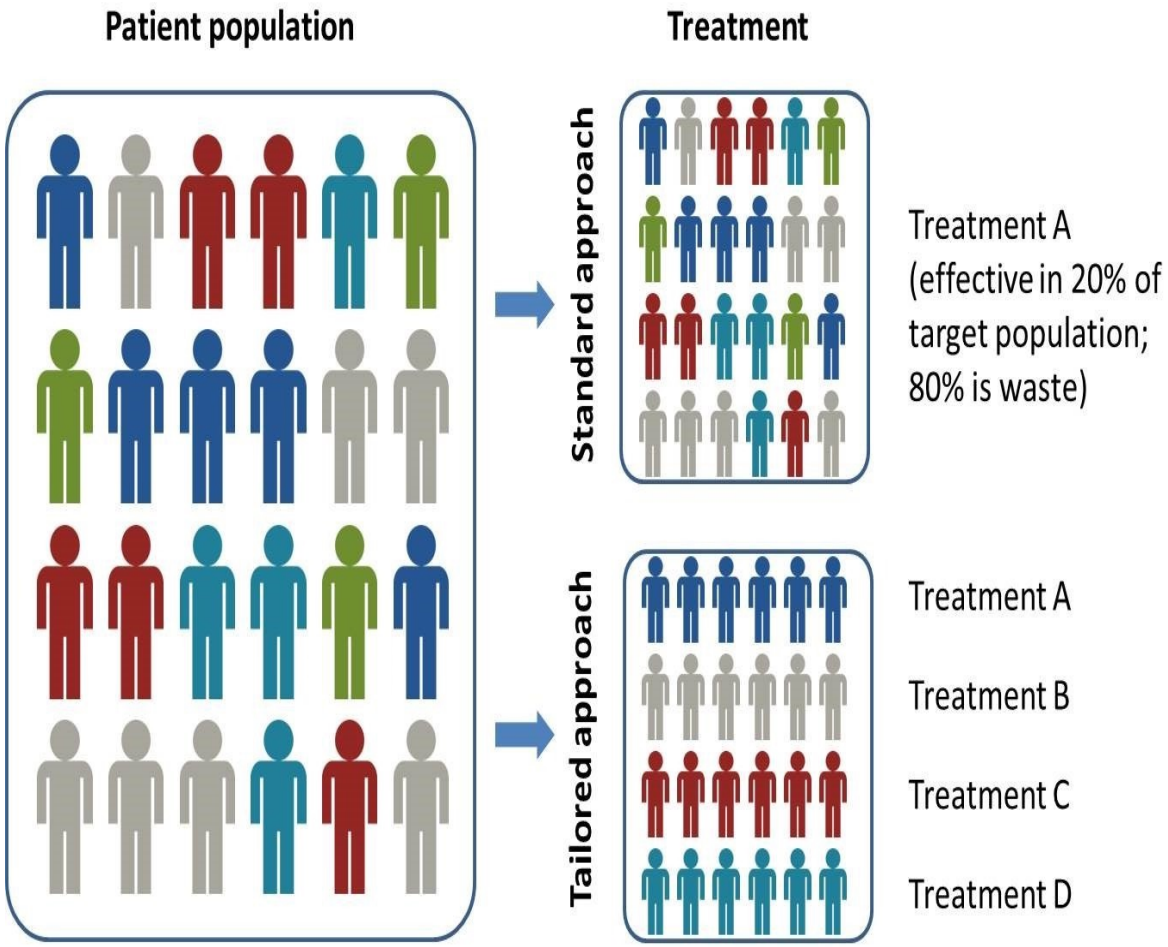
Putting data into practical example – using only tau and NfL with age and gender

- 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

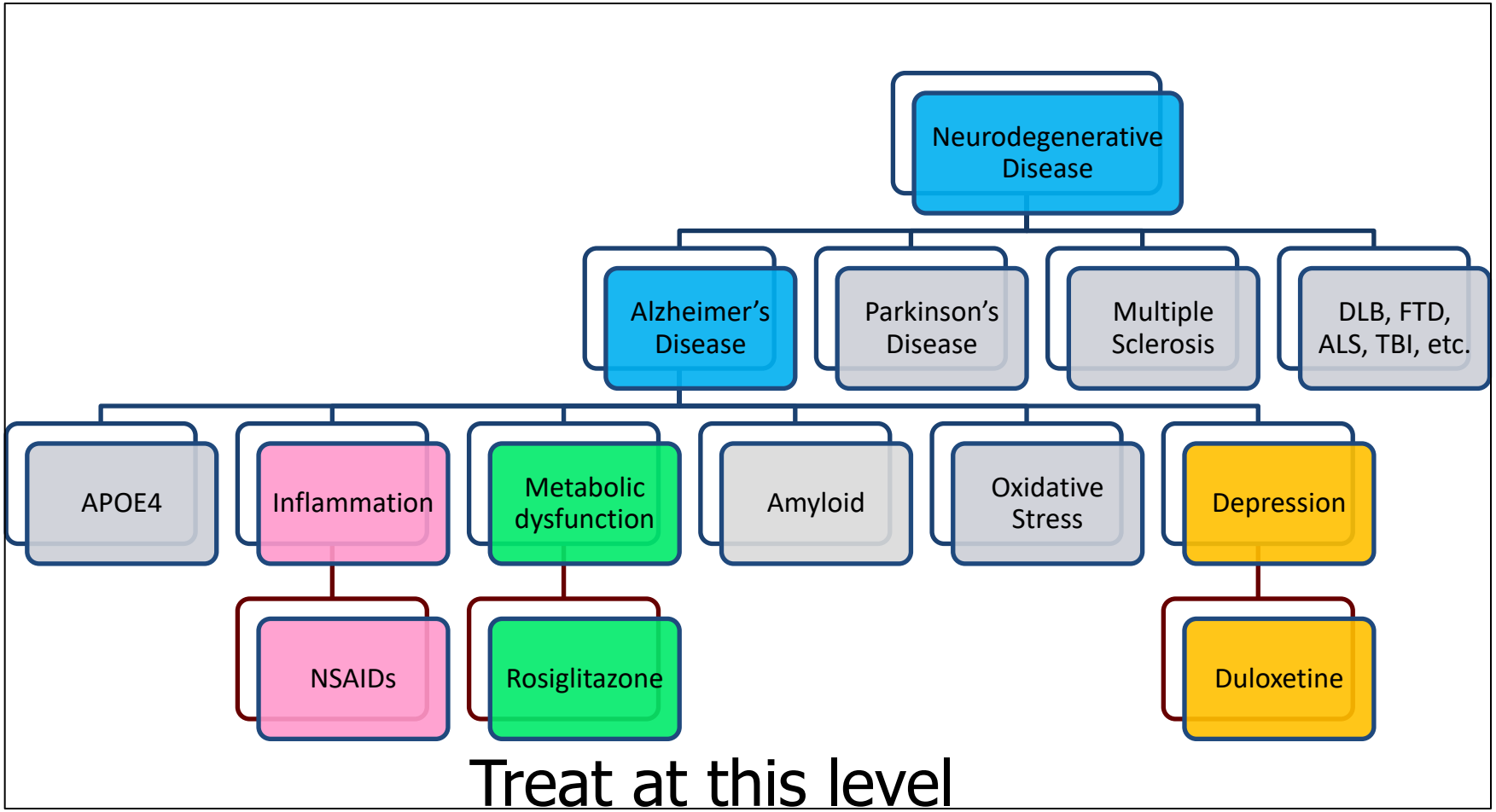
COU3: Predictive Biomarker

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

Think: cancer model



New Model



O'Bryant 2009, 2009, 2010, 2011, 2011, 2013; Johnson 2013, 2013; Cunningham 2014; Hall 2013, 2014

Targeted therapeutics

Journal of Alzheimer's Disease 66 (2018) 97–104
DOI 10.3233/JAD-180619
IOS Press

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

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

Table 1
Demographic characteristics of the sample cohort

	Naproxen ($n = 68$)	Rofecoxib ($n = 55$)
Age	74.0 (7.8)	73.8 (7.3)
Education	13.9 (3.2)	13.9 (3.2)
Gender (% female)	48%	54%
ApoE4 positive	71%	69%

Table 2
Treatment response prediction using proteomic profiling analyses

	SVM Predicted Decliner	SVM Predicted Non-Responder	SVM Predicted Responder
Total Sample (93% accurate)			
Actual Rapid Decliner	41	1	4
Actual Non-Responder	1	22	0
Actual Responder	7	1	46
Naproxen Arm (97% accurate)			
Actual Rapid Decliner	26	0	2
Actual Non-Responder	0	10	0
Actual Responder	0	0	30
Rofecoxib Arm (98% accurate)			
Actual Rapid Decliner	23	0	1
Actual Non-Responder	0	14	0
Actual Responder	0	0	17

Table 3
Inflammatory profile variable importance By NSAID

	NSAID-general	Naproxen	Rofecoxib
Marker Rank			
1	CRP	CRP	IL6
2	IL6	IL6	CRP
3	IL10	TNFα	IL10
4	TNFα	IL10	TNFα

Journal of Alzheimer's Disease 81 (2021) 557–568
DOI 10.3233/JAD-201610
IOS Press

A Precision Medicine Approach to Treating Alzheimer's Disease Using Rosiglitazone Therapy: A Biomarker Analysis of the REFLECT Trials

Sid E. O'Bryant[a,b,*], Fan Zhang[a,c], Melissa Petersen[a,c], Leigh Johnson[a,b], James Hall[a,b] and Robert A. Rissman[c,d]

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

	Actual	
Predicted	response	Nonresponse
response	170	4
nonresponse	3	183
Precision/PPV	97.70%	
Accuracy	98.06%	
Sensitivity	98.27%	
Specificity	97.86%	
NPV	98.39%	
AUC	99.10%	

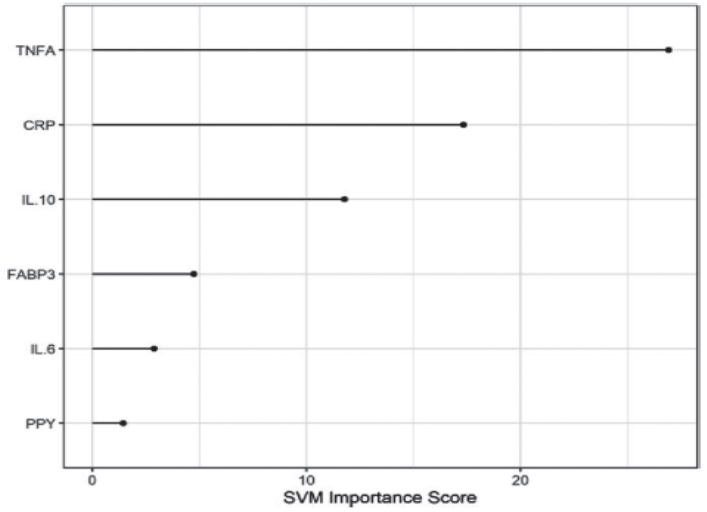
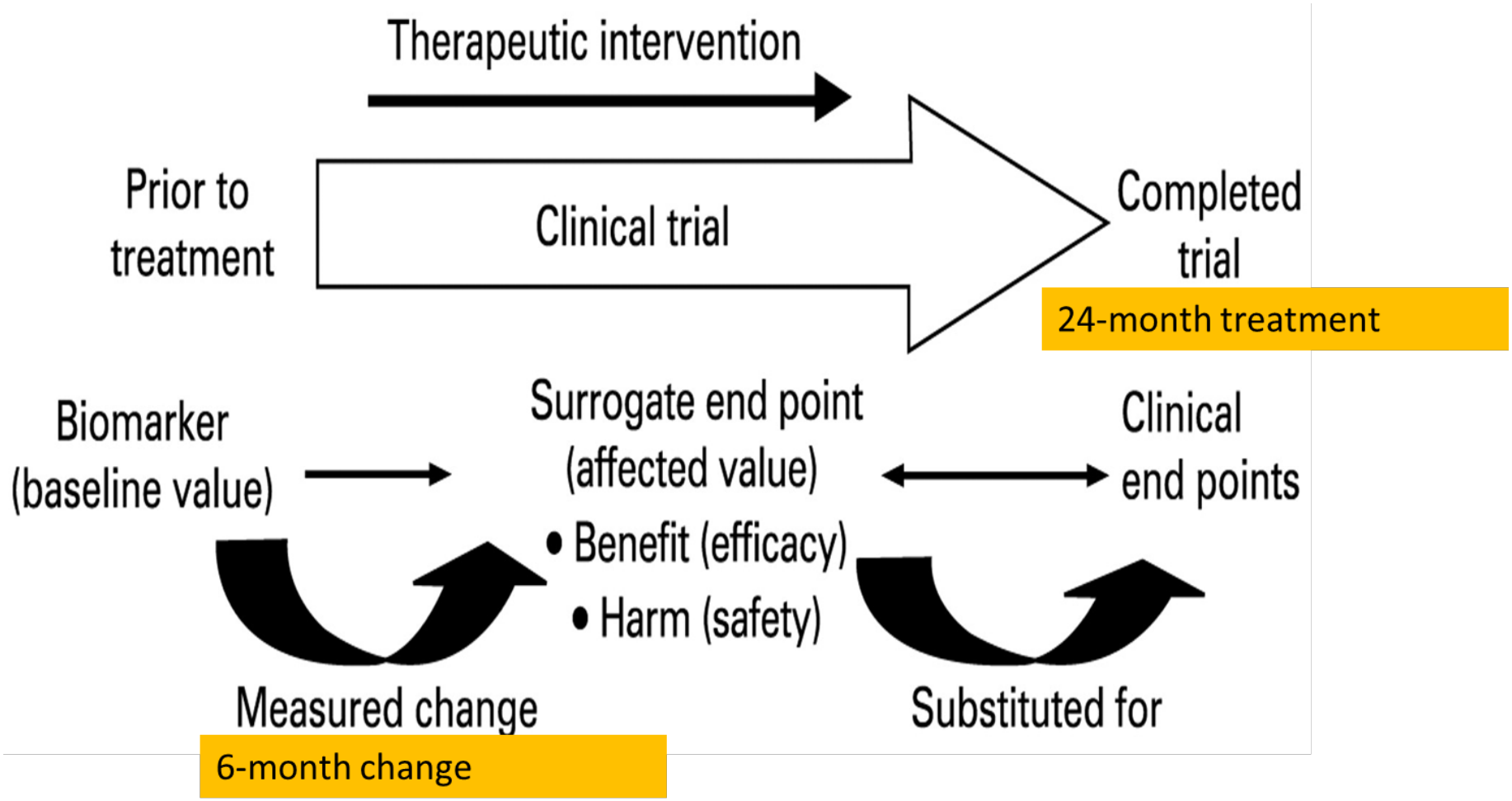


Fig. 7. Predictive accuracy in identifying responders versus non-responders dosages.

COU4: Surrogate endpoints



Summary

Questions?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