Critical Path Institute:
Coalition Against Major Diseases (CAMD)

Qualification at FDA and CHMP

IMI, Barcelona

Marc Cantillon, MD

Executive Director, CAMD, Critical Path Institute

C-Path & FDA MOU
October 14, 2005

amendments thereto, is hereby

ORLISTAT (tetrahydrolipstatin)

Memorandum of Understanding Between the United States Food and Drug Administration and the C–Path Institute

AGENCY: Food and Drug Administration, HHS.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[FDA 225–05–8000]

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AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

"purpose… to establish an overarching framework for collaboration… to foster development of new evaluation tools to inform medical product development"

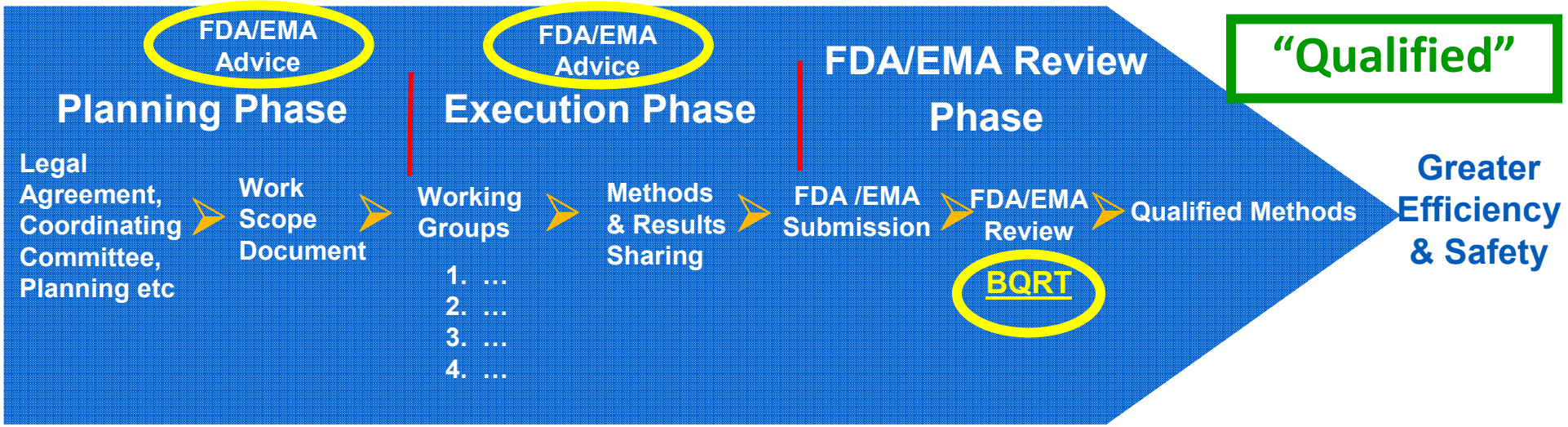
Vision

Independent and Trusted Third Party

- Public & foundation funding of infrastructure
  - No funding from regulated companies
- Federal Grants – Critical Path Public/Pvt Partnerships
- Philanthropy
- Transparency
- FDA, EMA and PMDA participation

Qualification of New Testing Methods

A **new** pathway…..



Scientific Consensus → FDA EMA

Creating New Regulatory Science

Predictive Safety Testing Consortium (PSTC)

DRUG SAFETY

Patient-Reported Outcome (PRO) Consortium

DRUG EFFICACY

Coalition Against Major Diseases (CAMD)

UNDERSTANDING DISEASE

Polycystic Kidney Disease Consortium (PKD)

IMAGING BIOMARKERS

Critical Path to TB Drug Regimens (CPTR)

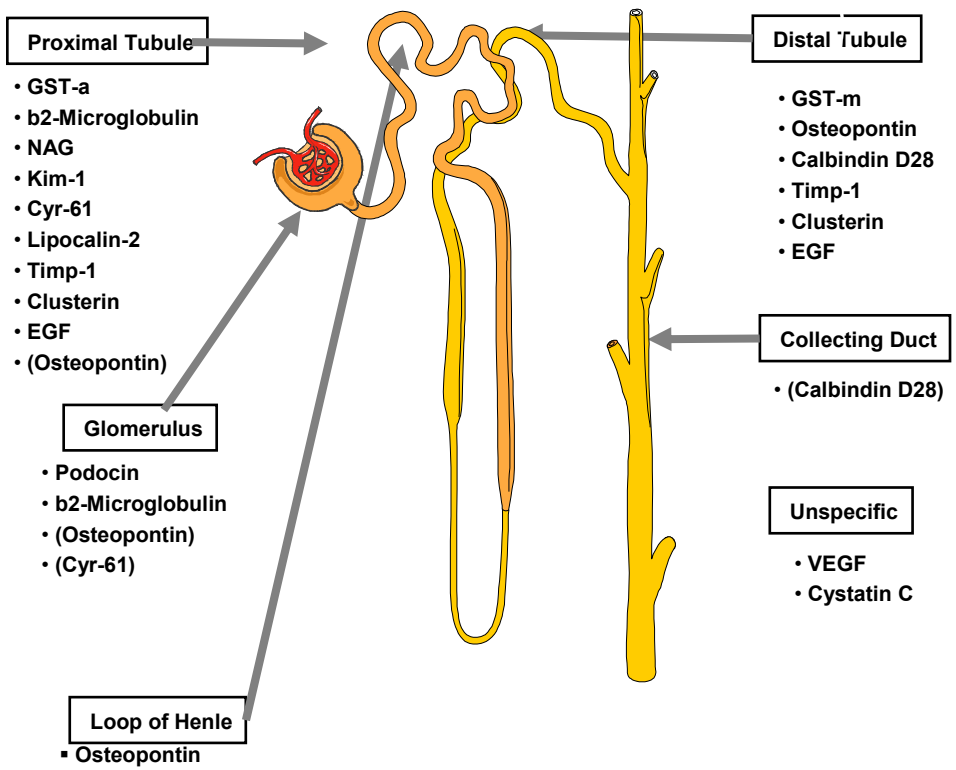
COMBINATION DEVELOPMENT PARADIGM

Type of Biomarker

- Safety
  - Kidney earlier than BUN /creatinine
- Predictive & Prognostic for decision making
  - Safety monitoring
  - Go/No Go
    - at nomination-intermediate-confirmatory stage
    - Phase I in normals
    - Phase 2/3 in patients

Ideal features of biomarkers to detect Kidney Injury

- Identifies injury early
- Reflects degree of toxicity
- Similar reliability across multiple species, including humans
- Localizes site of injury
- Tracks progression of injury and recovery
- Well-characterized with respect to limitations
- Accessible in readily available body fluids/tissues



Bonventre J et al. Nature Biotech 2010. 28:5; 436-440

Nephrotoxicity Biomarkers: Injury Location & Assay

Biomarker	Proximal Tubules	Distal Tubules	Glomerulus	Injury Response Markers	Leakage Markers	Functional Biomarkers
Osteopontin	X	X		X		
Serum & Urine Clusterin	X	X		X		
NGAL	X	X		X		
Serum & Urine Cystatin C	X	X				X
Urine Total Protein		X	X			X
GST-π					X	
β-2 Microglobulin	X		X	X		X
GST-α	X				X	
Interleukin-18	X					
Liver FABP	X					
Retinol Binding Protein 4	X					X
Urine KIM-1	X			X		
Urine NAG	X				X	
Osteoactivin				X		
Trefoil Factor 3	X			X		
Urine Creatinine	X					X
Urine Microalbumin	X					X

Injury location based on: Bonventre, J.V., et al. *Nat Biotech* **28**, 436-440 (2010).

Biomarker	Distal Tubules	Proximal Tubule	Glomerulus	Collecting Duct	Functional Biomarkers
Calbindin	X			X	
GST-π	X				
Urine Total Protein			X		
α-1 Microglobulin			X		
γ-Glutamyl Transferase					X
CXCL-10					X
Hepatocyte Growth Factor		X			
Osteoactivin					X
Serum urea nitrogen					X
Tamm-Horsfall Protein or Uromodulin					X
TIMP-1					X
VEGF					X

Biomarker Prioritization:
Green: tier 1 Blue: tier 2 Red: tier 3

Summary of "Fit for Purpose" Claims and Decisions

Urinary Biomarker	Rat Kidney Pathologies			Clinical
	Can Outperform BUN & Serum Cr	Monitor Glomerular Pathology	Monitor Tubular Pathologies (Necr., Degen., Dilatat'n, Regen.)	Supporting Published Evidence
Cystatin C	✓	✓		✓
β2-Microglobulin	✓	✓		✓
Total Protein	✓	✓		✓
KIM-1	✓		✓	✓
Albumin	✓		✓	✓
Clusterin	✓		✓	
Trefoil Factor 3	✓		✓	

Predictive Safety Testing Consortium (PSTC)

U.S. Food and Drug Administration

U.S. Department of Health and Human Services

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FDA News

FOR IMMEDIATE RELEASE
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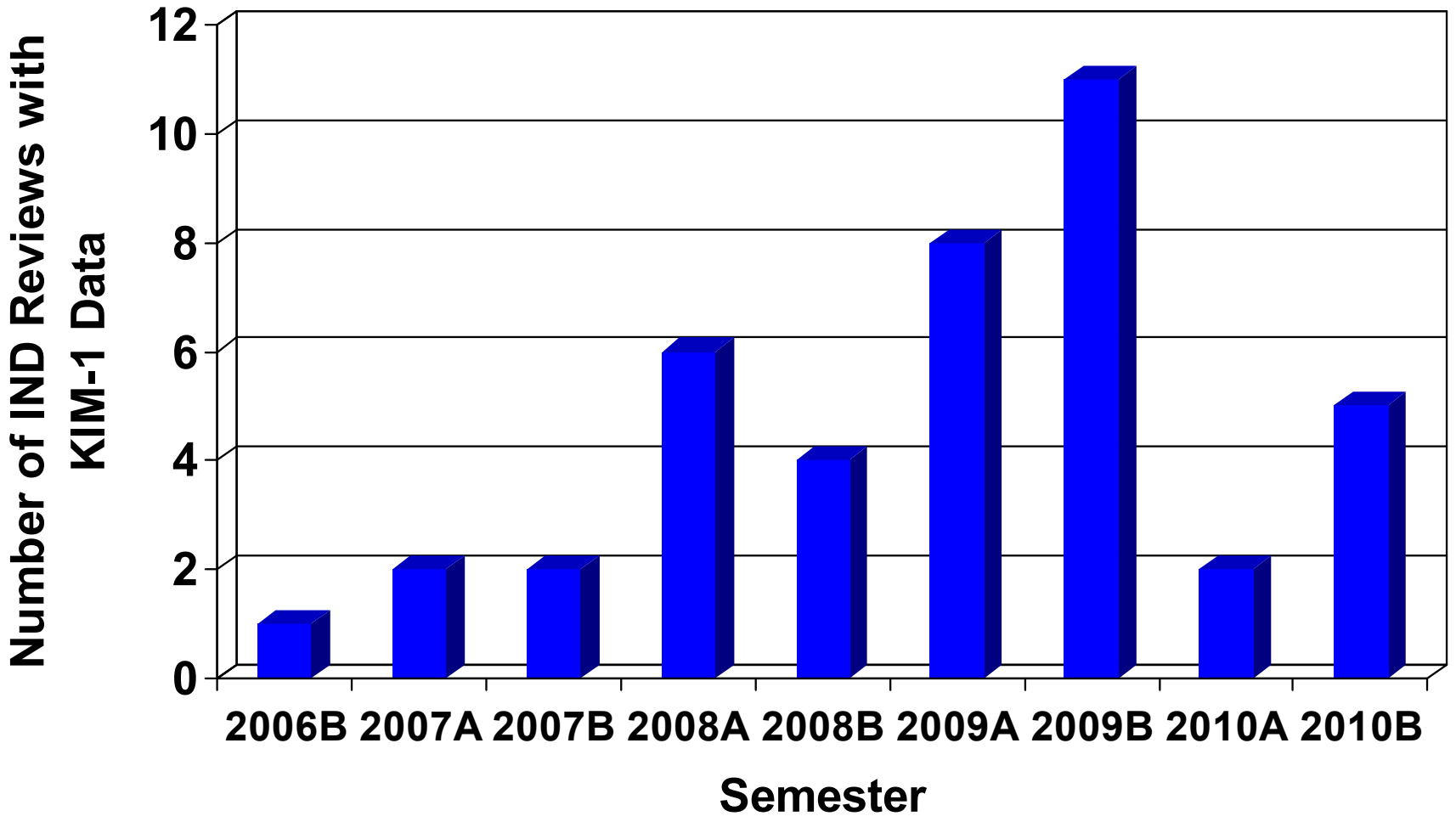
FDA and the Critical Path Institute Announce Predictive Safety Testing Consortium

Consortium Will Share Tests to Understand Safety of Potential New Drugs Earlier

The Food and Drug Administration (FDA) and The Critical Path Institute (C-Path) today announced the formation of the Predictive Safety Testing Consortium between C-Path and five of America's largest pharmaceutical companies to share internally developed laboratory methods to predict the safety of new treatments before they are tested in humans. The FDA, while not a member of the Partnership, will assist it in an advisory capacity. This unprecedented sharing of potential early indicators of clinical safety may streamline the cost and time of preclinical drug safety evaluation and better inform the use of "personalized medicine". The Consortium was announced today at a press conference detailing the release of the Critical Path Opportunities List -- 76 initial research priorities that, if accomplished, will modernize the drug development process by 2010 and help get new medical discoveries to Americans faster and at a lower cost.

IND Reviews with KIM-1 Data



3 Critical Questions

1. **WHEN is a new biomarker ready for use?**

2. **WHEN should it be used – under what conditions, and for what specific purpose?**

3. **WHEN does a change constitute a real signal that warrants interrupting dosing?**

Objectives

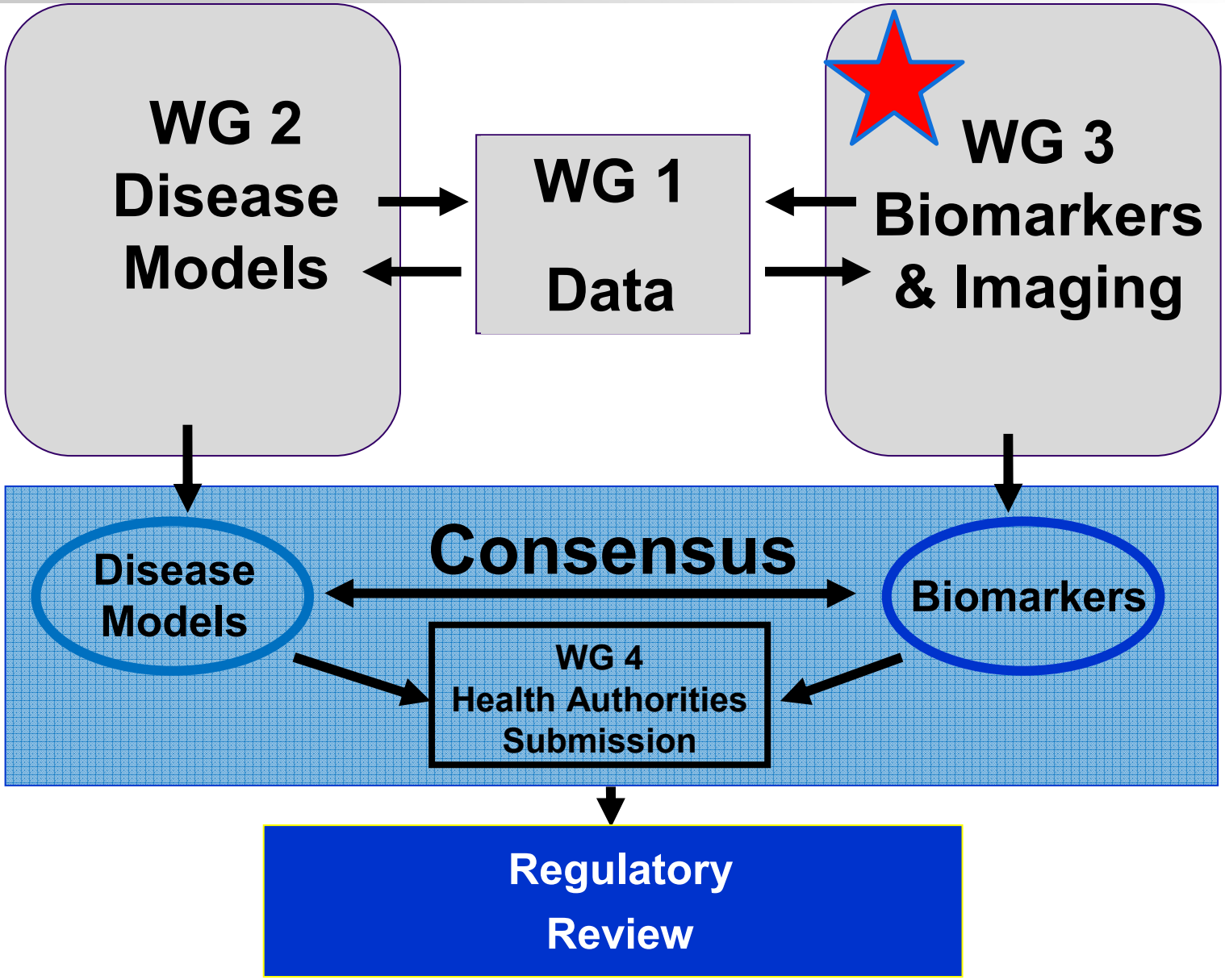
Develop a scientific consensus on which methods are "qualified for use" in drug development among……

1) those who will **use the methods** (industry),

AND

2) those who will **accept the methods** (RA).

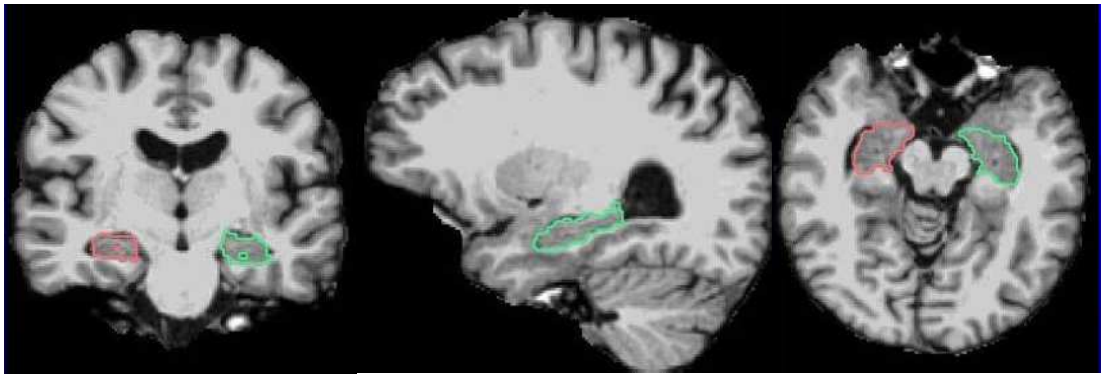
Workgroup Workflow



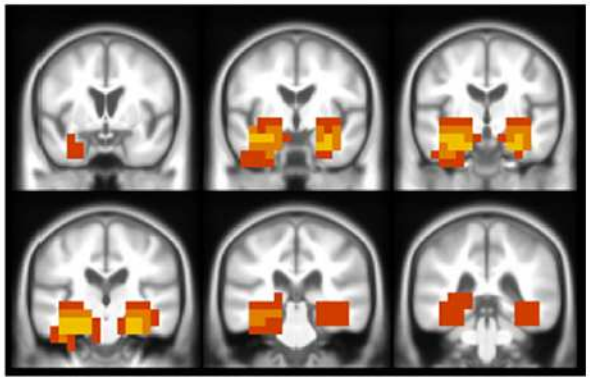
Advantages of predictive biomarker in AD, PD

- Early Identification allows early intervention
  - Identifies before dementia stage in AD
  - Identifies before full motor spectrum in PD
- Diagnostic Specificity: Increased likelihood of successful intervention
- Progression to AD dementia or full PD (or study endpoint) within a reasonable time
- Shorter studies with smaller sample size
- More uniform patient populations

Hippocampal Atrophy as Predictor of MCI Progression to AD

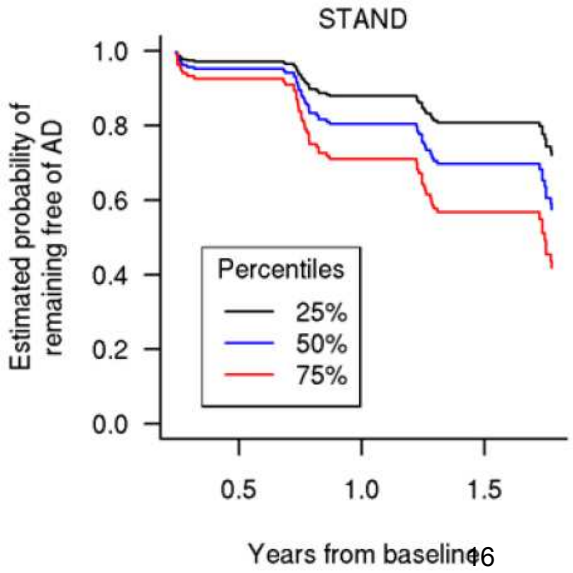


Figures from Norbert Schuff and Mike Weiner: SF VA and UCSF



STructural **A**bnormality i**ND**ex (STAND)-score
Colored regions indicate regions with maximum descriminatory power

	STAND
AUROC	0.90
Threshold*	0.25
Sensitivity (%)	71
Specificity (%)	95
Test accuracy (%)	84
Positive predictive value (%)	93
Negative predictive value (%)	79
Likelihood ratio	15.6



- STAND score shows high test accuracy in differentiating AD from Controls
- Those with highest STAND scores show lowest probability of remaining dementia free.

Data from Vemuri (2009) Neurology 73:287 and from ADNI Seattle 2009

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