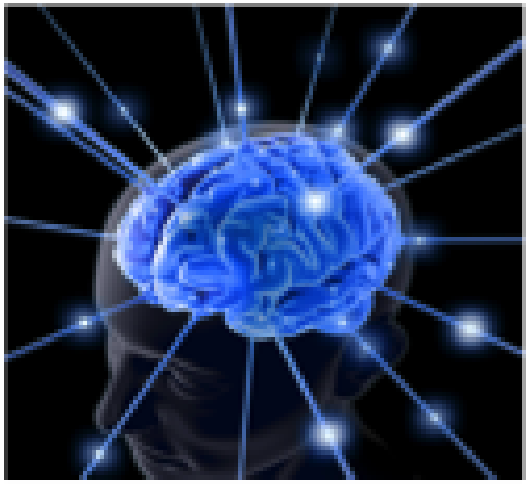


# TBI Endpoints Development

*A Collaborative for Advancing Diagnosis and Treatment of TBI*

## Consensus Conference 1

**TED Contact Principal Investigator | Geoffrey T. Manley, MD PhD**

Geoff Manley is Professor and Vice Chairman of Neurological Surgery at the University of California, San Francisco, and the Contact PI for the TED Initiative, as well as TRACK-TBI. He is an internationally recognized expert in neurotrauma, with a wide range of research interests from molecular aspects of brain injury to the clinical care of head trauma patients. He has helped to define new molecular mechanisms of injury to the nervous system that may lead to treatments for these devastating injuries. He is also considered a leader in the rapidly growing field of advanced neuromonitoring and clinical informatics for critical care.

# Welcome

Government Partners

Philanthropic Partners

Private Partners

Academic Partners

# Groundhog Day

# Traumatic Brain Injury: 2015

Classification

**GCS**

(Glasgow Coma Scale)

*Severe*

*Mild*

*Concussion*

Outcome

**GOS**

(Glasgow Outcome Scale)

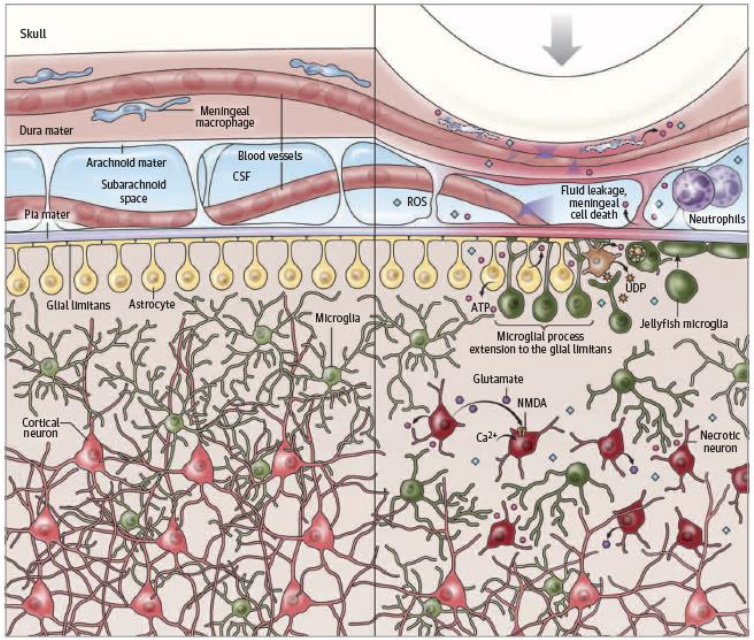
*Vegetative*

*Death*

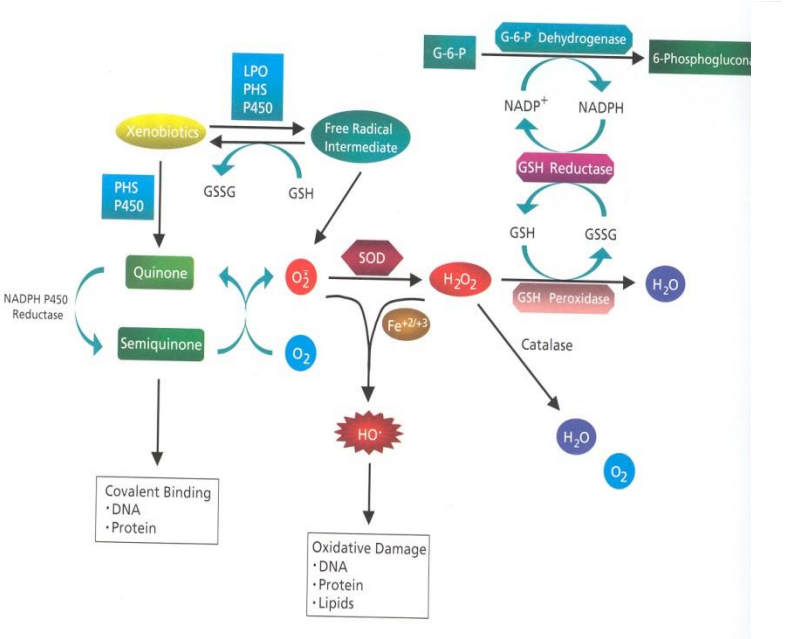
*Good Recovery*

***A Complex and Heterogeneous Disease***

# Cellular and Molecular Mechanisms




Inflammation and Neuroprotection




SOD Pathway

The NEW ENGLAND JOURNAL of MEDICINE



ORIGINAL ARTICLE

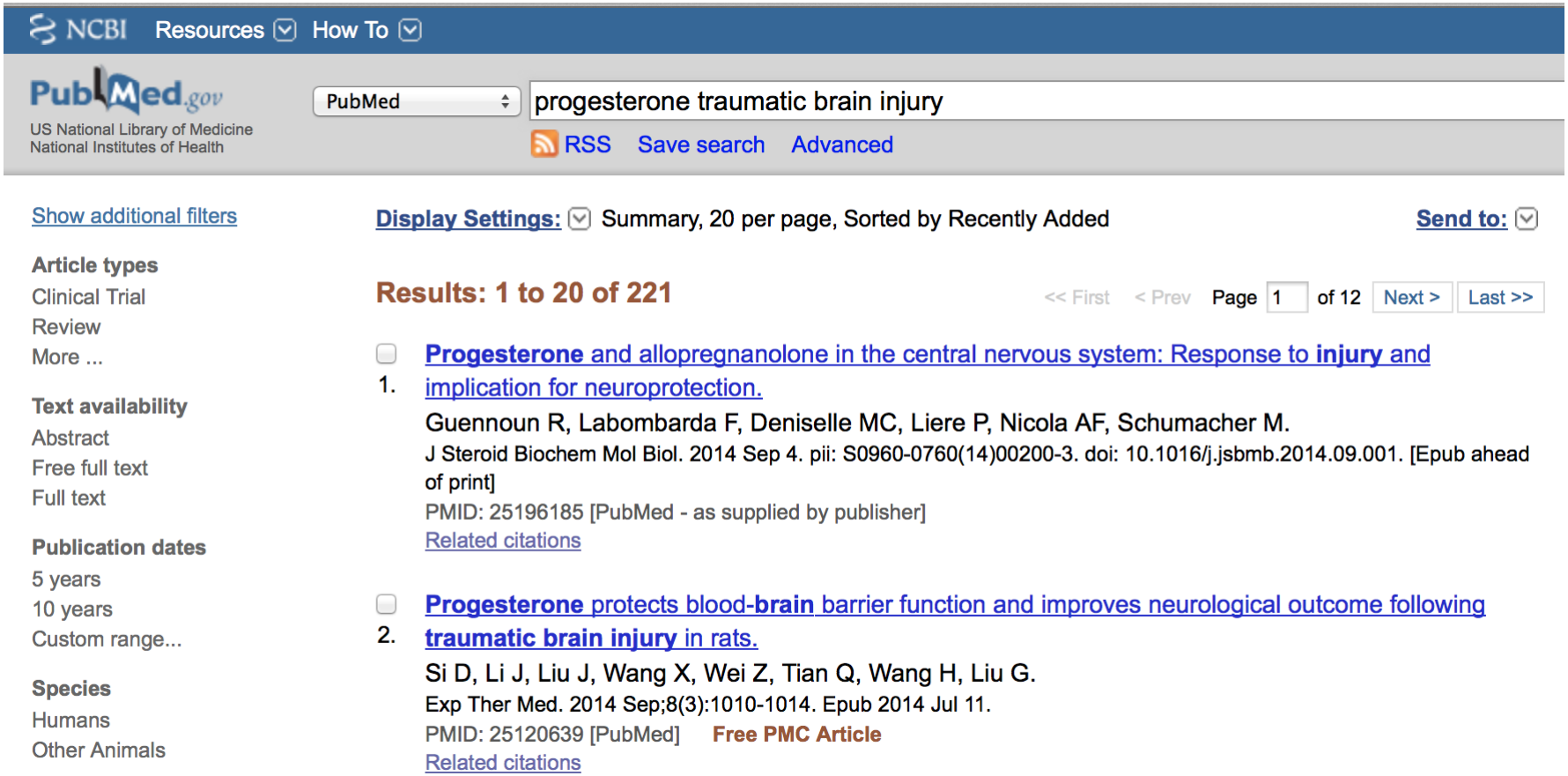
# Very Early Administration of Progesterone for Acute Traumatic Brain Injury

David W. Wright, M.D., Sharon D. Yeatts, Ph.D., Robert Silbergleit, M.D., Yuko Y. Palesch, Ph.D., Vicki S. Hertzberg, Ph.D., Michael Frankel, M.D., Felicia C. Goldstein, Ph.D., Angela F. Caveney, Ph.D., Harriet Howlett-Smith, R.N., Erin M. Bengelink, M.A., Geoffrey T. Manley, M.D., Ph.D., Lisa H. Merck, M.D., M.P.H., L. Scott Janis, Ph.D., and William G. Barsan, M.D. for the NETT Investigators

N Engl J Med 2014; 371:2457-2466 | December 25, 2014 | DOI: 10.1056/NEJMoa1404304

Should we be surprised at the results of the the ProTECT trial ?

# Preclinical Data for Progesterone

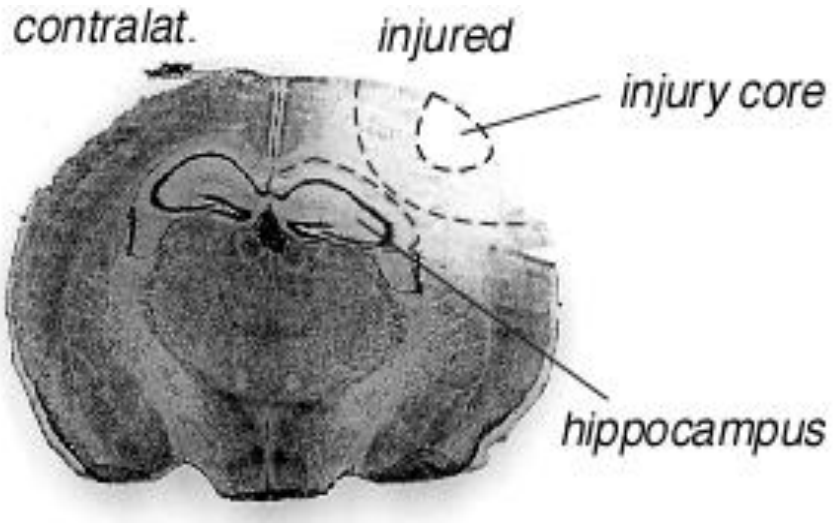



Over 200 studies – *no primate studies*

# Study Execution

# Study Subjects

## Rodent

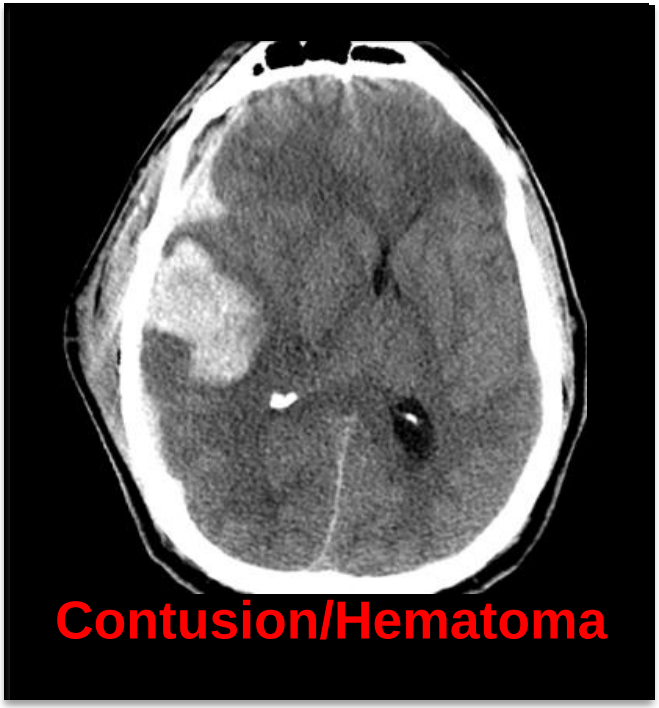



25-30 gm littermates

3 mm anterior to bregma
5 mm tip, 2.25 m/s

Depth 2.5 mm

## Human

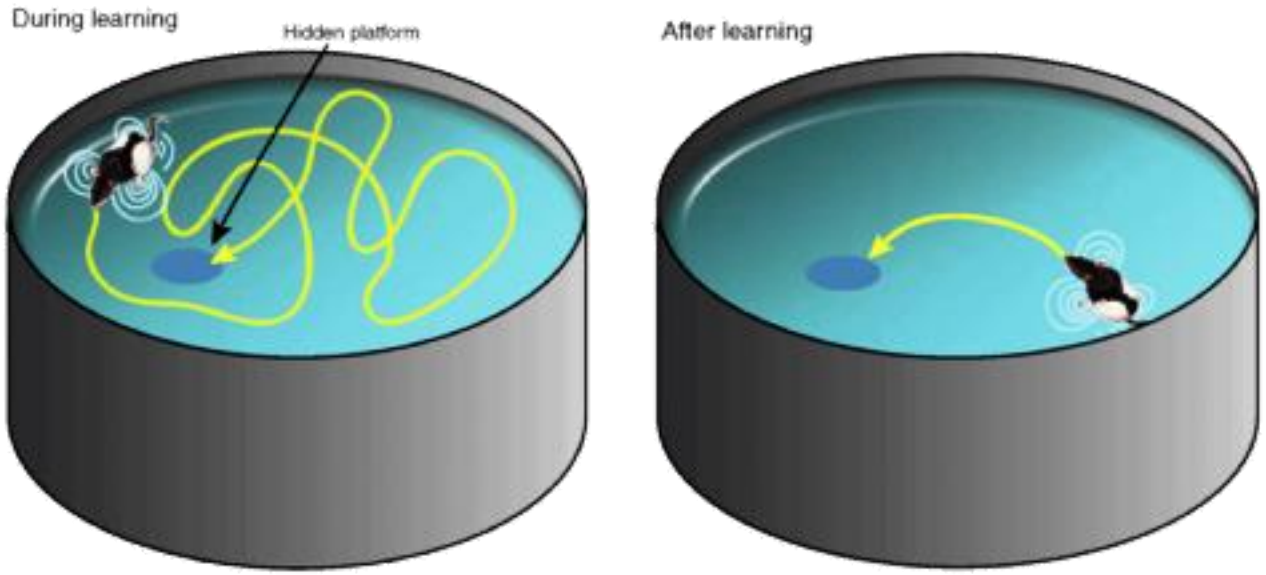



17 – 94 years old

**GCS 4 - 12**

# Outcome Assessment

## Rodent

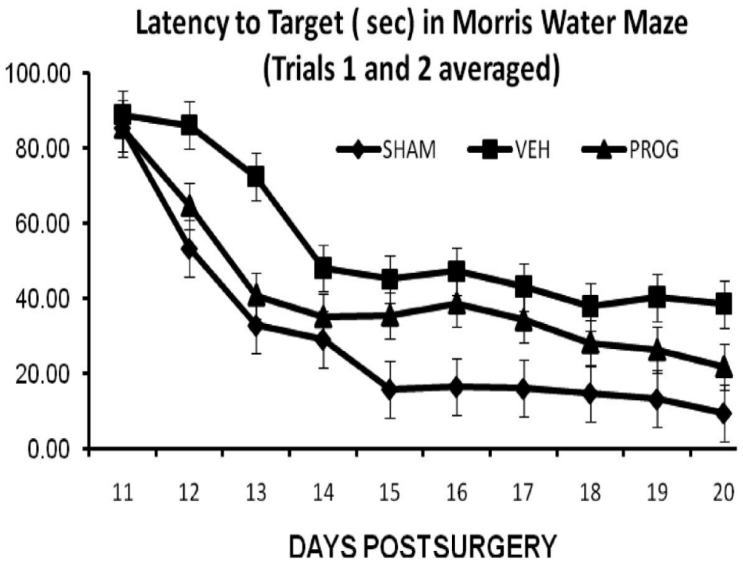



## Morris Water Maze

*A test of memory and learning*

# Outcome Assessment

## Rodent




Morris Water Maze

## Human

| | |
|---|---|
| 1 = Dead | |
| 2 = Vegetative State | Condition of unawareness with only reflex responses but with periods of spontaneous eye opening. |
| 3 = Low Severe Disability<br><br>4 = Upper Severe Disability | Patient who is dependent for daily support for mental or physical disability, usually a combination of both. If the patient can be left alone for more than 8h at home it is upper level of SD, if not then it is low level of SD. |
| 5 = Low Moderate Disability<br><br>6 = Upper Moderate Disability | Patients have some disability such as aphasia, hemiparesis or epilepsy and/or deficits of memory or personality but are able to look after themselves. They are independent at home but dependent outside. If they are able to return to work even with special arrangement it is upper level of MD, if not then it is low level of MD. |
| 7 = Low Good Recovery<br><br>8 = Upper Good Recovery | Resumption of normal life with the capacity to work even if pre-injury status has not been achieved. Some patients have minor neurological or psychological deficits. If these deficits are not disabling then it is upper level of GR, if disabling then it is lower level of GR. |

**GOS-E**

at 6 months

# Outcome Assessment: GOS-E

**Independence outside home:**

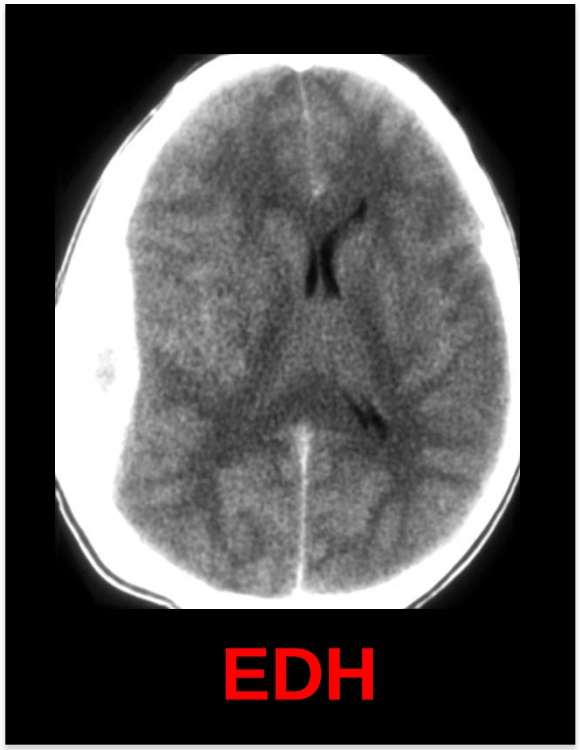
3a. Are they able to shop without assistance?

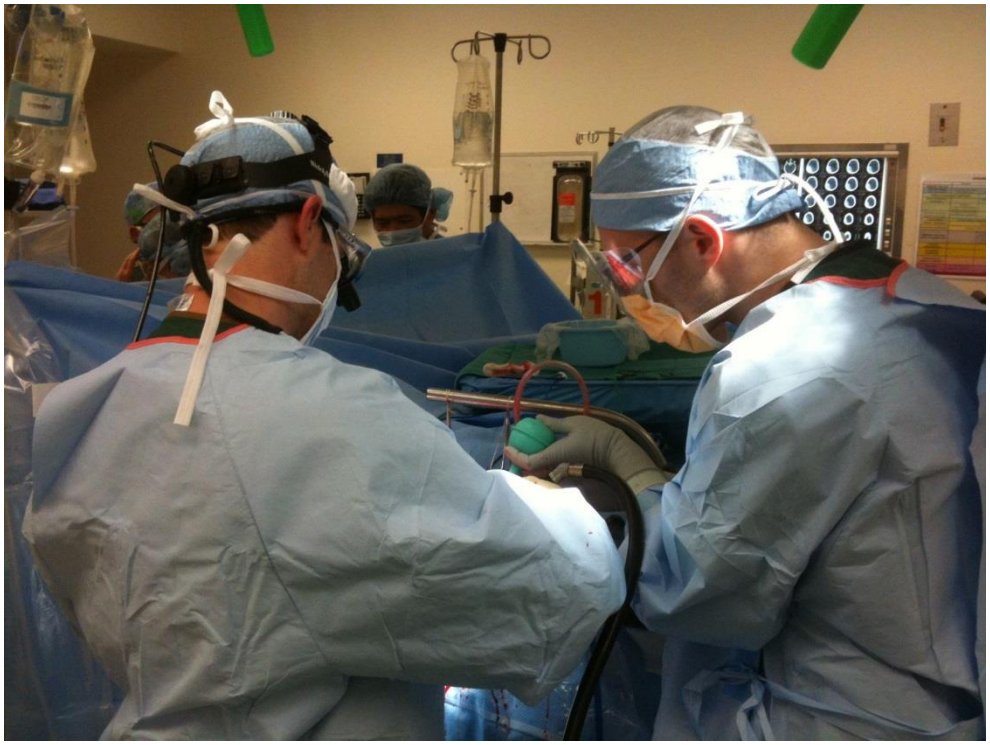
◯ Yes ◯ No (upper SD)

Note: this includes being able to plan what to buy, take care of money themselves and behave appropriately in public. They need not normally shop, but must be able to do so.

Disability Score – *not brain specific*

# The End or a New Beginning ?



Accurate
Diagnosis

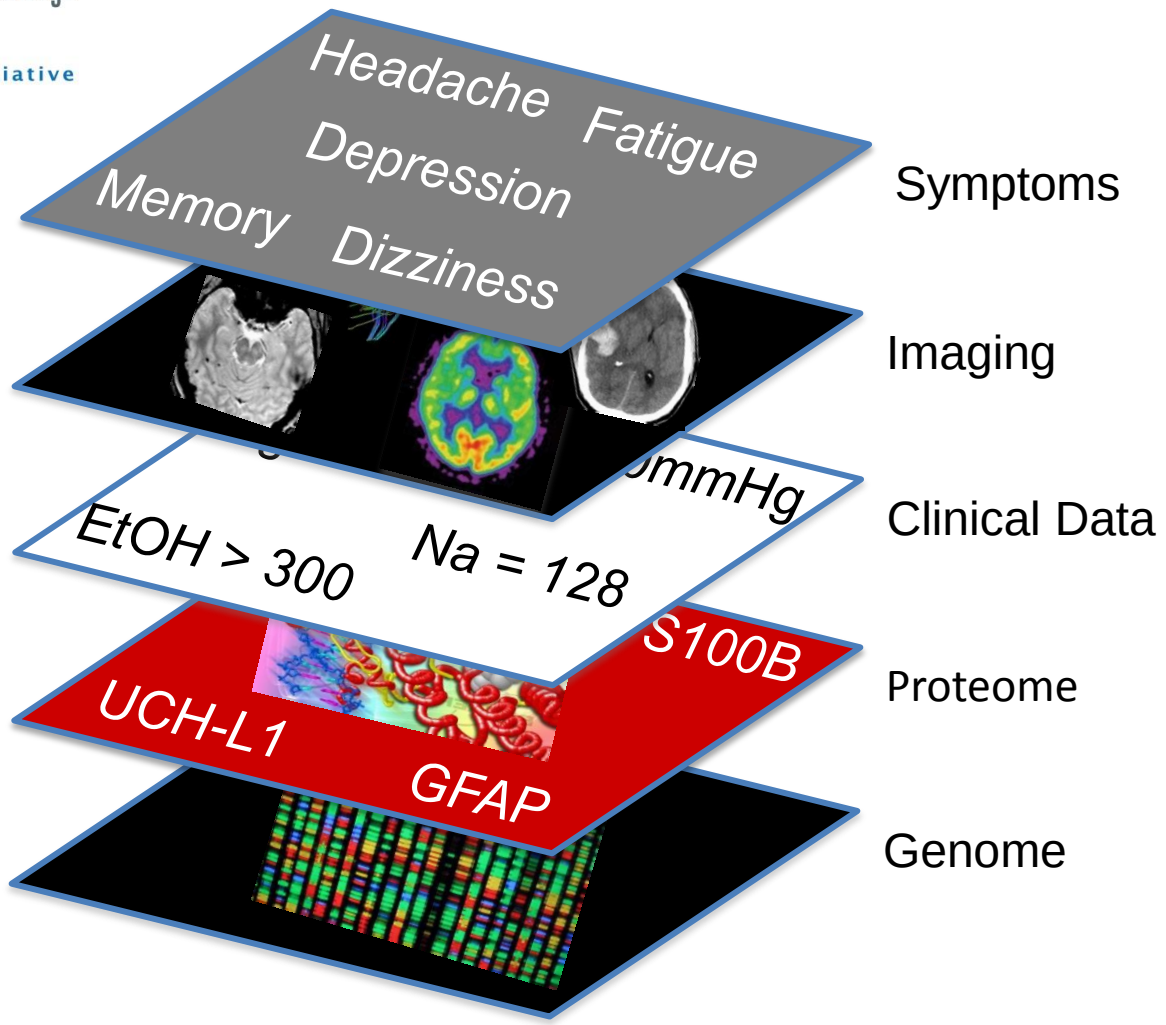
Targeted
Treatment

**Precision Medicine**

TRACK-TBI

Transforming Research and Clinical Knowledge in Traumatic Brain Injury

International Traumatic Brain Injury Research Initiative




# A Precision Medicine Approach to TBI

# Public-Private Partnership









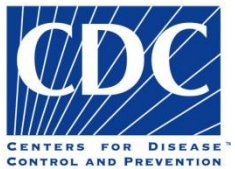














# Government Partners


U.S. Department of Defense





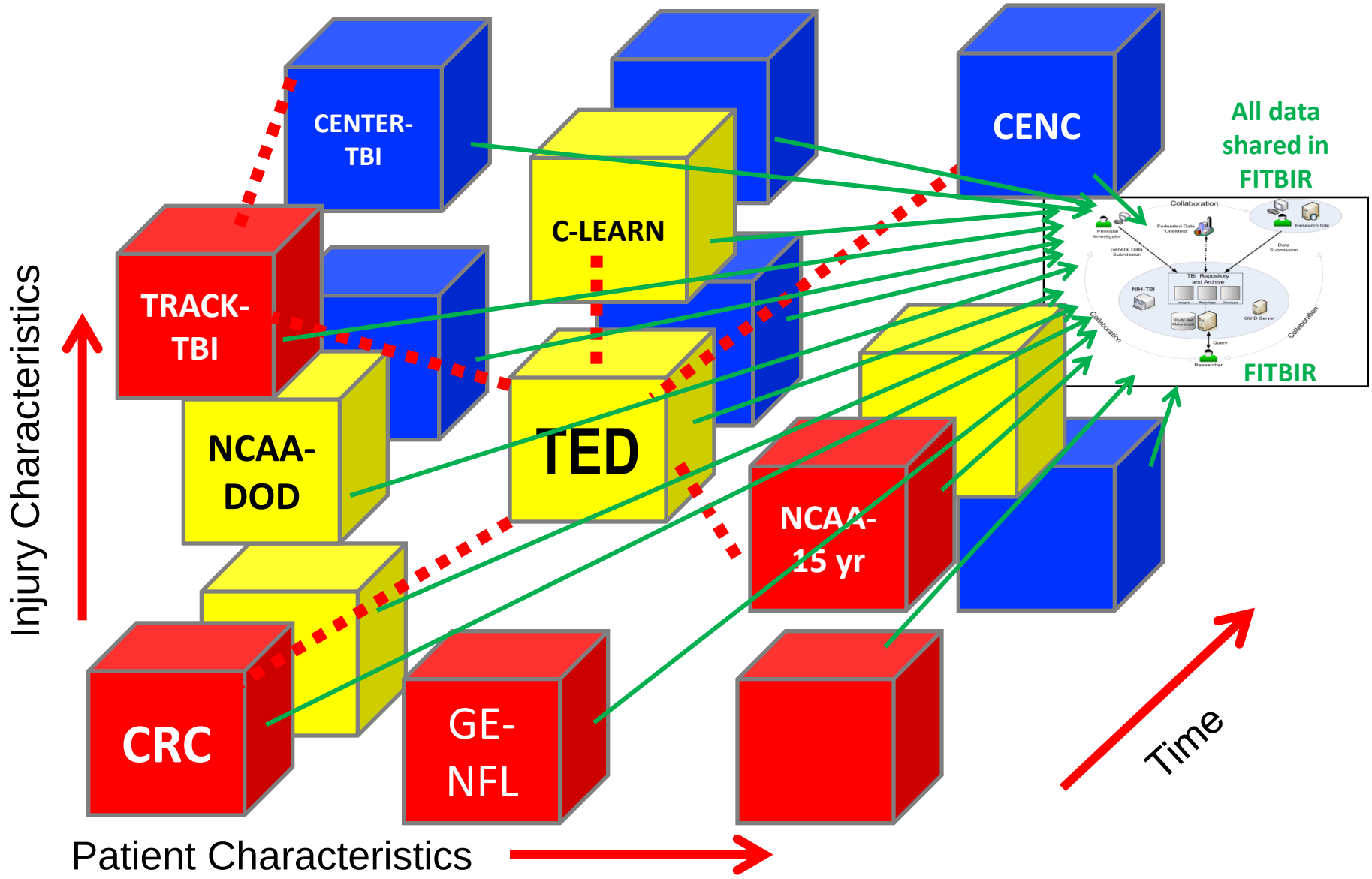


# Academic/Research Partners

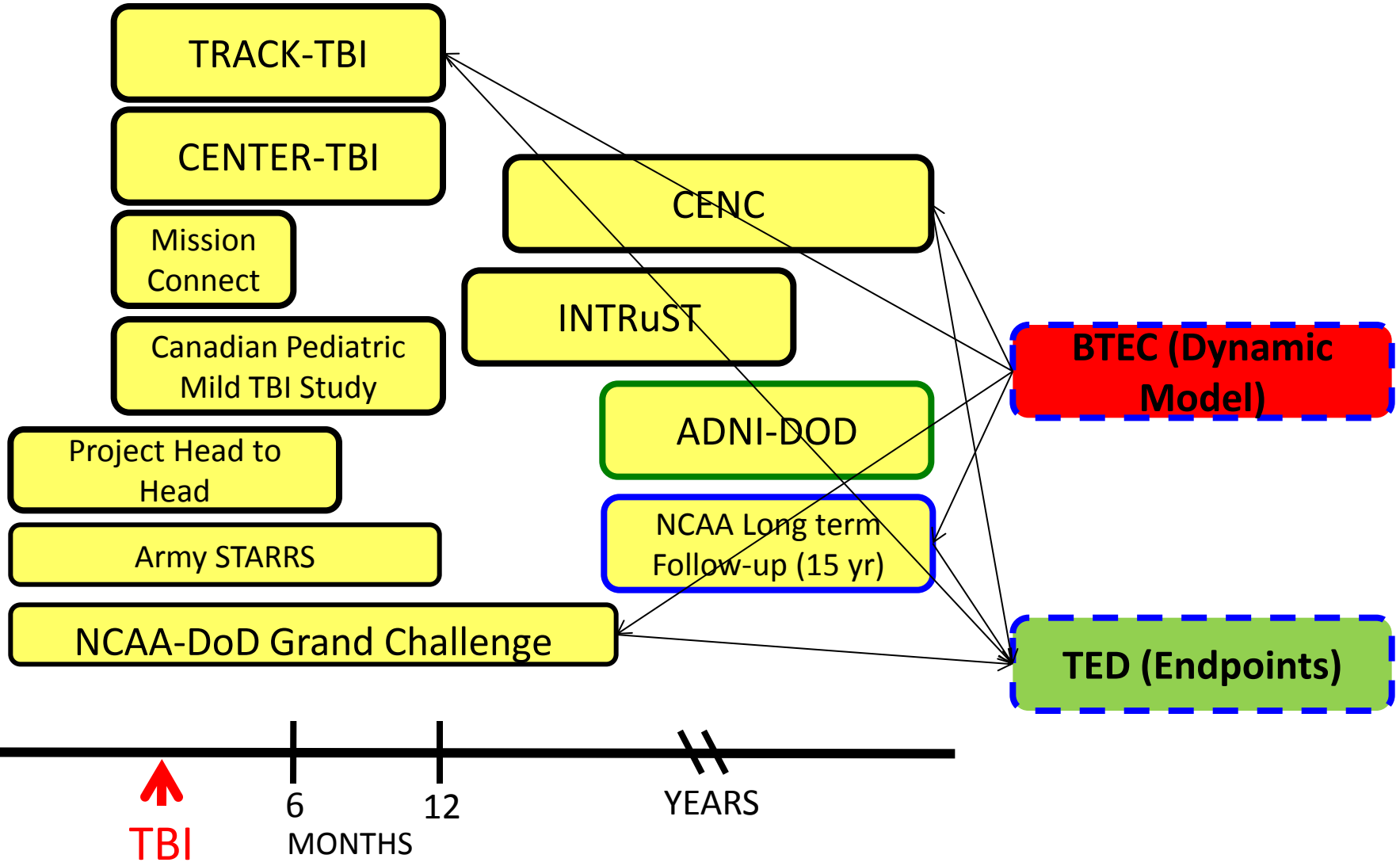
Albert Einstein Healthcare Network (MRH)
Baylor College of Medicine
Emory University
Massachusetts General Hospital
Medical College of Wisconsin
Northern California Institute for Research and Education
Research Triangle Institute
Spaulding Rehabilitation Hospital
Stanford University
University of California, Berkeley
University of California, San Diego
University of California, San Francisco
University of Cincinnati
University of Florida
University of Maryland Baltimore
University of Miami
University of Pittsburgh
University of Southern California
University of Texas at Austin
UT Southwestern Medical Center
University of Washington
Uniformed Services University of the Health Sciences
Virginia Commonwealth University

# Big Picture Solutions:

## Collaborative, Integrated, Multidimensional Research Networks



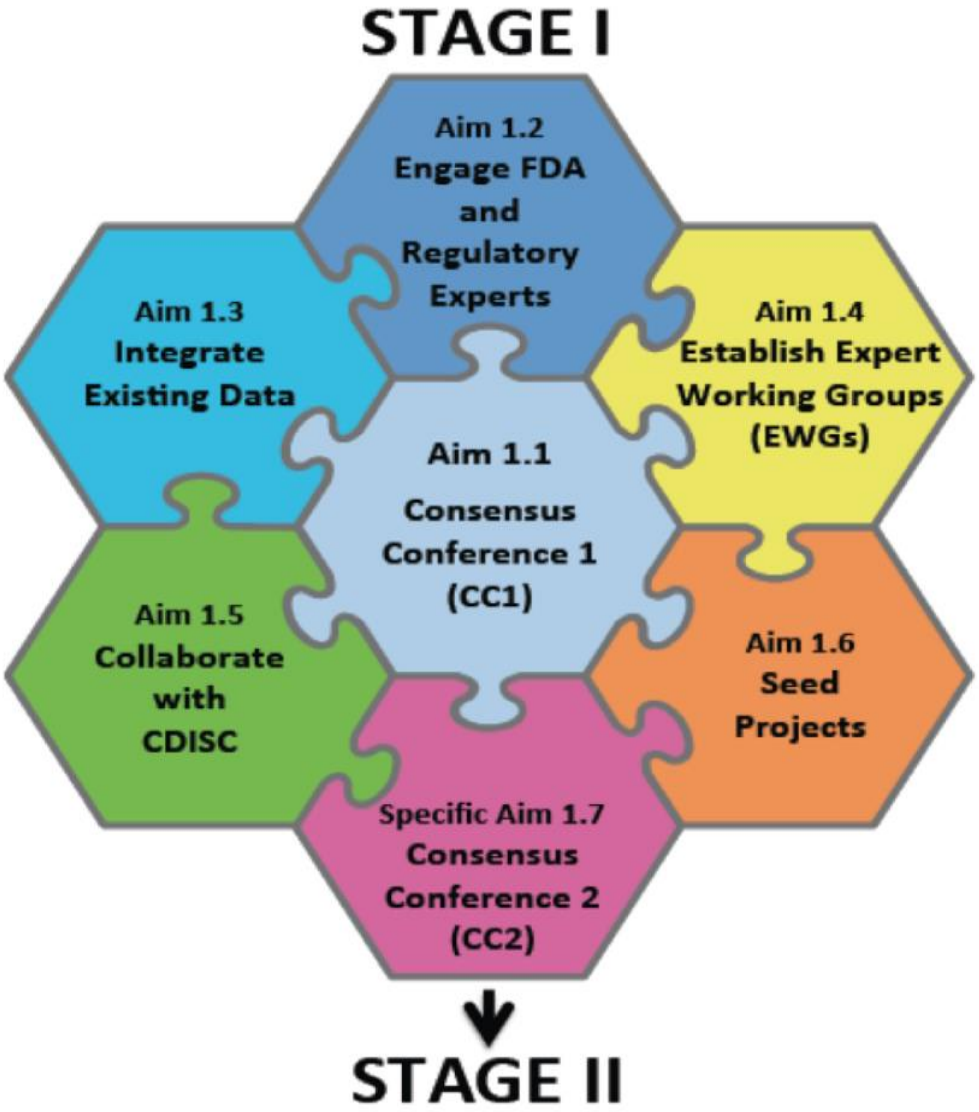
# Study Landscape



# TED Aims: Stage I

**STAGE I Technical Objective 1:**

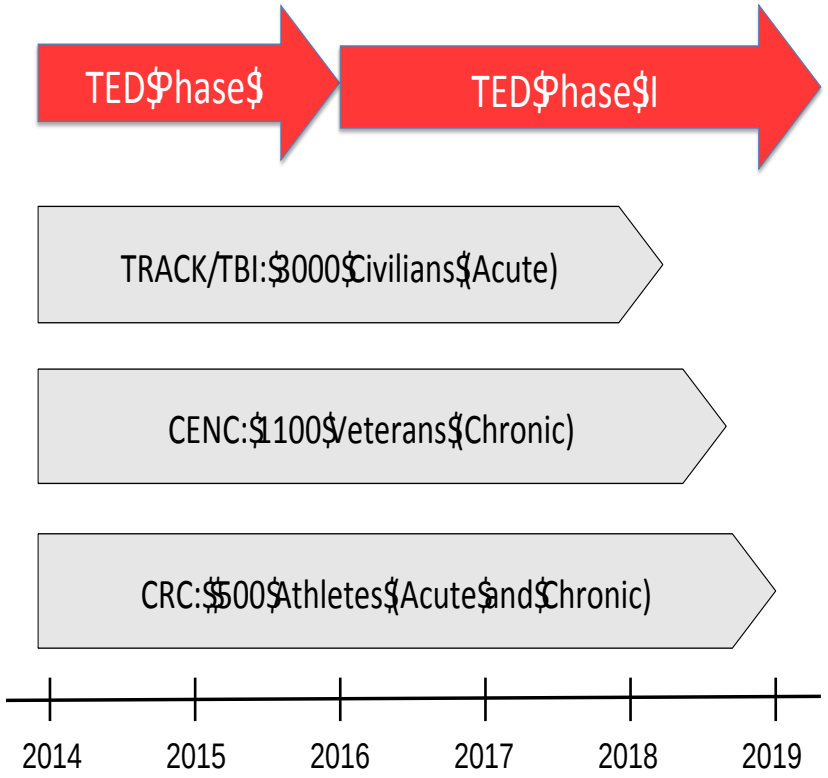
Establish a collaborative, multidisciplinary team to advance the identification and validation of clinical outcome assessments (COAs) and biomarkers for use as potential FDA-qualified drug development tools (DDTs), and initiate development of CDISC data standards for trials involving diagnosis and treatment of mTBI to modTBI.



# TED Aims: Stage II

**STAGE II Technical Objective: 2**

Validate candidate COAs and biomarkers selected in Stage I, leveraging the existing research infrastructure and clinical study networks of TRACK-TBI, CENC, and CRC for potential qualification as DDTs



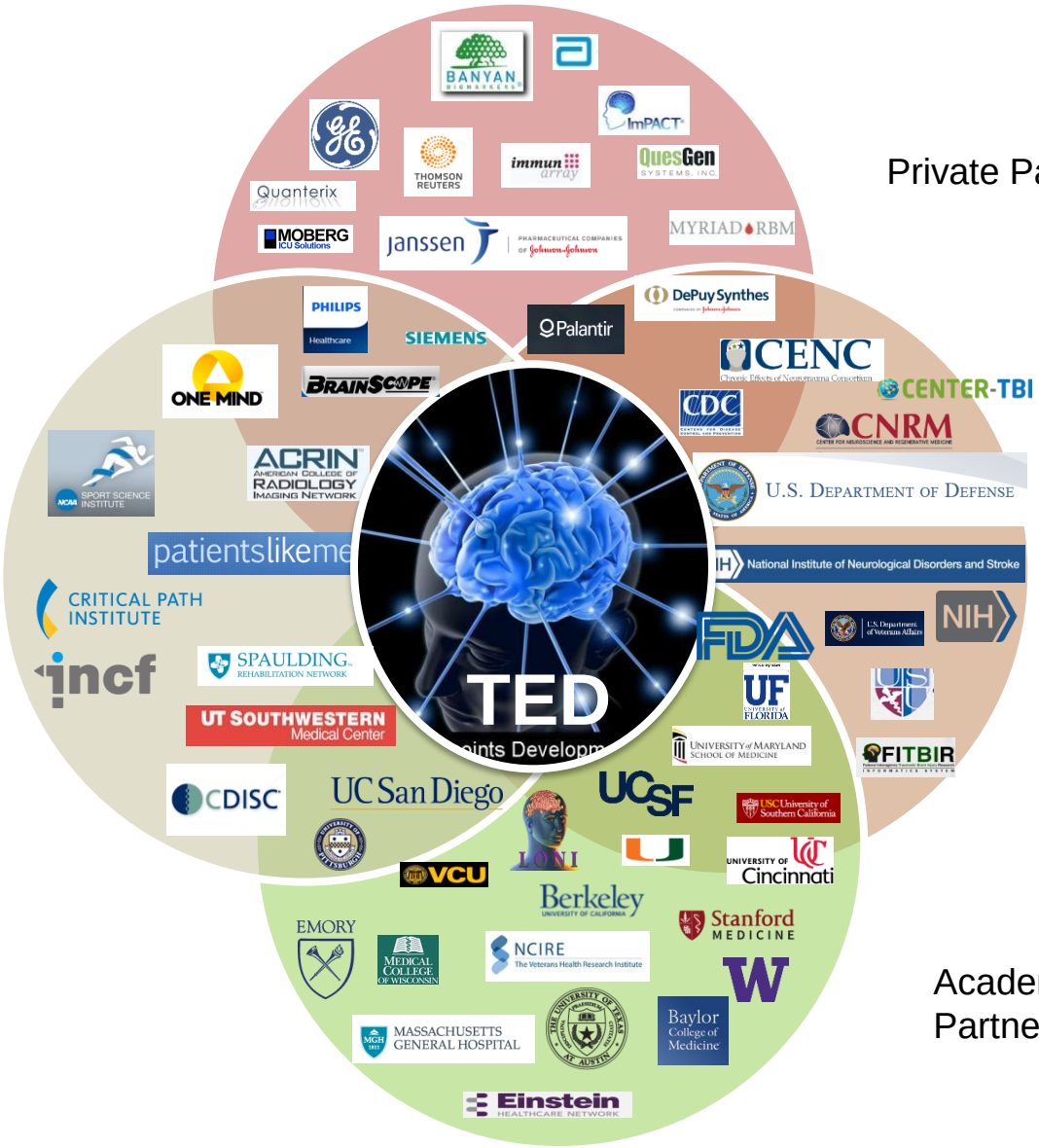
# How do we move forward?

# Public -Private Partnership

Private Partners

Not for Profit and Philanthropic Partners

Government Partners




Academic Partners

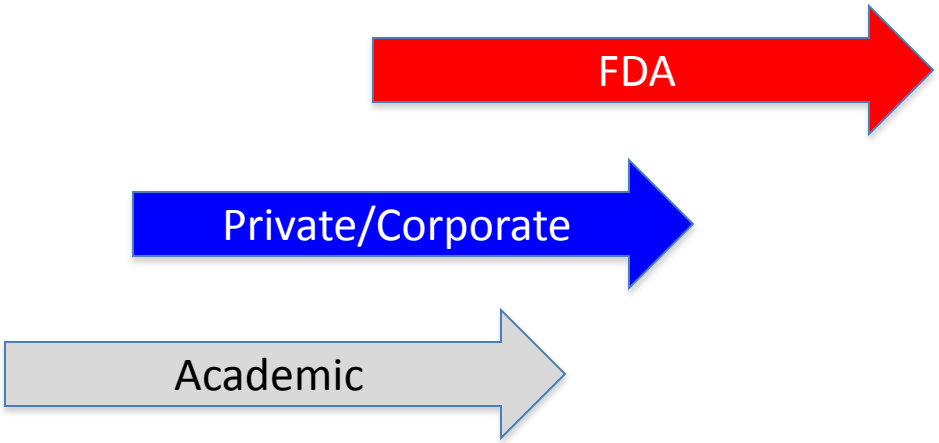
# Collaboration

Early and Open with Shared Rewards

# The Many Faces of TBI

# Current Cycle

# Collaboration



## Douglas C. Throckmorton MD - Deputy Director for Regulatory Programs, Center for Drug Evaluation and Research

**Dr. Throckmorton** shares responsibility for overseeing the regulation of research, development, manufacture and marketing of prescription, over-the-counter, and generic drugs in the United States.

# Overview of FDA Support for Innovation

**Douglas C. Throckmorton MD**
**Deputy Director for Regulatory Programs**
**Center for Drug Evaluation and Research**
**U.S. Food and Drug Administration**
**February 2, 2015**

# Disclosure Statement

I have no financial relationships with proprietary entities that produce health care goods and services

The opinions and information in this presentation are my own and do not necessarily reflect the views and policies of the FDA

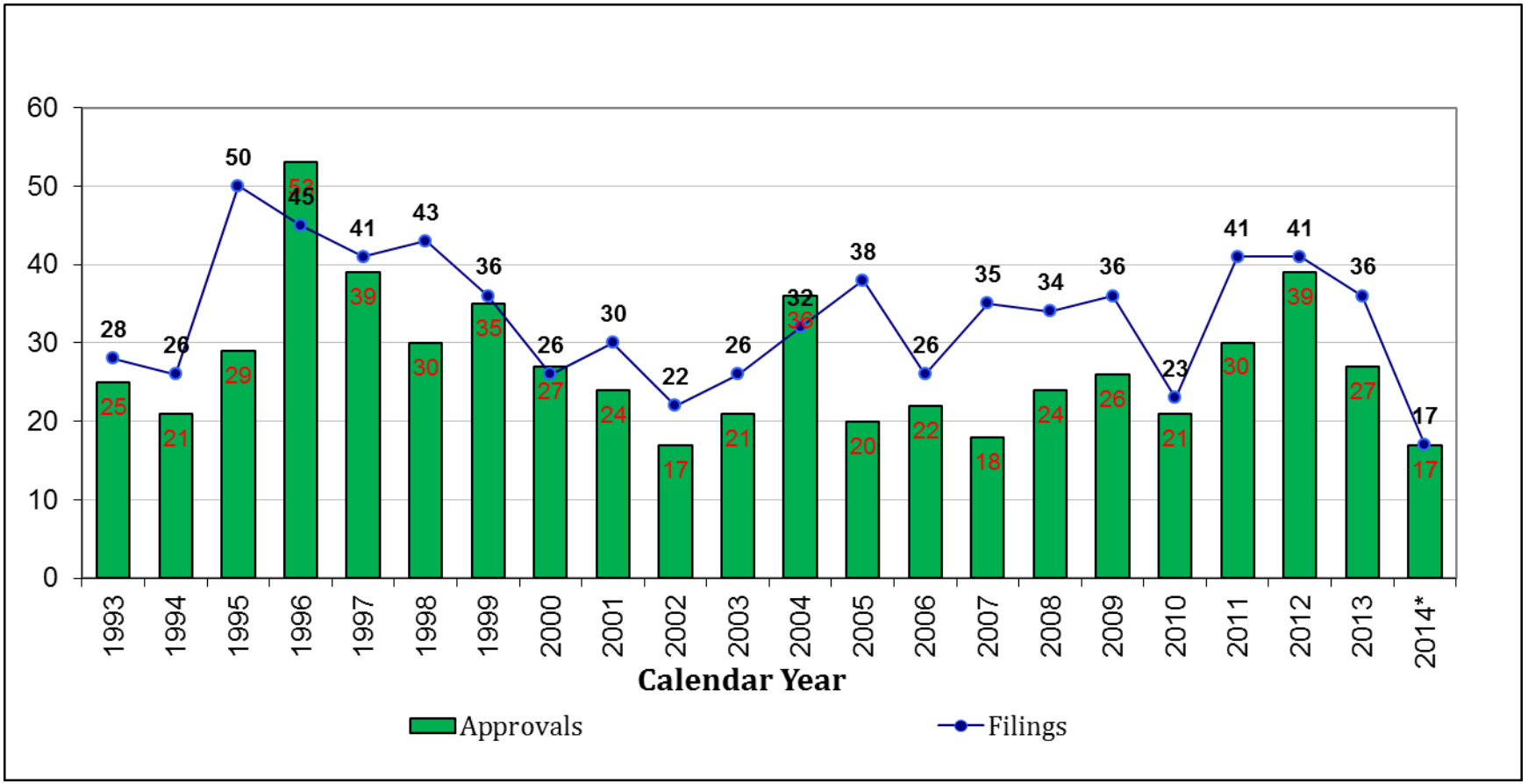
# Outline

- Importance of innovation for TBI
- FDA role in supporting innovation
- Power of consortiums in innovation

# FDA Challenge

- Patients and Caregivers want:
  - Rapid access to safe and effective new drugs
  - Better information about how to use these drugs after approval
- Inefficient medical product development:
  - Is failing to keep pace with the new scientific discoveries
  - Is delaying access to new innovations and limit information on appropriate use of approved drugs

# CDER NME NDAs/BLAs† Filings and Approvals




Data as of 6/30/2014

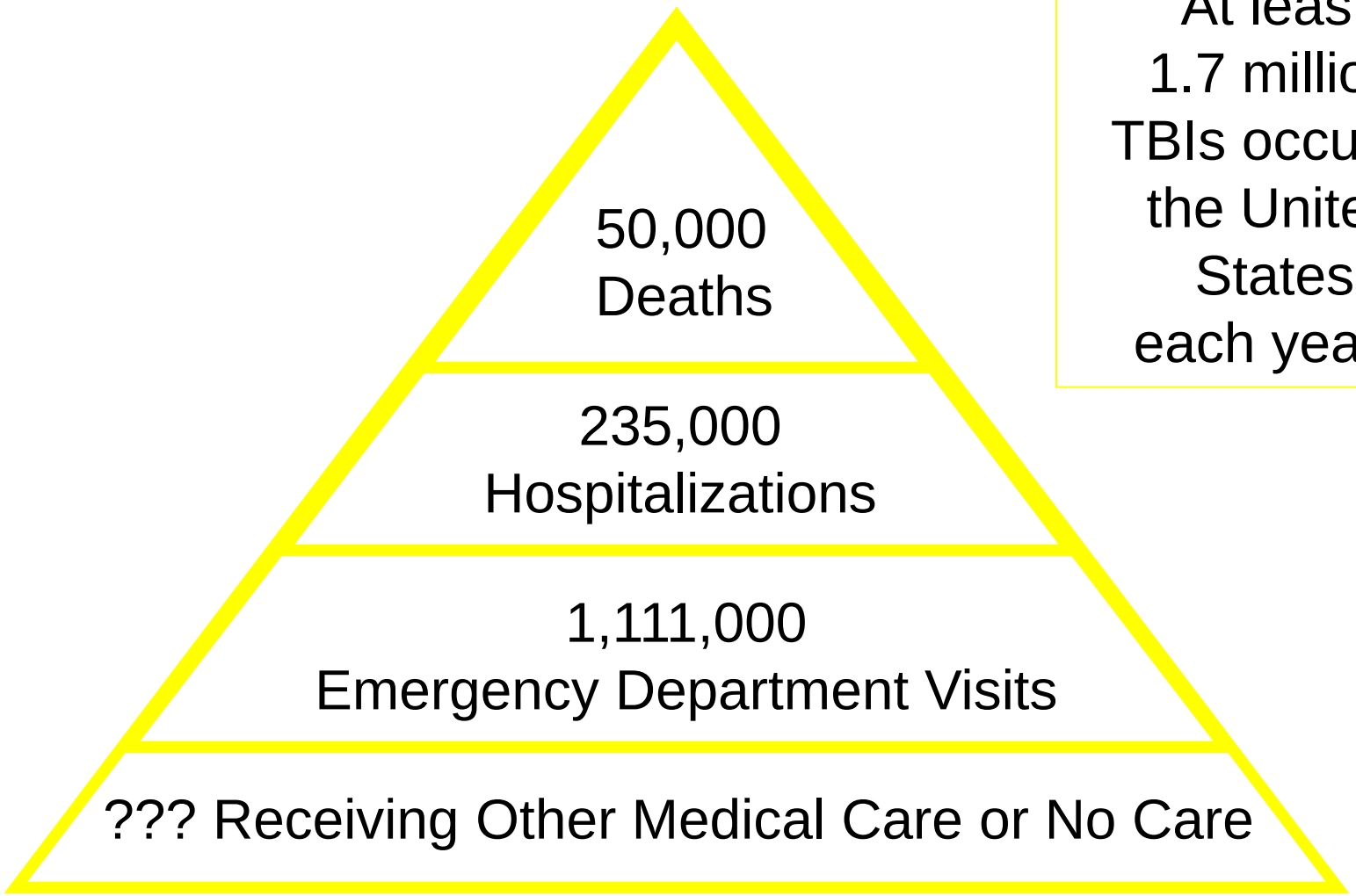
† Multiple applications pertaining to a single new molecular/biologic entity (e.g. single ingredient and combinations) are only counted once. Therefore, the numbers represented here for CY14 filings are not indicative of workload in the PDUFA V Program.

† Original BLAs that do not contain a new active ingredient are excluded

*Since applications are received and filed throughout a calendar year, the filed applications in a given calendar year do not necessarily correspond to an approval in the same calendar year. Certain applications are within their 60-day filing review period and may not be filed upon completion of the review.

# Importance of Innovation in Treatments for Traumatic Brain Injury (TBI)

# Challenge of TBI in the United States




At least
1.7 million
TBIs occur in
the United
States
each year.*

# Challenge of TBI (cont)

- TBI is a complex condition (not an 'event')*
- New tools promise better differentiation of patients and responses to treatment
- Traditional classification schemes are based on symptoms and may be insensitive to mechanistic targeting using new imaging and diagnostic tools.
- Data standards needed

*--Manley and Maas, JAMA (2013) 310:473

# FDA Role in Supporting Innovation

# FDA's Role In The Science of Drug Development

- **Develop infrastructure and tools for product development (not focus on development of specific products but rather areas of need)**
- **Encourage collaborative efforts among government, academia, industry, and patient groups**
- Develop relevant data standards and regulations
- Build support for relevant academic science
- Create opportunities to share existing knowledge and databases

# Critical Targets: Drug Development Tools (DDTs)

# Gains for Use of DDTs

- High potential to reinvigorate drug development and improve efficiency of development
  - Earlier information about benefits and risks
  - Consistent data collection across studies
  - Reduce the need for clinical data

# Challenges to Developing DDTs

- Time, money, people….
- Progress needs
  - Focus on science that will make a difference
    - Multiple views can be taken into account
  - Process that works
    - Mechanism to support a balanced collection and review of available data
    - Mechanism to support appropriate transparency
    - Example:  CDER DDT Qualification Process
  - Champion
    - Collaboration….

# Critical Additional Element of Success: Collaboration

# Power of Collaboration

- It's the most efficient game in town
  - Multiple stakeholders with multiple needs
    - No single company, university, or governmental agency will have sufficient resources, expertise, or information bas to undertake the work.
  - Builds consensus, expanding use
  - Many examples of success of collaboration
    - PCAST report calls for it,
    - IOM is applying it, work on clinical trials certification
    - FDA is applying it in a variety of situations

# Power of Collaboration (cont)

- FDA has experience in appropriate ways for government to partner…
  - Transparent, open, inclusive, rigorous
  - Results broadly applicable, maximally transparent, for maximum value
- FDA is highly supportive of groups looking to form collaborations to support innovation

# Conclusion: Dr. Woodcock's Advice

- "…MS community needs to build on current foundations by applying creativity to the development of modern outcome assessments that will ignite innovation in MS treatments and ultimately improve the lives of MS patients and their families."*

• Woodcock, J and Rowzee, A.M., Multiple sclerosis outcome assessment consortium: bringing the community together to shape the future of multiple sclerosis drug development. *Therapeutic Innovation and Regulatory Science* (September, 2013).


WARNING
CHALLENGES
AHEAD

**Yasmin Choudhry, M.D. -** Study Endpoints Team, Office of New Drugs (OND),Center for Drug Evaluation and Research (CDER) Dr. Choudhry is an anesthesiologist and a pain specialist with Board certifications from the American Board of Anesthesiology (ABA) in Anesthesia and Pain Medicine. Dr. Choudhry has been with the FDA for over 8 years. She has been with the Study Endpoints team, Immediate Office, CDER since January of 2014. Prior to joining the Study Endpoints team, she worked in the Division of Anesthesia, Analgesia and Addiction Products (DAAAP) and the Division of Risk Management (DRISK) in the Office of Surveillance and Epidemiology (OSE).

# CDER Drug Development Tools Qualification Program

Traumatic Brain Injury Endpoints Development Initiative, NIH

February 2, 2015

**Yasmin Choudhry, M.D.**

Study Endpoints Team

Office of New Drugs (OND)

Center for Drug Evaluation and Research (CDER)

# Disclaimer

The views expressed in this presentation are those of the speaker, and do not necessarily represent an official FDA position

# Overview

- FDA's Drug Development Tools (DDT) Qualification Programs
- CDER DDT Qualification Program
  - Background
  - CDER's review process
  - Steps in DDT Qualification
- FDA Resources
- Frequently asked questions

# FDA Pathways for Review of Tools

- FDA's DDT Qualification Programs
  - Clinical Outcome Assessments (COA) - CDER
  - Biomarkers
  - Animal Models
- Currently FDA has 2 pathways for COAs:
  1. In the context of an Investigational New Drug (IND), New Drug Application (NDA ) & Biologics License Application (BLA)
  2. Drug Development Tool s (DDT) Qualification program

**The same FDA review principles apply to both processes**

# Background

- CDER DDT Qualification Program was created by CDER as part of the FDA's Critical Path Initiative to provide a framework for development & regulatory review of scientific tools with a well-defined context of use (COU) but independent of a specific drug development program
- **Qualification**: *a conclusion that within the stated context of use, the DDT (e.g., biomarker or COA) can be relied upon to have a specific interpretation and application in drug development and regulatory review*

## *Background:*

- DDT qualification results in public acknowledgment by FDA that the qualified tool can be used during drug development without a sponsor's need to request that CDER reconsider and reconfirm the suitability of the tool for the particular COU
  - A qualified DDT is publicly available for use in clinical trials

# CDER's Review Process

- A multidisciplinary team called the Qualification Review Team (QRT) participates in the review process
- Allows CDER to work with submitters
  - Public-private partnerships
  - Industry consortia
  - Academic collaborative groups
  - Other government agencies
  - Individuals
- In some cases, the FDA staff may identify a need for a new or revised DDT

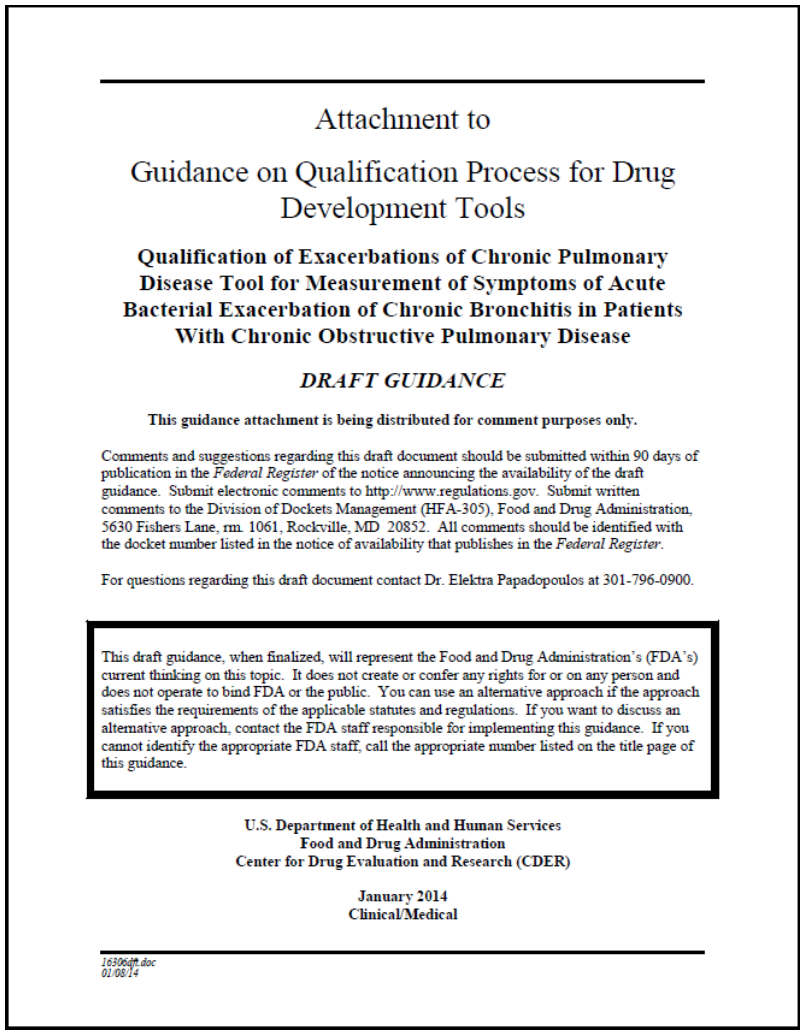
# Steps in DDT Qualification

- Occurs in 3 stages as described in the 2014 FDA DDT Qualification Guidance:
  - Initiation
  - Consultation & advice
  - Review of full qualification package (FQP)
- Once qualified, the tool can be used in:
  - Exploratory studies
  - Phase 3 studies as primary, co-primary and secondary endpoints

# Choice of COA Type

- Determine the most appropriate reporter for the COI in the COU
  - **PRO**: If symptom intensity is the concept of interest in a patient population that can respond themselves
  - **ClinRO:** If clinical judgment is required to interpret an observation
  - **ObsRO:** If the COI can only be adequately captured by observation in daily life (outside of a healthcare setting), and the patient cannot report for him or herself
  - **PerfO**: When it would be useful to observe an actual demonstration of defined tasks demonstrating functional performance in the clinical setting

# First COA Tool Qualified in January 2014



Attachment to

Guidance on Qualification Process for Drug Development Tools

**Qualification of Exacerbations of Chronic Pulmonary Disease Tool for Measurement of Symptoms of Acute Bacterial Exacerbation of Chronic Bronchitis in Patients With Chronic Obstructive Pulmonary Disease**

***DRAFT GUIDANCE***

**This guidance attachment is being distributed for comment purposes only.**

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Dr. Elektra Papadopoulos at 301-796-0900.

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**

**January 2014**
**Clinical/Medical**

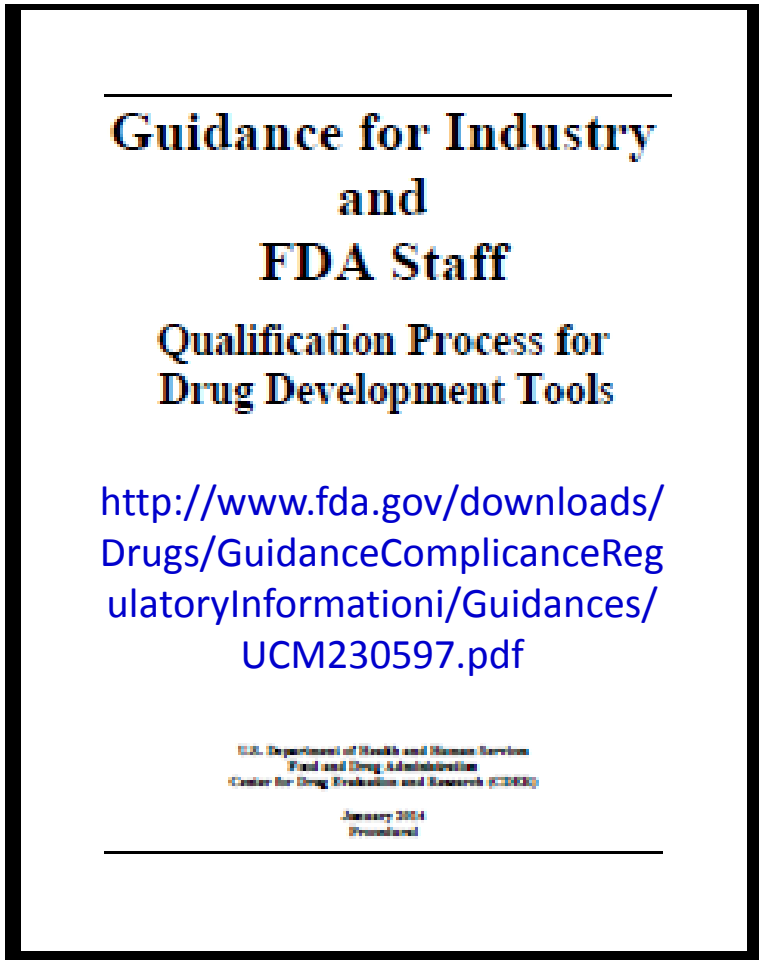
*16306dft.doc*
*01/08/14*

- EXACT
  - A PRO for the measurement of symptoms of acute bacterial exacerbation of chronic bronchitis in patients with chronic obstructive pulmonary disease

# CDER DDT Qualification Projects: Updated December 2014

| | All Drug Development Tool (DDT) Qualification Programs | DDT - Animal Model Qualification Program | DDT - Biomarker Qualification Program | DDT - Clinical Outcome Assessments |
|---|---|---|---|---|
| Total Number of Active Projects | 84 | 8 | 23 | 53 |
| Number in Initiation Stage | 27 | 5 | 1 | 21 |
| Number in Consultation and Advice Stage | 52 | 3 | 20 | 29 |
| Number in Review Stage | 4 | 0 | 2 | 2 |
| Number Qualified | 5 | 0 | 4 | 1 |

# DDT Guidance (Final January 2014)


Guidance for Industry
and
FDA Staff

Qualification Process for
Drug Development Tools

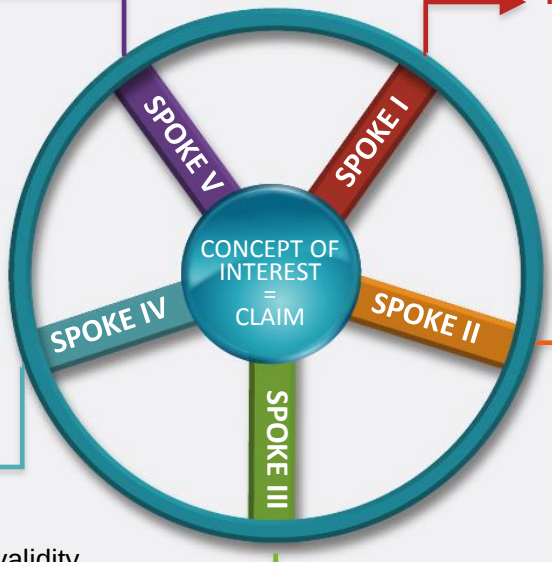
http://www.fda.gov/downloads/Drugs/GuidanceComplicanceRegulatoryInformationi/Guidances/UCM230597.pdf

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2014
Procedural

- Describe a process NOT evidentiary standards
- Qualification process described for Biomarkers, Animal Models, and Clinical Outcome Assessments (COA)

# Qualification of **CLINICAL OUTCOME ASSESSMENTS** (COAs)




## V. Modify Instrument

- Identify a new COU
- Change wording of items, response options, recall period, or mode/method of administration/data collection
- Translate and culturally adapt
- Evaluate modifications using spokes I – IV
- Document all changes

***Consider submitting to FDA for qualification of new COA, as appropriate.***

## I. Identify Context of Use (COU) and Concept of Interest (COI)

- Outline hypothesized concepts and potential claims
- Determine intended population
- Determine intended application/characteristics (type of scores, mode and frequency of administration)
- Perform literature/expert review
- Develop hypothesized conceptual framework
- Position COA within a preliminary endpoint model
- Document COU and COI

## IV. Longitudinal Evaluation of Measurement Properties/ Interpretation Methods

- Assess ability to detect change and construct validity
- Identify responder definition(s)
- Provide guidelines for interpretation of treatment benefit and relationship to claim
- Document all results
- Update user manual

***Submit to FDA for COA qualification as effectiveness endpoint to support claims.***

## II. Draft Instrument and Evaluate Content Validity

- Obtain patient or other reporter input
- Generate new items
- Select recall period, response options and format
- Select mode/method of administration/data collection
- Conduct cognitive interviewing
- Pilot test draft instrument
- Finalize instrument content, format and scoring rule
- Document content validity

## III. Cross-sectional Evaluation of Other Measurement Properties

- Assess score reliability (test-retest or inter-rater) and construct validity
- Establish administration procedures & training materials
- Document measure development
- Prepare user manual

***Consider submitting to FDA for COA qualification for use in exploratory studies prior to longitudinal evaluation.***

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
**http://www.fda.gov/Drugs**

Updated on February 11, 2014

# Roadmap to **PATIENT-FOCUSED OUTCOME MEASUREMENT** in Clinical Trials

## 1 Understanding the Disease or Condition

**Natural history of the disease or condition**
- Onset/Duration/Resolution
- Diagnosis
- Pathophysiology
- Range of manifestations

**Patient subpopulations**
- By severity
- By onset
- By comorbidities
- By phenotype

**Health care environment**
- Treatment alternatives
- Clinical care standards
- Health care system perspective

**Patient/caregiver perspectives**
- Definition of treatment benefit
- Benefit-risk tradeoffs
- Impact of disease

## 2 Conceptualizing Treatment Benefit

**A. Identify the *meaningful health aspect* that is the intended benefit to patients in their daily lives**
- Survives (e.g., length of survival)
- Feels (e.g., symptom severity)
- Functions (e.g., walking ability)

**B. Identify the measureable *concept of interest* that represents the meaningful health aspect, which can be:**
- Equivalent to the meaningful health aspect (e.g., patients' self-reported ambulatory activities in daily life) OR
- Distinct from, but related to the meaningful health aspect (e.g., 6-minute walk test)

**C. Define context of use for clinical trials, e.g.:**
- Disease/Condition entry criteria
- Clinical trial design
- Endpoint positioning

**D. Consider appropriate clinical outcome assessment type(s):**
- Patient-Reported Outcome (PRO)
- Observer-Reported Outcome (ObsRO)
- Clinician-Reported Outcome (ClinRO)
- Performance Outcome (motor, sensory, cognition)

## 3 Selecting/Developing the Outcome Measure

**A. Search for existing clinical outcome assessment measuring the concept(s) of interest in the context of use :**
- Measure exists
- Measure exists but needs to be modified
- No measure exists
- Measure under development

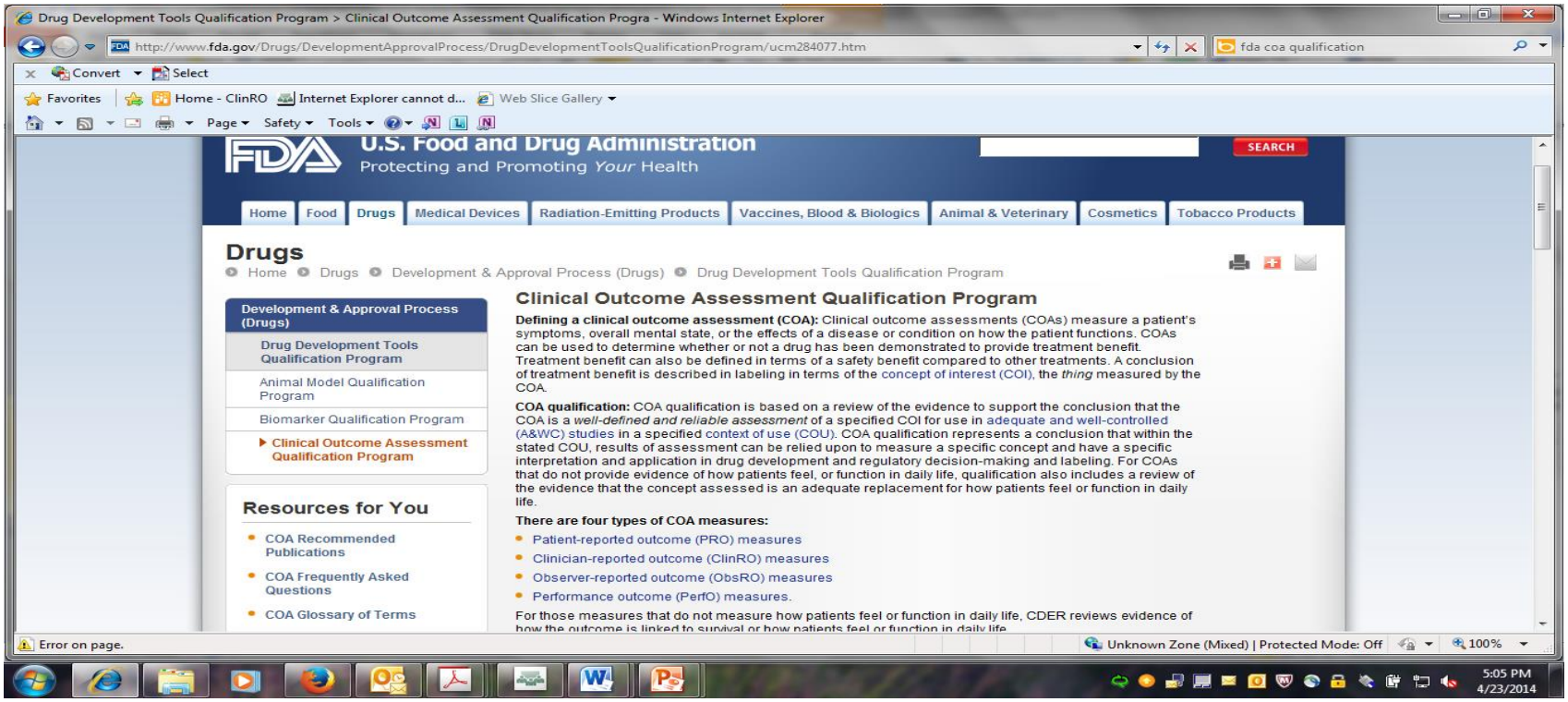
**B. Begin clinical outcome assessment development**
- Document content validity (qualitative or mixed methods research)
- Evaluate cross-sectional measurement properties (reliability and construct validity)
- Create user manual
- Consider submitting to FDA for qualification for use in exploratory studies

**C. Complete clinical outcome assessment development:**
- Document longitudinal measurement properties (construct validity, ability to detect change)
- Document guidelines for interpretation of treatment benefit and relationship to claim
- Update user manual
- Submit to FDA for qualification as effectiveness endpoint to support claims

Updated on March 14, 2014

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
**http://www.fda.gov/Drugs**

# Qualification website updated 12/2014




http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm409960.htm

# Frequently Asked Qualification Questions

- *Is qualification required in order to use an instrument in a clinical trial*
  - NO! A tool that is not formally qualified should be discussed with the review division within an IND. And of course, we recommend discussing as early as possible.
- *Are sponsors required to use only qualified instruments?*
  - NO! While we believe there are benefits of using a qualified tool, sponsors are free to select whatever tool they believe will be best suited for their clinical trial(s), and again, discuss those decisions with the review division.

# *Questions:*

- *An instrument has been used to support claims in labeling. Does this mean that tool is qualified?*
  - NO! Only tools that have been reviewed through the formal DDT qualification process, about which a positive qualification decision has been made, and are made publically available… are considered "qualified". Tools that have not been formally qualified may still be acceptable for use.

# *Questions:*

- *What does the Qualification Review Team (QRT) team look like?*
  - SEALD, Division(s), Biostatistics, representatives from other centers when appropriate
- *How do FDA and EMA work together on COA qualification?*
  - Harmonization efforts on projects submitted concurrently to FDA and EMA
  - Regular and ad hoc TCs to discuss

# Critical Path Innovation Meeting

## Overview

- New CDER program
- Promotes understanding challenges in drug development and innovative strategies to address them
  - Potential biomarkers not ready for DDT Qualification Program
  - Potential Clinical Outcome Assessments not ready for formal Qualification
  - Natural history study design and implementation
  - Emerging technologies or new uses of existing technologies
  - Novel clinical trial designs and methods
- Nonbinding on FDA and other participants
- No advice on specific approval pathways

# Critical Path Innovation Meeting (2)

## Overview (continued)

- Requests may come from anyone with a role in drug development
  - Disease advocacy organizations, public-private partnerships, industry, academia, government
- FDA experts participate as resources allow
- Advance meeting materials are brief; include summaries, not primary data

# Critical Path Innovation Meeting (3)

Outcomes include:

- Identification of issues facing development of proposed innovations
- Identification of avenues for further information: consortia, patient advocacy groups, interest groups, other collaborators
- Perspective on potential drug development uses for proposed innovations
- Exposure of FDA to emerging science

# Critical Path Innovation Meeting (4)

## Resources

- Draft Guidance
- Internet site
  - Link to Draft Guidance
  - Link to request form
  - CPIM email address
  - Telephone contacts

Internet address

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm395888.htm

# Critical Path Innovation Meeting (5)

## Contact information

- Inquiries: CPIMInquiries@fda.hhs.gov
- Project Manager: Alicia Barbieri Stuart
  301-796-3852
- Scientific Lead: James Kaiser
  301-796-1237

**Allison Kumar**, Sr. Program Manager, Military Liason has been actively working with the military on several TBI programs and therapy development efforts.

C·D·R·H
Center for Devices and Radiological Health

# Early Collaboration with the Food and Drug Administration

# CDRH's Regulatory Support for the TED Initiative

**Office of the Center Director**

**Emergency Preparedness and Medical Countermeasures Program**

**Allison Kumar, Sr. Program Manager, Military Liaison**

FDA

C·D·R·H
Center for Devices and Radiological Health

**Feb 2, 2015**

# Recognized Challenges of Neurotrauma

- TBI is a broad title encompasses the scope of very heterogeneous insults to the cellular structures and functions of the brain with life-long effects
- Co-morbidities (PTS, Pain, Depression) often complicate studies
- Currently, physical and mental rest is the only validated “treatment”
- Regulatory science is inadequate
- Limited understanding of the pathobiology and lack of biomarkers
- Subjective interpretations and weak science supporting correlations between clinical conditions and animal models.

# Current Regulatory Landscape

- Outcomes measures for effectiveness have not been widely established
- Variable diagnostic criteria
- Issues with subject eligibility
- Length of trials vary
- Need to adequately define safety endpoints, risk analysis and mitigation strategies and adverse event monitoring

No device has received FDA approval for diagnosis or treatment specific to TBI.

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# Realization and Alignment of Efforts to Achieve Success

Engage in collaborative research and support development of diagnostics and therapies that provide improved methods and devices to reduce death and injury associated with TBI.

- Neurophysical , biochemical, and objective physiological marker screening tools and methods for determining injury
- Refine and standardize preclinical models of TBI to optimize translation from animal to human studies
- Improved diagnostic criteria
- Imaging methods that assess level of damage caused by injury
- Therapies and evaluations that reduce morbidity and mortality, and return patients to previous standards of life.

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# Strategic Priorities

- Strengthen Clinical Trial Enterprise
- Pre- and Post-market Balance
- Customer Service

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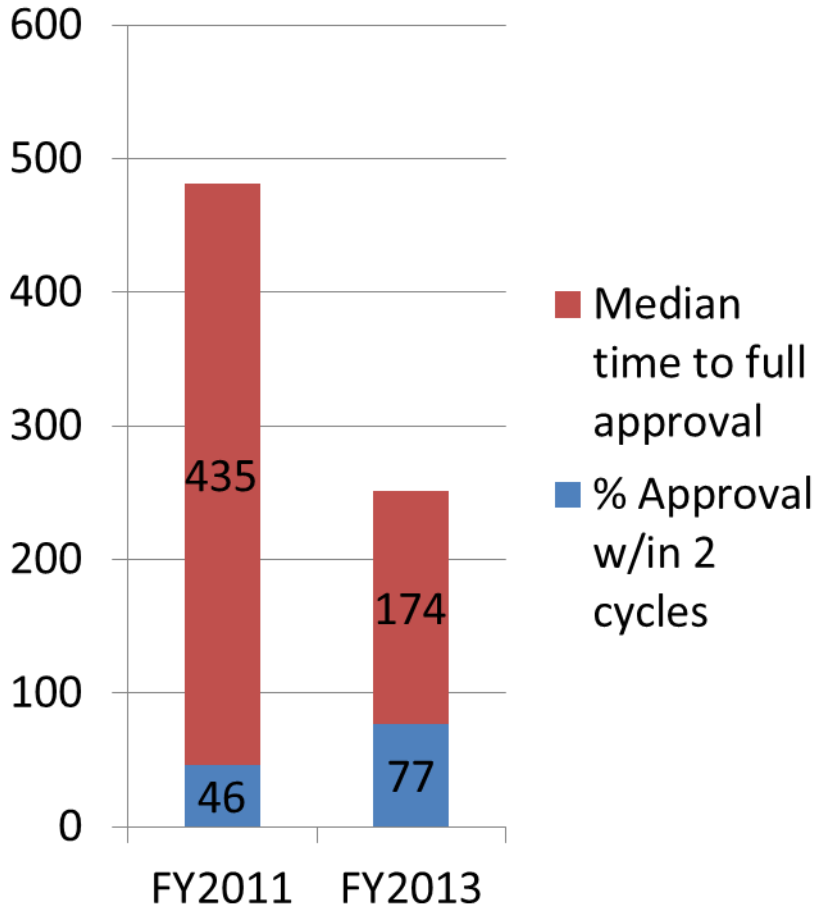
# Strategic Priority #1

- Strengthening the Clinical Trial Enterprise
  - Early collaboration gives review teams greater opportunity to find ways to influence and shorten the whole timeframe by defining clear pathways.
  - Identify intended patient population early and design appropriate studies to evaluate risk / benefit profiles

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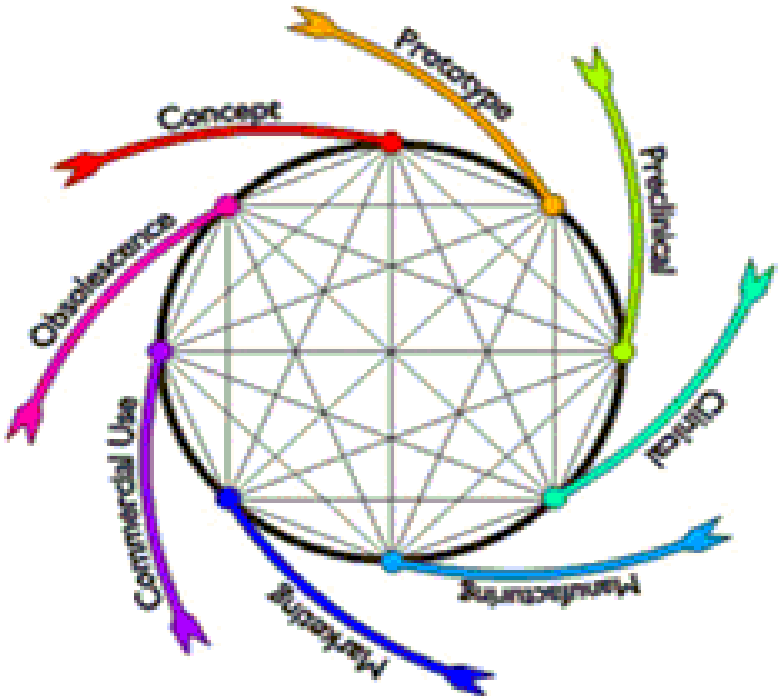
# Strategic Priority #2

- Pre- and Post-market Balance
  - Advanced technology provides new space to explore a balanced approach for high-priority / high-risk products.
  - Use of new regulatory tools to analyze potential benefits /risks of a device



# Medical Device Development Tool (MDDT)

- Draft Guidance issued November 13, 2013.
- Voluntary process for qualification of MDDT for use in device development evaluations programs in CDRH
- Guidance describes the framework & process for MDDT qualification
  - Definitions of applicable criteria for evaluating an MDDT for a specific context of use,
  - considerations for qualification, and
  - contents of a qualification submission
- Application of this policy will facilitate the development and evaluation of innovate medical devices by providing a more efficient and predictable means for collecting the necessary information to make regulatory assessments.

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# MDDT – Pilot Program

- Three defined categories of MDDT
  - Clinical Outcome Assessment
  - Biomarker Test
  - Nonclinical Assessment Model
- Pilot Program currently under way
  - No fees
  - Any tool developer can submit a proposal
  - MDDT@fda.hhs.gov

C·D·R·H Center for Devices and Radiological Health

# Strategic Priority #3

- Customer Service
  - External – Supporting the success of military projects that have translational benefits to civilian populations.
  - Internal – SME involvement and first-hand knowledge of innovative new technology which will be brought back to review branches in support of the overall success of their daily work.


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Center for Devices and Radiological Health


Allison Kumar
Allison.kumar@fda.hhs.gov

*More Information on MDDT*

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**Chris Leptak, MD/PhD**, *OND Biomarker and Companion Diagnostic Lead, OND IO/CDER/FDA*

# Biomarker Utility and Acceptance in Drug Development and Clinical Trials: an FDA Regulatory Perspective

**Chris Leptak, MD/PhD**

***OND Biomarker and Companion Diagnostic Lead***

***OND IO/CDER/FDA***

***TBI Endpoints Development Initiative Meetin***

***February 2, 2015***

# Disclaimers

- **Views expressed in this presentation are those of the speaker and do not necessarily represent an official FDA position**

- **I do not have any financial disclosures regarding pharmaceutical drug products**

# Outline

- Approach to biomarkers in regulatory science and drug development programs
- Opportunities for FDA engagement
- Resources

# Approach to Biomarkers in Regulatory Science and Drug Development Programs

# Regulatory Science:
## Bridging Basic Science, Clinical Practice, and Regulatory Authority

- Basic Science:  Understanding of molecular pathways, inter-cellular communication, and organ system physiology
- Clinical Practice:  Understanding disease pathology, diagnosis, and physiological response to treatment interventions
- Regulatory Authority:  Endowed by Congress through laws, Codes of Federal Regulation are the backbone for over-sight of drug development and approval standards

# OND Biomarker Lead

- **Biomarker data collection to determine impact on scientific and regulatory decisions**
  - Identification and qualification
  - Goals: consistency and standardization
- **Biomarker Resource Development**
  - Training for reviewers
  - Workshop planning
- **Policy and Process Development**
  - Guidance and MAPPs for biomarker-related endeavors
  - OND Liaison to Biomarker Qualification Program
  - CDER contact for Companion Diagnostics Guidance and co-development issues
- **Outreach and partnerships focused on common goals**

# FDA Regulatory Approach to Biomarkers

- Broadly defined (i.e, serum protein, change in tumor size by imaging study, algorithm for QT determination on ECG)
- Consistent with long-standing goals and drug development processes (i.e., data driven)
- Definition: characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or biological responses to a therapeutic intervention (2001 NIH Consensus Group)
- Characteristic is not a *clinical* assessment of a patient (contrasted with Clinical Outcome Assessments [COAs])
  - *Not* a measure of how a patient feels or functions or of survival
- Categorized by *how used* in *drug development* (contrasted with clinical biomarkers used in doctor/patient treatment decisions)

# Types of Biomarkers: Disease-focused

- Natural history of disease
  - **Diagnostic Biomarker**: presence or absence of pathology (progression: descriptive to diagnostic)
  - **Prognostic Biomarker**: predicts progression of pathology over time (focus on disease life cycle)
- Indicates future clinical course of a patient regarding a specified clinical outcome *in the absence of treatment intervention*
- Examples: For HIV, viral load, or CD4 count

# Types of Biomarkers: Response to Therapeutic Intervention (1)

- **Predictive Biomarker**
- Measured *prior* to a therapeutic intervention
- Differentiates patients who are more or less likely to respond to a particular drug's effect *or* are more or less likely to develop an adverse event associated with a particular drug (efficacy- or safety-focused)
- By definition, therapeutic or therapeutic-class specific
- Not necessarily prognostic of the post-treatment course
- Example: Her2/neu and Trastusumab

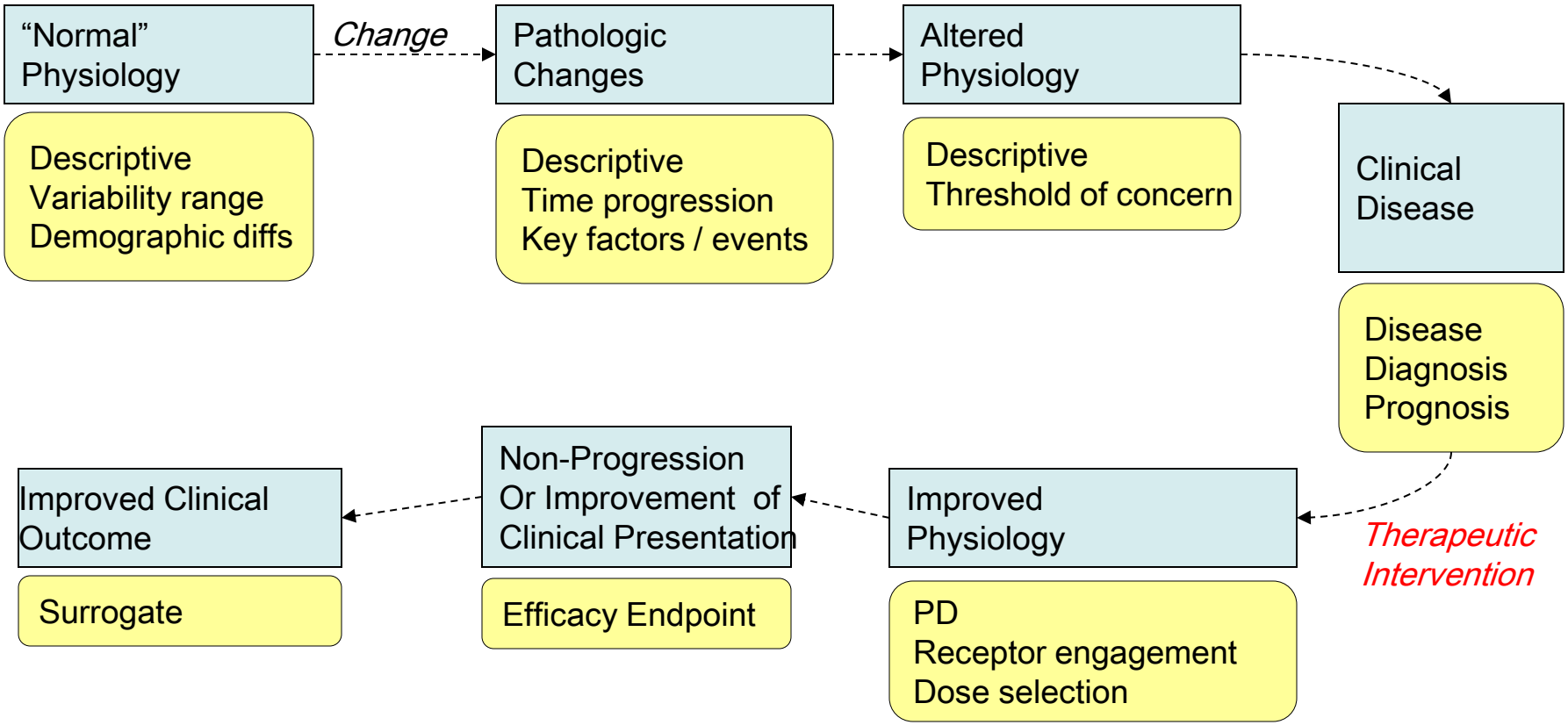
# Types of Biomarkers: Response to Therapeutic Intervention (2)

- **Pharmacodynamic (PD) Biomarker**
- Biologic response indicator to therapeutic intervention
- *Comparison* between pre- (baseline) and post-treatment
- Reveals if a response has occurred and degree of effect
- May or may not be treatment-specific
- Treatment response does *not* necessarily correlate with a clinical benefit. And if so, not necessarily a causal relationship
- Examples: BP, HbA1C, LDL

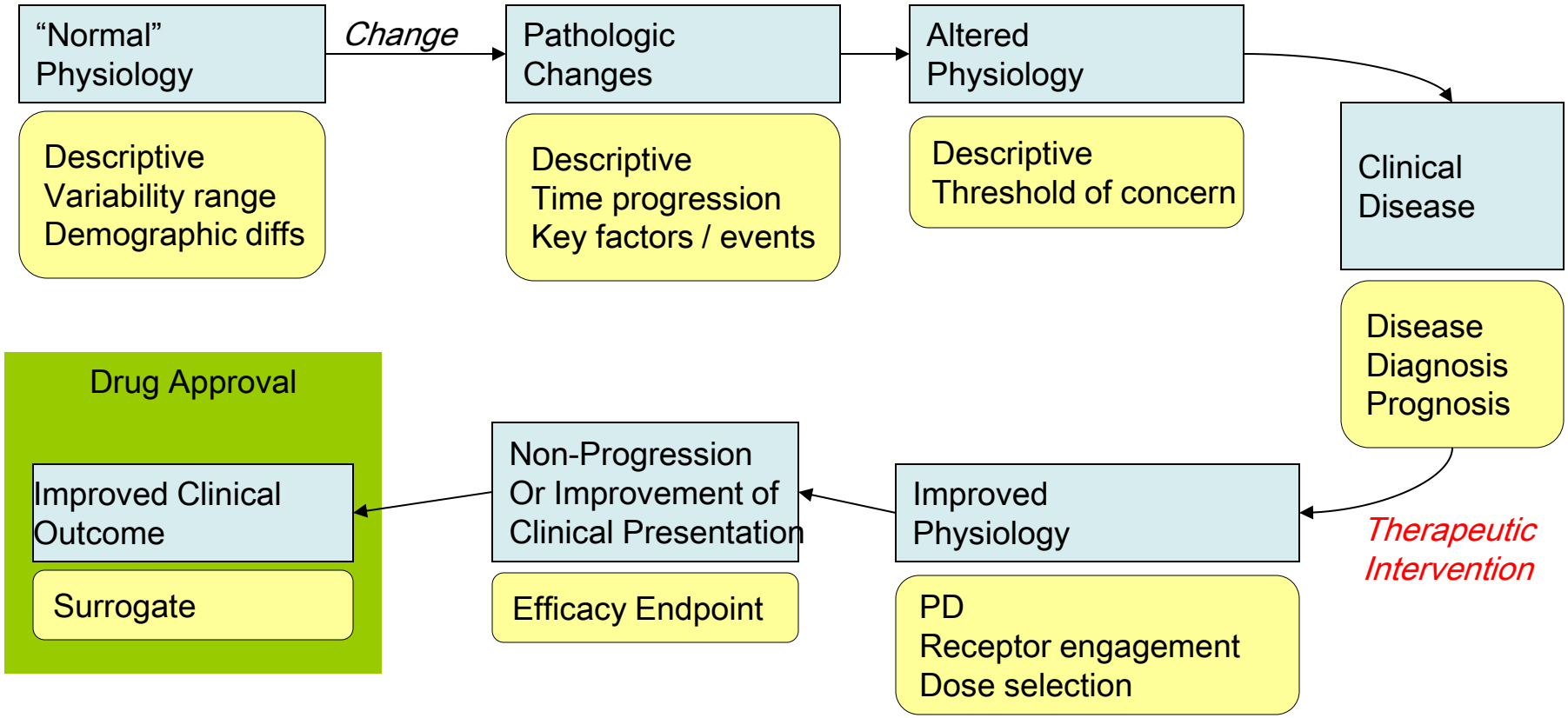
# Types of Biomarkers: Response to Therapeutic Intervention (3)

- **Efficacy Response/Surrogate Biomarker**
- *Small* subset of PD biomarkers
- Intended to substitute for a clinically meaningful outcome measure
- Treatment-specific
- Predicts the clinical outcome of a patient over time after a given treatment
- Potential benefit: reduced lengths of clinical studies
- Higher bar for level of evidence

# "Fit for Purpose": Match Biomarker to Your Goal, Your Data and Causal Relationship



# "Fit for Purpose": Match Biomarker to Your Goal, Your Data and Causal Relationship



# Two Approaches to Biomarkers in Regulatory Science and Drug Development Programs:

- **Drug-specific applications**
- **Formal qualification process**

*Note: Both equally valid, are data driven, and can have the same types of uses in drug development programs*

# How can biomarkers become accepted?

- General use accepted over extended time period
  - Accumulation of scientific knowledge and experience
  - Information not cohesively collected and can delay recognition of potential utility
- Case by case development for a specific drug
  - As part of IND/NDA/BLA/labeling update
  - Driven by a particular drug developer's needs
- Biomarker Qualification Process

# Drug Development Tool (DDT) Qualification Process:

Formalized process for multi-disciplinary review that involves a regulatory outcome that is data-driven

Intended for biomarkers that are broadly applicable and not product specific

Stages: Initiation, Consultation/Advice and Review

*Guidance: Qualification Process for Drug Development Tools*

# CDER's Interest in Biomarkers

- Use of biomarkers to impact and to improve drug development programs as well as regulatory and scientific decision making
- Inter-Office endeavor requiring communication and collaboration
- Goals of Biomarker Qualification efforts include:
  - Promotion and encouragement of external stakeholders to develop good biomarkers
  - Exploration of the possibility of personalizing therapy within the context of both safety and efficacy

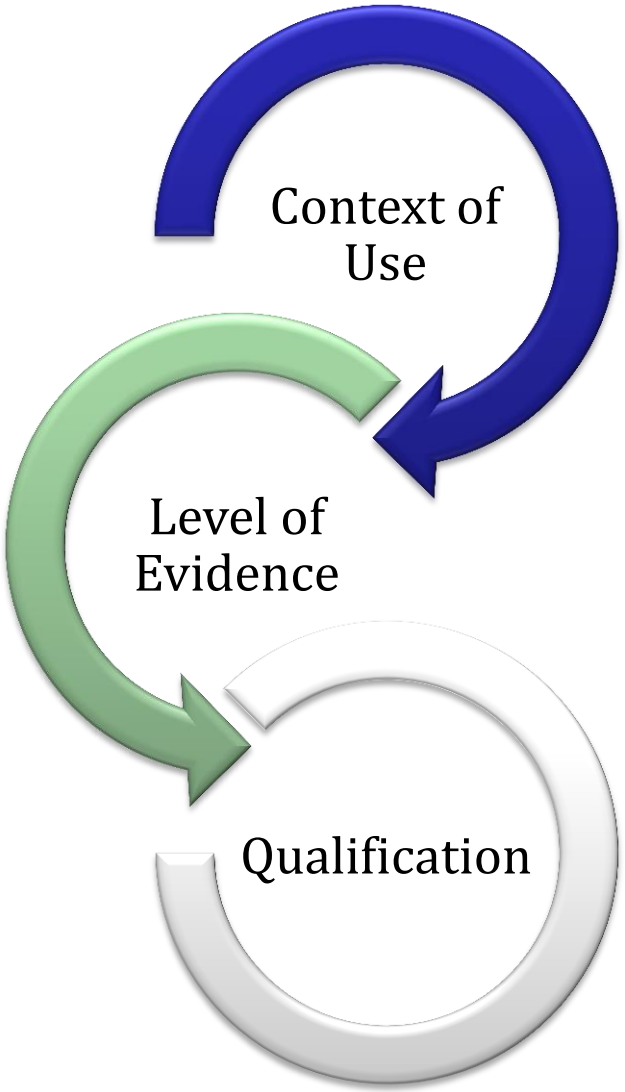
# What is Biomarker Qualification?

- *Definition:* Qualification is a conclusion that within the stated context of use, the results of patient assessment with a biomarker can be relied upon to have a specific interpretation and application in drug development and regulatory decision-making.

- *Regulatory implication:* Once qualified, drug developers will be able to use the biomarker in the qualified context in IND and NDA/BLA submissions without requesting that the relevant CDER review group reconsider and reconfirm the suitability of the biomarker.

# "Context of Use"

- Short-hand term for a comprehensive statement of manner and purpose of use in drug development
- May include:
  - Range of animal species (nonclinical)
  - Range of clinical disorders
  - Range of drug classes
  - Procedures and criteria for how samples are obtained
  - How the results are interpreted
    - Limitations on the interpretation
- Defines boundaries of known reliability
- Potential of expansion of context of use with additional studies/data supporting future qualifications


Context of Use
Level of Evidence
Qualification

# Opportunities for Engagement in addition to Biomarker Qualification

# Critical Path Innovation Meeting (CPIM)

**What is a CPIM?** Opportunity for industry, academia, patient advocacy groups, and govt to engage to improve efficiency and success in drug development. Topics are therapy independent and can include: natural history studies, emerging technologies, biomarker development, Clinical Outcome Assessments (COAs), innovative clinical trial designs

**Why Request a CPIM?** To have an opportunity to meet with FDA staff with expertise in an area for which you have questions. The discussions are nonbinding on the part of FDA and outside participants

**For more information, please contact**

CPIMInquiries@fda.hhs.gov

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm395888.htm

# Letter of Support (LoS)

**What is a LoS?** Describes CDER's thoughts on the potential value of a biomarker and encourages further evaluation to enhance visibility of the biomarker, encourage data sharing and stimulate additional studies that may support future qualification

**Why Issue a LoS?** Encourage identification, development and qualification of new drug development tools to overcome hurdles in drug development programs and to enhance drug safety and efficacy.

**For more information, please contact**

CDER-BiomarkerQualificationProgram@fda.hhs.gov

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm412833.htm

# Resources:

**www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default**

- Qualification Process for Drug Development Tools
- Clinical Pharmacogenomics: Premarketing Evaluation in Early Phase Clinical Studies
- In vitro Companion Diagnostic Devices
- Standards for Clinical Trial Imaging Endpoints
- Clinical Trial Designs Employing Enrichment Strategies to Support Approval of Human Drugs and Biological Products

# Questions?

**Jonathan Murray**, Managing Director of Research Circle Technology for GE, is driving the development and commercialization of disruptive technology that is re-imagining healthcare toward a vision of Healthymagination.

During his career, Mr. Murray has held numerous product and process roles including: Design Engineer; Champion, Design for Six Sigma; Engineering Manager for a ECG Division and General Manager for a $700M premium CT division.

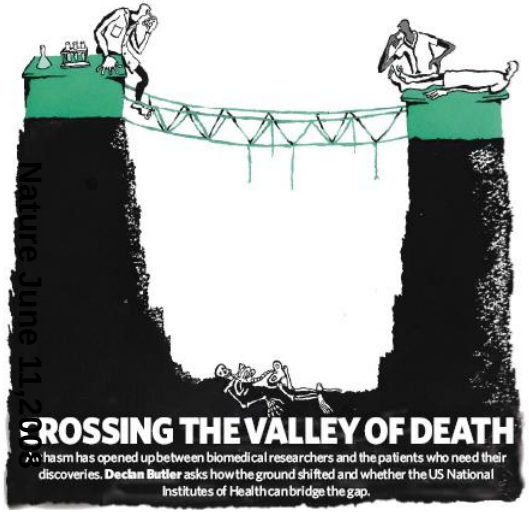
# Accelerating Medical Innovation

*Plenty of Ideas*

*Plenty of Discovery*

*Plenty  Effort*

*Plenty of Cost*

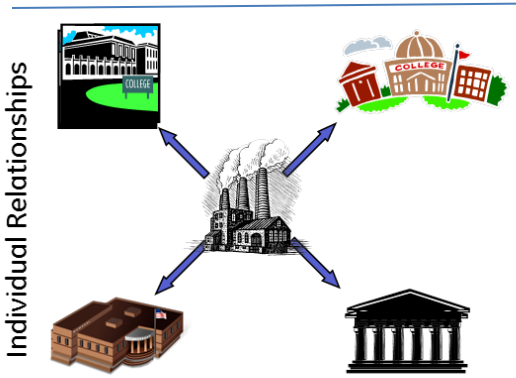



*Fewer Solutions*

*Fewer New Products*

*Fewer Rewards*

***"…many costly, time-consuming bottlenecks exist in the translational pipeline."***

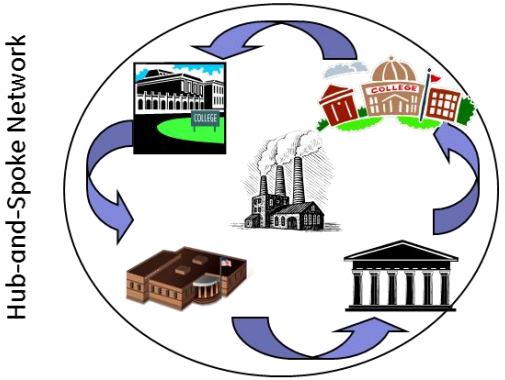



Multiple IP "fences"

***Traditional restrictive Bi-Lateral Agreements***



***Updated with Leading concepts in Innovation***

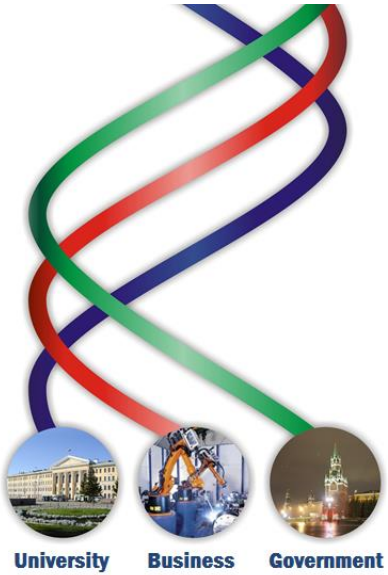



Single IP "fence"

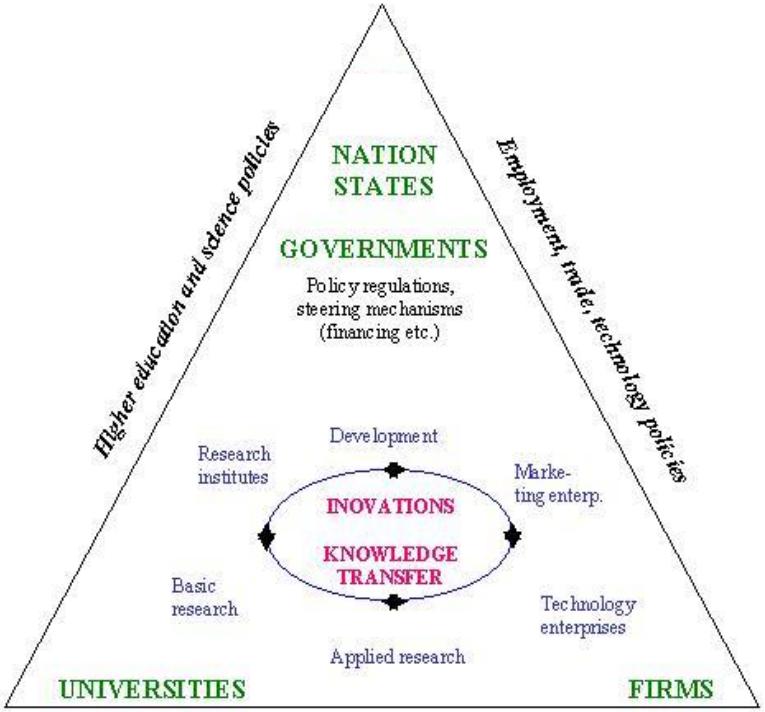
***Progressive access: Research Circle***

# *Models of Public & Private sector communities*

## Triple Helix




## Golden Triangle

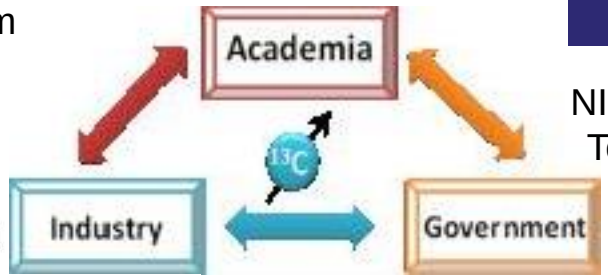


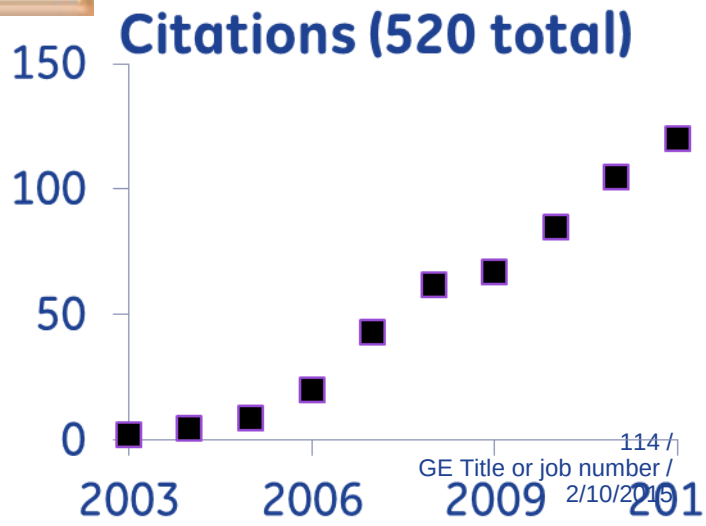

Together, We Can Do Great Things!

# Research Circle Experiment…

4th International DNP Symposium
August 2013, Denmark


NIH Funded : Hyperpolarized MRI Technology Resource Center @ UCSF



# Research Circles: Lessons Learned

## Observations

- **Great Science leads => Best Products.**
- Common Goal:  Wide adoption will maximize benefits for Industry, Academia & Society.
- Economics of modern Healthcare demand responsible IP protection.
- Relationships succeed with people… cultivated by organizations.
- People and organizations want  to behave responsibly – train & trust.
- Part of Something, Better than All of Nothing
- Today Translational medicine requires early Industry participation.
- Democratized/Open Innovation is both Natural & Efficient.

ScienceBuisness
Magic Circles

## Industry Actions

- ❑Embrace Democratized/ Open Innovation
- ❑Encourage Site- Site Cooperation
- ❑Respect Academic competition & secrets
- ❑Streamline publication processes
- ❑Promote Technology and Acad. Researcher
- ❑Enable responsible access to technology

## Academic Actions

- ❑Align efforts to – Advance the technology
- ❑Practice Coop-ition, when possible
- ❑Respect IP needs & Industry  Realities
- ❑Comply with  processes
- ❑Promote Technology and Indus. Collaborator
- ❑Ensure Responsible use of the technology

## Together, We Do Great Things!


# Thank You

Jonathan.Murray@ge.com

**Beth McQuiston, MD, RD**, is a board certified neurologist (American Board of Psychiatry and Neurology) and registered dietitian. She completed her training at University of Chicago, Rush University Medical Center, and Harbor UCLA. She is currently a Medical Director at Abbott Diagnostics with a primary focus on neuroscience and traumatic brain injury biomarker research.

# From Benchtop to Bedside: Critical Considerations in Novel Biomarker Development

Beth McQuiston  MD, RD

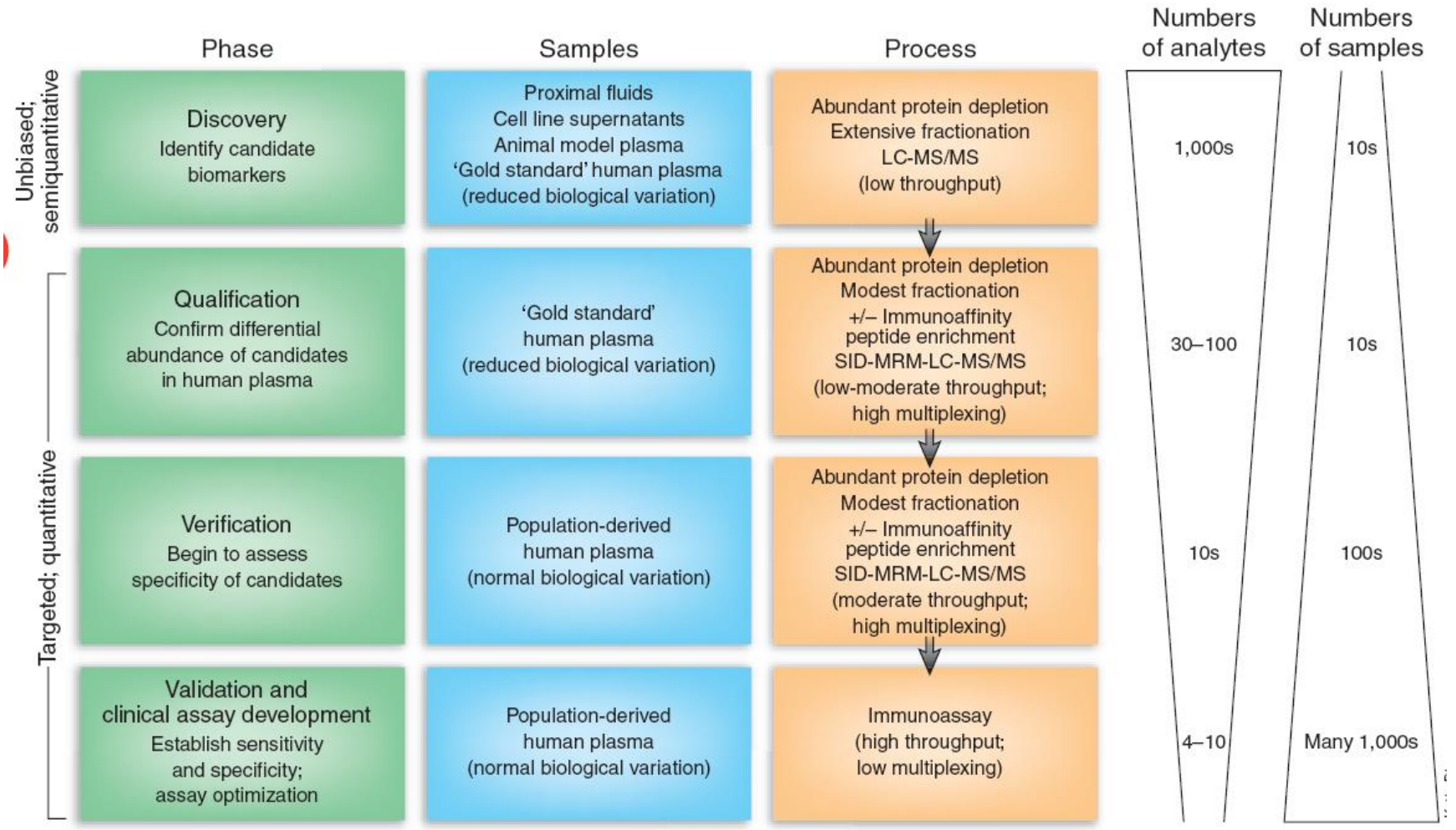
Abbott Diagnostics

Abbott
A Promise for Life

# Novel vs Established Biomarkers

- Novel Biomarkers need to have their clinical effectiveness proven before they can become part of medical practice.
- Agreement/Alignment of what constitutes a gold standard
- Much larger hurdle than with established biomarkers
- More extensive clinical data required
- Usual development studies PLUS health economic and outcomes data
- Need FDA approved assays on accessible platforms

# Discovery and Development of Novel Biomarkers




Nifai et al. Nature Biotechnology 2006

# Determining Clinical Utility

- What is the clinical utility…specifically how will doctors use this to make treatment decisions?
  - Several potential clinical uses may be evaluated.
  - Clinical utility could involve:
    - assessment of risk of getting a disease,
    - screening (general or population specific)
    - aid in diagnosis and/or monitoring the effectiveness of treatment
    - use as a companion diagnostic
    - prognosis

- For each of these potential uses, one needs to understand how these results behave in a normal population, what is the biological variability, what other disease states can impact the results, what interfering substances can impact the results, and many other factors.

# Determining Clinical Effectiveness

**The results of the test should**:

- Help the clinician and patient make a treatment decision
- Improve patient outcomes
  - Increase disease-free survival
  - Improve quality of life
  - Reduce cost of care
- Be easy for the clinician to use and interpret
  - example: blood test vs. csf test, normal range results far from disease range results, specific for disease under consideration
- Be transferrable and based upon a recognized standard

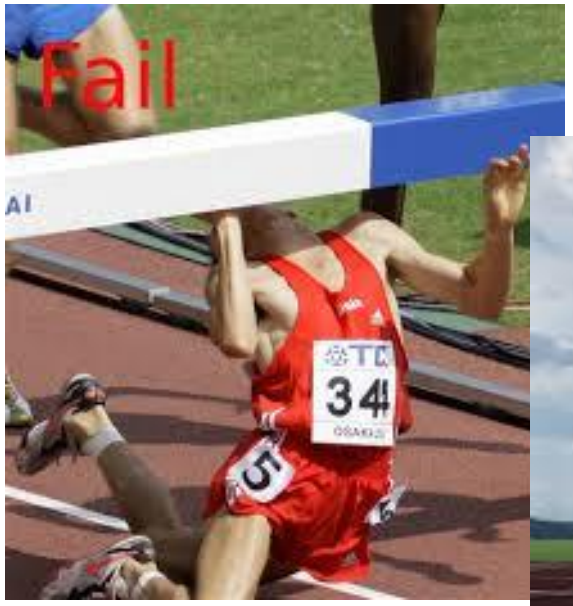
# What data does a clinician need to adopt a novel biomarker?

- Pathophysiological mechanisms must make sense and align with the clinical picture
- Requires different clinical studies across intended use population.
- Requires replication in multiple clinical settings for a particular intended use
- Interventional trials demonstrating that interventions based upon biomarker results improves patient outcomes

# Clinical Utility Studies

- Must be coordinated in order to:
  - Minimize costs by preventing duplication of efforts
  - Compare study data
  - Improve clinical adoption and minimize physician confusion
- Aligned to a clear medical/clinical strategy
- Best if aligned/compared to a recognized gold standard

# Hurdles




**Donna J. Edmonds**, Active Chairman of the Board at ImmunArray Ltd., brings over 30 years of experience in both the provider and the industry side of the healthcare business. Her primary focus has been in the introduction, management and commercialization of new technologies. She was one of the early and continuing contributors to the evolution of use of biomarkers in cardiovascular care.

# BioMarker Driven Clinical Practice Perspectives Re: The Journey from Clinical Development to Routine Use in CV

# TED Mtg.

# February 2015

www.immunarray.com

# The Biologic Hard Drive

## Potential roles

- Diagnosis/differential diagnosis
- Risk stratification
- Therapeutic decision-making
- Disease monitoring
- Identification of drug targets
- Better understanding of pathophysiology

**Courtesy R Jesse MD PhD, VCU**

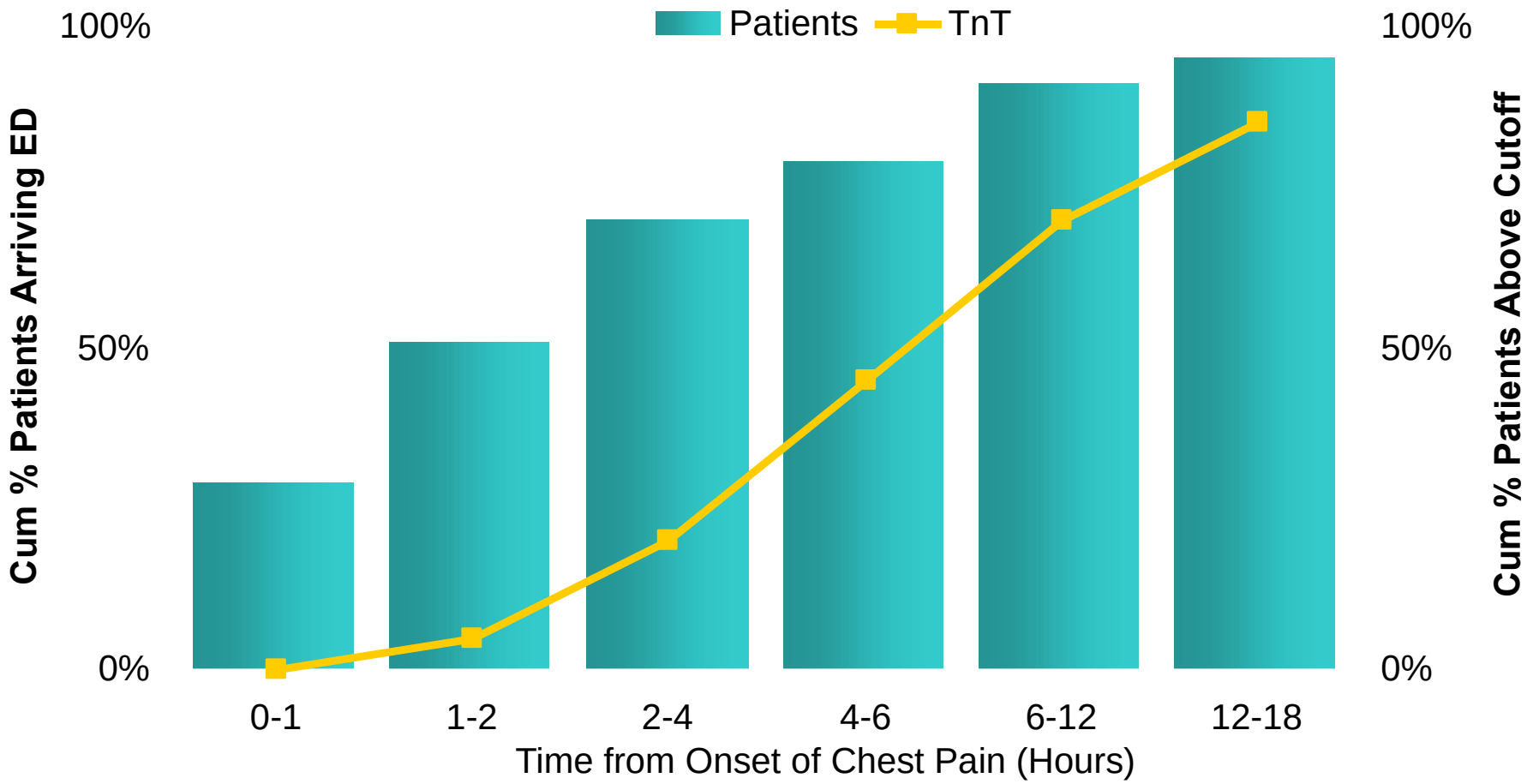
**Easiest to Access/Rich in Information**

# Practice Driven by Standardized Process Risk Level and Goal Strategy in CV

| Risk Level | Very Low 5 | Low 4 | Mod 3 | High 2 | Very High 1 |
|---|---|---|---|---|---|
| Primary Goal | Alternate Diagnosis | Prognosis | Diagnosis | Intervention | Intervention |
| Secondary Goal | | Prevention | Prevention | Diagnosis | |
| Time to Goal | | 3 hr | 8 hr | 30 min | 30 min |

**Need Same in TBI**

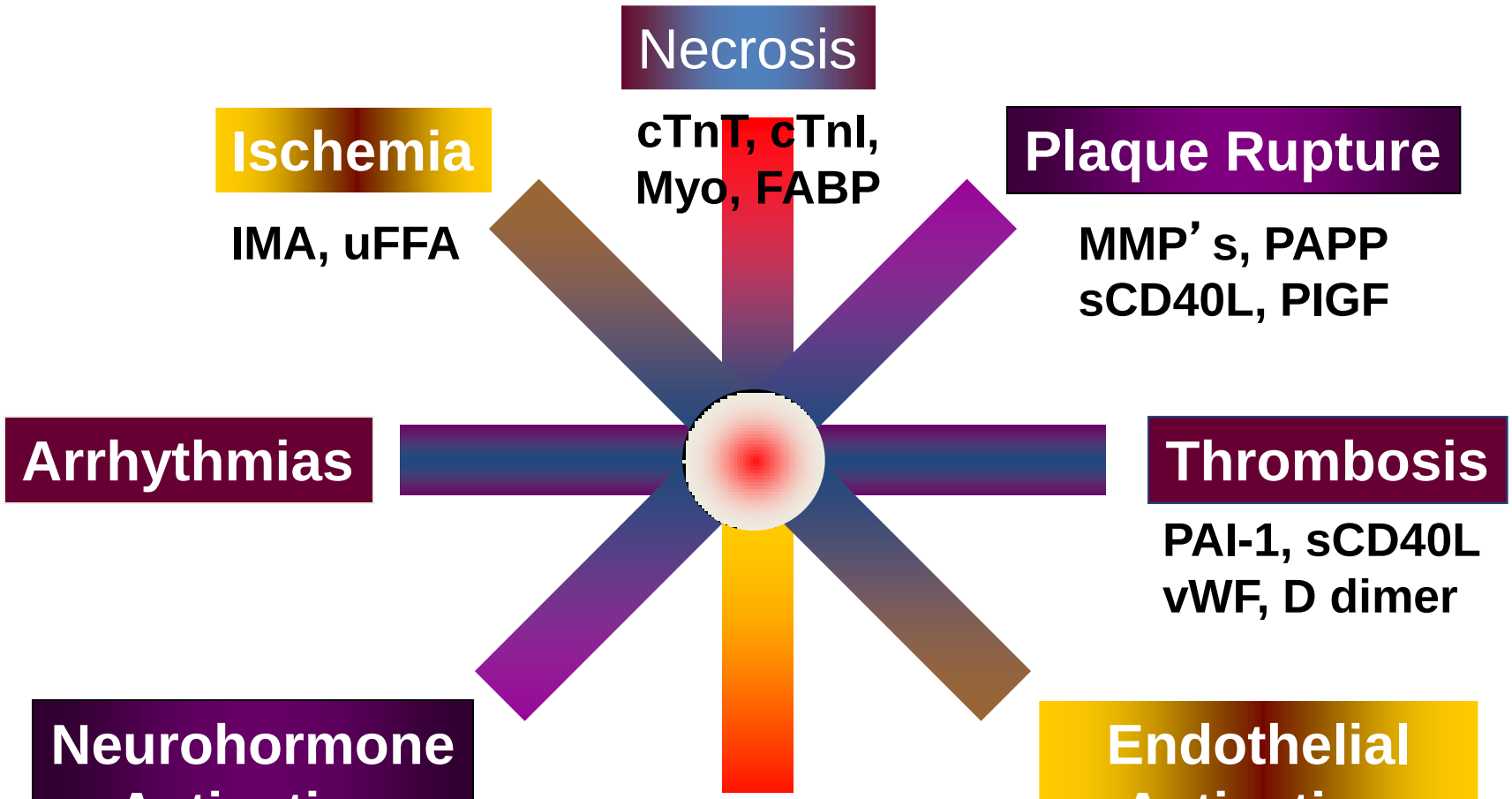
# Presentation Troponin & Risk Stratification (Before Sensitive Assays)




**Troponin rises too late for most patients to be diagnosed at presentation**

Goff et al, REACT, American Heart Journal, 1999
deWinter et al, Circulation 1995

# The Future--Even then-- was MultiMarker Strategies






Courtesy J deLemos, Univ of Texas SW

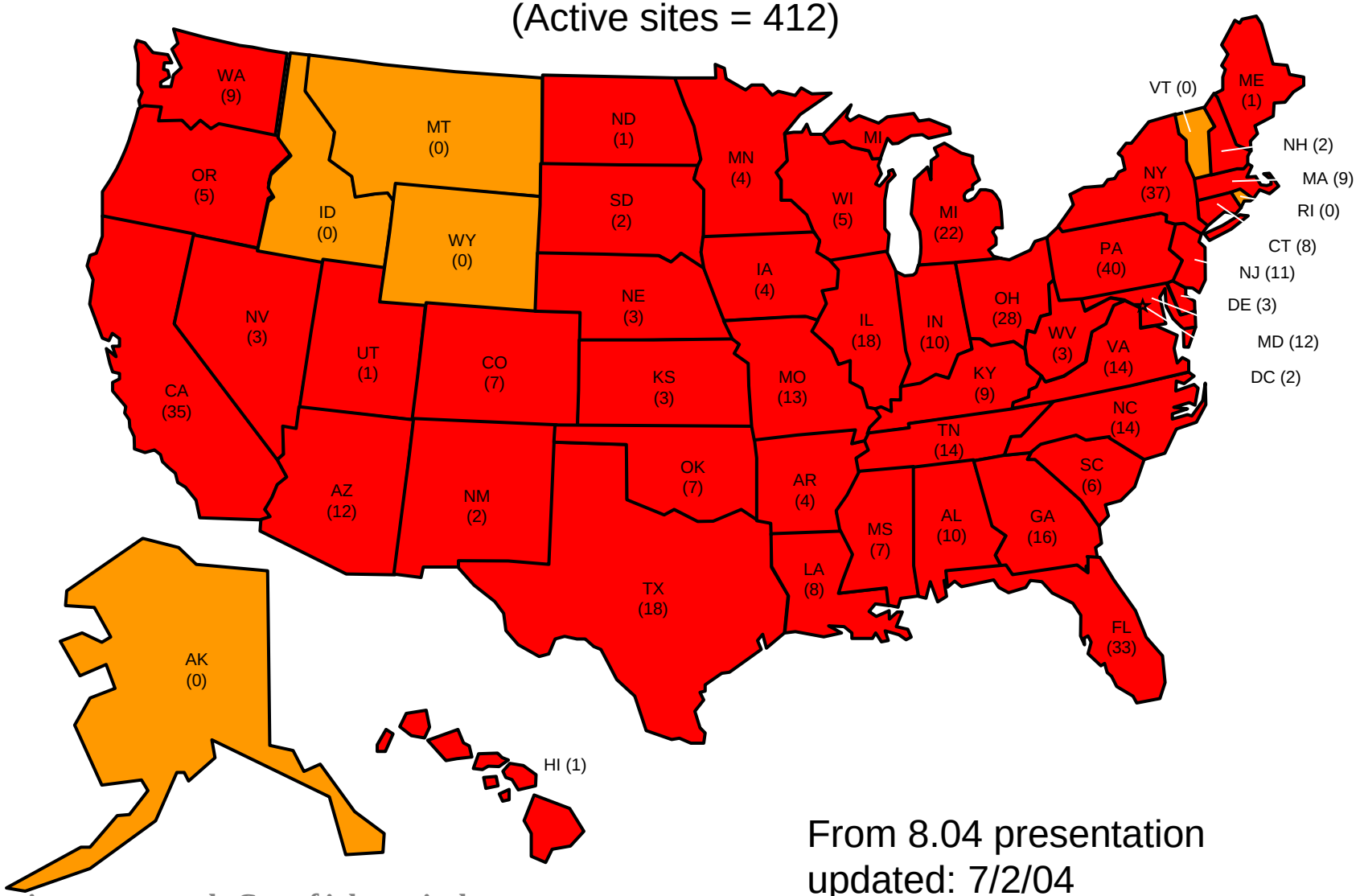
# Acute Care for Patients with NSTE ACS, Overview of Practice Guidelines, and National CRUSADE Results

***Can Rapid Risk Stratification of Unstable Angina Patients Suppress ADverse Outcomes with Early Implementation of the ACC/AHA Guidelines***

**The Power of Registry Based Practice Monitoring and Data Sharing (Initiated Dec. 2001)**

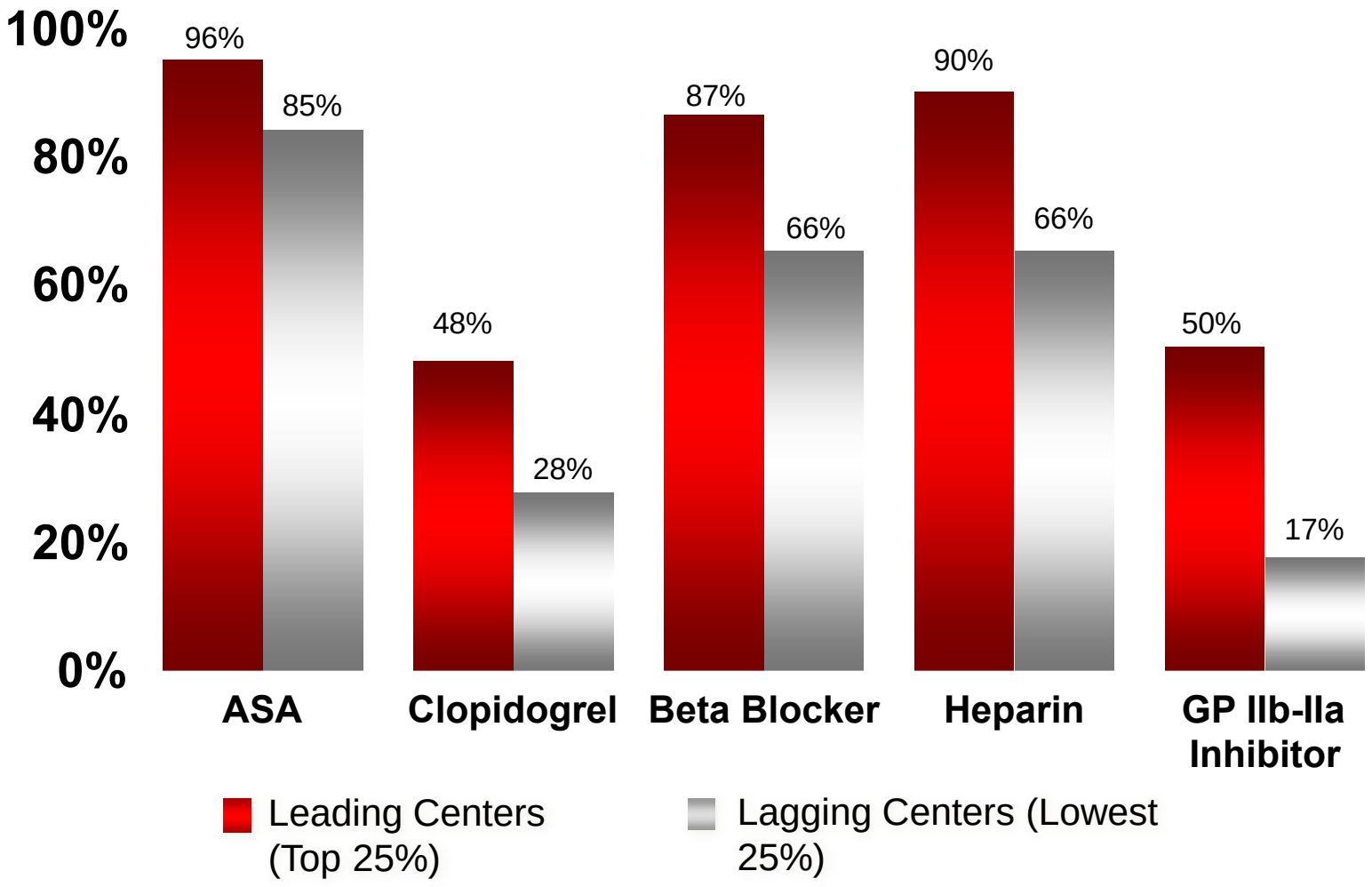
# CRUSADE Site Distribution

Total sites = 476
(Active sites = 412)




From 8.04 presentation
updated: 7/2/04

# Leading and Lagging Hospital Quartiles: Acute Care (< 24 hrs)




Peterson et al, ACC 2004

# "Creating the Rule Book/Following the Rules"

**An Example:**

SOCIETY OF CARDIOVASCULAR PATIENT CARE

**Mission**

- To develop and share quality practices that optimize the care and outcomes of patients with acute cardiovascular disease worldwide through innovative cross-disciplinary processes and education that bring science to the bedside.

# Start the Journey Building on Lessons Learned

- **Early Risk Stratification Standards**
- **Early BioMarker Clearance by FDA with Risk Stratification Claims**
- **Multi-Modality Based Study integrated into Real World Registry Approach**
- **Drive <u>with</u> Pharma**

**Mark Lovell, PhD**, served as the Chairman and Chief Executive Officer of ImPACT Applications from 2002 through 2013, and currently serves as Chairman of the Board and Chief Scientific Officer. In the early 1990s he developed the ImPACT® Test, which has become an internationally used tool in the comprehensive clinical management of concussions. He is internationally recognized as a concussion expert for his development of innovative neurocognitive testing programs and ground breaking research.

# The ImPACT Assessment Tool

## From Sports Medicine to Military Applications

Mark Lovell PhD, FACPN
Chairman and Chief Scientific Officer
ImPACT Applications, Inc.

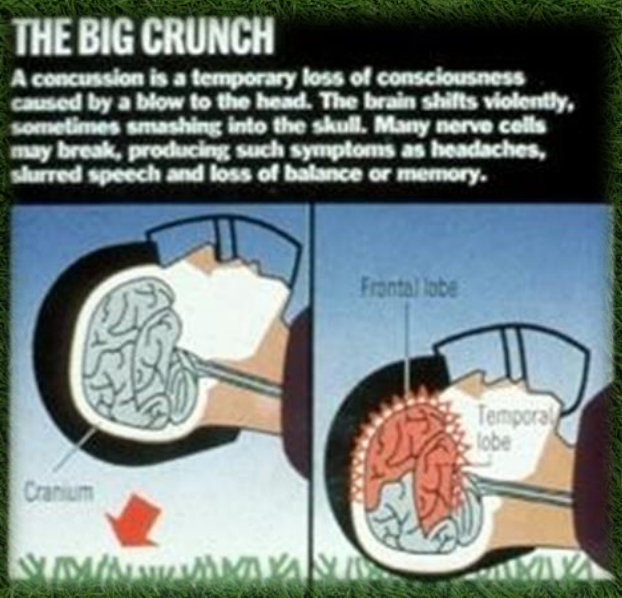
Founding Director and Professor
UMPC Sports Concussion Program
Departments of Orthopaedics and Neurosurgery
(retired)

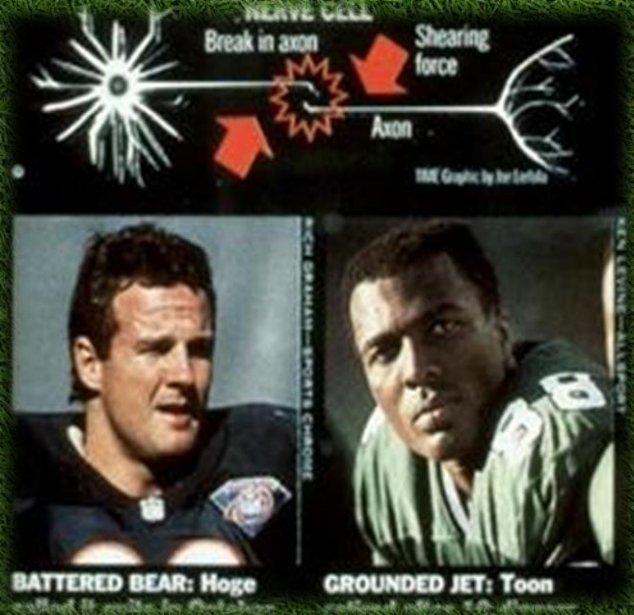
# Disclosure

- Dr. Lovell developed ImPACT test and is Chairman of the Board of ImPACT
- Dr. Lovell has serves or is serving as a consultant (voluntary and unpaid) For the following organizations:
  - The National Football League
  - The National Football League Players Association
  - The National Hockey League
  - Major League Baseball
  - NASCAR
  - Indianapolis Racing League
  - The US Ski and Snowboard Team
  - Irish National Rugby Team
  - The Jockey's Guild
  - South African Rugby
  - Maine National Guard
- Dr. Lovell is a paid consultant to World Wrestling Entertainment (WWE)

# The Pittsburgh Steelers Program (1980's and 1990's)

- First program to monitor professional athletes
- Resulted in league wide programs in NFL/NHL/MLB
- Led to development of ImPACT Program
- Currently over 8 million athletes have been tested
- Over 30,000 Military personnel baseline tested (USASOC)
- Recent studies published



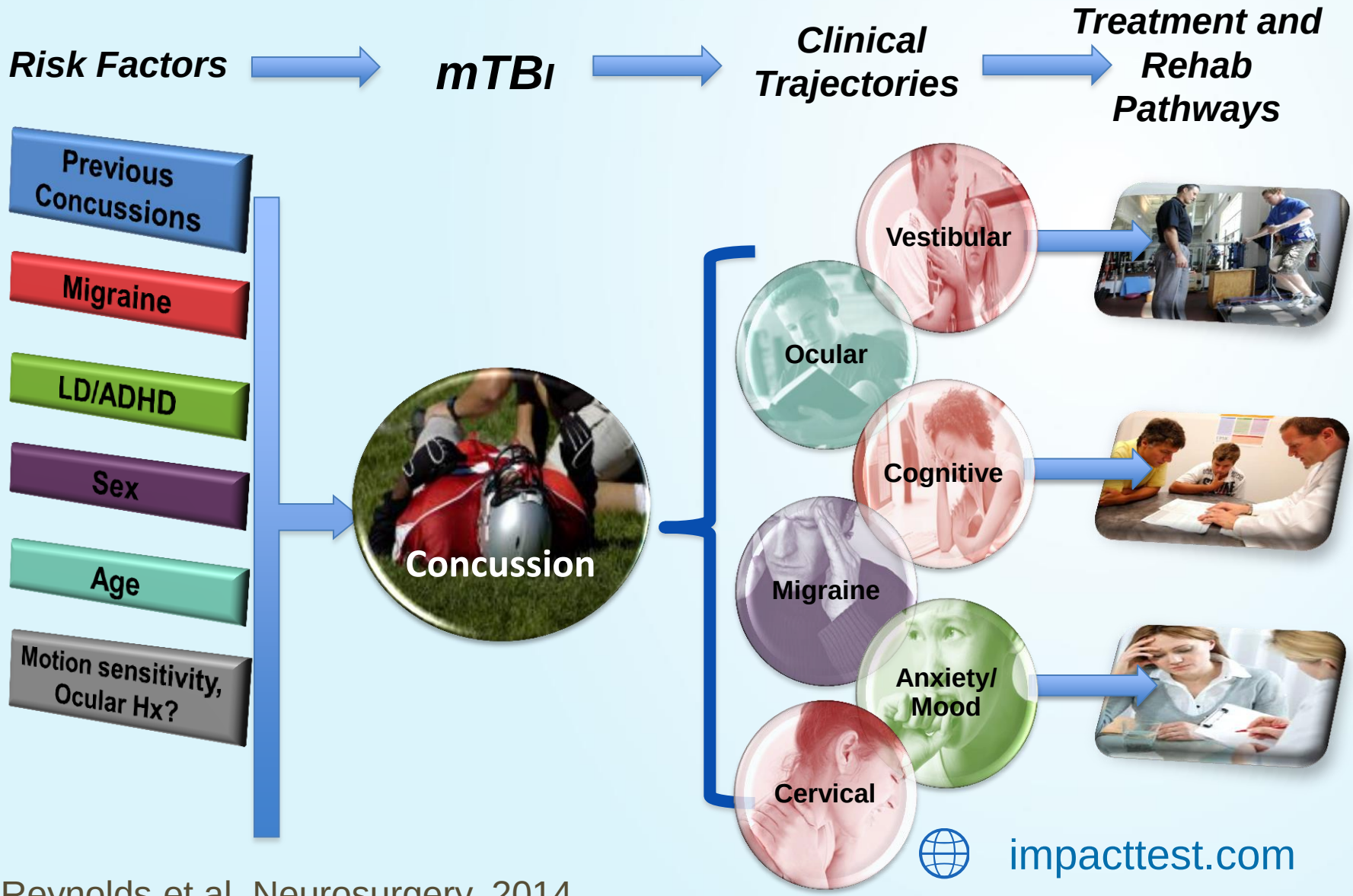



# What is ImPACT ?

- A brief test battery that measures important components of neurocognitive functioning.
- Is part of a mutli-modality assessment program that relies on multiple disciplines and professionals
- ImPACT was developed over a twenty year period through research with multiple sports.
- Has been utilized in a number of studies of TBI in the Military
- ImPACT has been heavily researched (over 220 peer-reviewed papers)
- **ImPACT is not a stand alone approach to recovery but is**

  **part of a multi-disciplinary approach to brain injury and brain injury recovery**

# Using Concussion Clinical Trajectories to Inform Targeted Treatment Pathways




Reynolds et al. Neurosurgery, 2014

# Important Components

- ImPACT can be administered with or without a baseline. (Baseline testing is preferable but not always possible).
- ImPACT has built-in validity indicator to identify unrealistic test results.
- ImPACT also measures subjective symptoms

# ImPACT® and the Military

- ImPACT Military created in 2009 at the request of Col. Robert Lutz (USASOC)
- Inclusion of military specific items and questions

- Approximately 57,000 baselines completed to date (USASOC and Navy SW))
- 22,203 individuals met criteria for inclusion in initial study

- Utilized downrange, 2,813 had injuries
  - 1,700 blunt trauma
  - 861 were from blast trauma
  - 252 combination blunt/blast trauma

- Personnel with diagnosed blunt (OR=3.58) or blast (OR=4.23) or combination (OR 5.73) with more likely to report PTSD symptoms (.0001).

- Individuals with blast combination TBI's did worse on memory testing, reaction time and had more PTSD symptoms

Kontos, Kotwal, Elbin, Lutz, Forsten, Benson and Guskiewicz, *J. Neurotrauma*, 2013

# A Lifespan Model of Understanding Concussion

**Genetics?**

Migraine HX?

**LD/ADD?**

Genetic Expression? Brain Development?

Sports?

Bigger? Faster? Stronger? Injury HX? "Natural Selection"

CTE?

Aging?

Other Diseases?

Alzheimer's?

Obesity?

HTN/Stroke

Lovell, 1996

# Thank You!

Mlovell@impacttest.com

# Thank You!

Mlovell@impacttest.com

**Michael Ropacki, PhD** is a Director of Clinical Research, Neurosciences, for Janssen Research & Development, as well as an Associate Clinical Professor of Neurology at Loma Linda University School of Medicine.

For Janssen Research and Development, Michael is responsible for the development and execution of clinical programs within the neuroscience therapeutic area. Among other initiatives, he is co-chair of the C-Path's Coalition Against Major Disease Predementia Clinical Outcome Assessment team that is attempting to qualify a novel composite endpoint through FDA's Drug Development Tools Clinical Outcome Assessment Qualification Program.

# Segment III Panel: Regulatory Readiness Case Studies

Director, Clinical Research
Janssen Research & Development, LLC
Associate Clinical Professor of Neurology
Loma Linda University School of Medicine

# Disclosures

No apparent disclosures for the topic of discussion – TBI Endpoint Development

Activities influencing my opinion and shared information:

- Dissertation
- Clinical Lead of CHARIOT-PRO Program
- Translation/Validation Studies for BACE Development
- Clinical Development Leader Brain Health Registry

  Joint Steering Committee Member
- Co-Leader of NYAS-GAP Registries-to-Cohort Team
- Co-Leader of IMI-EPOC/EPAD Scientific Advisory Group

  Determination of clinical endpoints for EPOC & EPAD studies
- Co-Chair ADNI PPSB Cognitive Endpoint Working Group

  Developed Pilot Study on unsupervised computerized asst. to support ADNI3 NIH application
- NIH Advisor

  Expert working group advising the NIA, the NACC Steering Committee and the Clinical Core Steering Committee on cognitive and clinical endpoints
- Dementia Platform UK Work Package Team Member
- **Co-Chair Critical Path Institute CAMD pCOA Team**

  **EMA/FDA Qualification of novel clinical endpoint for future AD trials**

# Outline & Objectives

**Background slides to highlight parallels between AD and TBI research**

Objective: Better understanding of similarities between efforts

**Why qualification?**

Objective: Increased awareness of pitfalls of leveraging measures not qualified and need for and benefits of qualifying endpoints

**Brief qualification case example – pCOA DDT COA Qual. Program**

Objective: Provide real-life example of the qualification process

**Lessons Learned: Important issues for TED Initiative's consideration**

Objective: Improved understanding of important considerations impacting near-term decisions and future work

# Background

- Over 200+ Failed Clinical Trials (CTs) in AD since 1980's
- Commonly used measures in AD CTs numerous shortcomings
  - For instance, MMSE, ADAS-Cog, CDR
  - Especially early in disease course
- Statistical and/or Theoretical (S/T) Composites proposed as the 'solution'
  - Smaller samples
  - Greater power
  - Shorter studies…well maybe
- Proposed to-date rely on measures with poor psychometric properties
  - Repeatability of findings all based off retrospective data from ADNI+/- CT data does not provide proper validation
    - ADNI patients are more advanced
    - ADNI participants not representative of those in CTs
    - Cross sample validation is needed
    - Prospective data for validation is needed
  - Results may not be sensitive in earlier or later populations

# Background

- Long history of psychometrically developed and well validated NP measures and batteries
  - Many yield a Composite Score/Summary/Index Scores
  - Different from recent S/T Composite Endpoints
  - Clinical Meaningfulness of NP measures and batteries, and Composite/Summary/Index scores are better established
- New S/T Composite Endpoint research is in its infancy
  - More unanswered questions than answers
  - Clinical Meaningfulness yet to be established
- Problems with new S/T Composites
  - Sponsors & Regulators betting on these unvalidated Statistical Composites
  - Derived with more advanced patients, questionable sensitivity earlier
  - Components do not make sense clinically, and are often at ceiling
  - Questionable Clinical Meaningfulness of those derived to-date

# Background – Where are we at today?

- AD research moving earlier
  - Where treatments may have greater impact
- Traditional measures (MMSE, ADAS-Cog, CDR) lack sensitivity
- Pharmaceutical industry has largely ignored hundreds of well-validated neuropsychological measures that may be sensitive in early AD
  - Failed to implement them in clinical trials exploring their ability to measure treatment effects
- Lack of consensus on cognitive and functional endpoints
  - Which should be used in pre-dementia
- Researchers attempting to 'optimize' existing measures

- Identifying and combining sensitive sub-components
- Combining to create S/T Composite endpoints

# Why Qualification?

- **Belief**: FDA Review Division acceptance that a sponsor can proceed at-risk with a proposed non-qualified endpoint in their development program is all that is needed.
- **Reality**: Majority of the time this is fine. However, recent examples where this was not the case.
  - Changing of the guard
  - Evolving scientific data and opinion in the field
- **Benefits**:
  - Collaborative process with the regulators, learnings along the way
  - Alignment across the field and companies with consortia-based model
  - Data sharing across consortia – advances science
  - Avoids need to repeatedly build case in each submission BDs
  - Assurance that submitted endpoint will be accepted at data read-out
- **Potential Downsides:**
  - Can be a long process dependent upon status of the science & available data
  - Need for *careful positioning* of qualified endpoint as "a" tool, NOT "the" tool

# Case Example – pCOA DDT COA Qual. Program

- Statistically-derived composite endpoint – ADCOMS
  - AD COMposite Score (ADCOMS)
    - Designed for pre-dementia AD population
      - Target population defined as MCI-AD/pAD
    - Comprised of the most sensitive bits of commonly used AD CT scales
      - Increased sensitivity compared to parent measures
    - Retrospectively derived from observational studies (e.g., ADNI) and CT data
      - Partial Least Squares regression modeling to fit linear disease model, using change from baseline
      - Weighted linear combination to achieve the highest Mean-to-SD Ratio (MSDR)
    - Prospective data collection for validation is ongoing
- Submitted for qualification to the FDA and EMA – Status Update
  - -Letter of Intent
  - -Briefing Document
  - -Scientific Advice Meetings – EMA and FDA conjointly
  - -Written Qualification Advice – Received EMA only

# Lessons Learned: Issues for TEDI's consideration

- What type of Composite?
  - Cognitive composite, functional composite, combination or multiple?
  - Leverage existing validated NP Composite/Index/Summary Score versus de novo derivation?
  - Theoretical, Statistical or combination of the two approaches?
    - ADCOMS Statistically-Derived example
    - ADCS-PACC Theoretically-Derived example
- What types of data are available to support creation?
  - Established NP measures – validation data from manual & literature?
  - Retrospective longitudinal observational cohort data?
  - Prospective observational cohort data?
  - Interventional study data (retrospective or prospective)?
- If creating from scratch:
  - Utilize existing tools and optimize (e.g., ADCOMS)?
  - Create from novel measures with improved sensitivity?
  - Combination approach?

# Lessons Learned: Issues for TEDI's consideration

- What will be required for validation?
  - Voice of the patient?
    - Linguistic validation with/out Cognitive Debriefing
  - Psychometric validation?
  - Cross-sectional of population-based normative data?
    - Healthy Normals versus a known-groups TBI sample
  - Longitudinal data in population of interest and healthy normals?
- Will translations and validations into other languages be needed?
  - Global International acceptance and use is important
  - Major implications for the types of needed validation
- Will alternate forms be needed?
  - Mitigation of learning and practice effects is crucial
  - Will the endpoint be designed to:
    - Track longitudinal change over time?
    - Measure interventional effects?

# Overall

- **There are many parallels between what has gone on in AD and TBI research-to-date.**
- **Qualification is a worthwhile endeavor**
  - **Benefits well outweigh the downsides**
  - **Advances the field and science**
  - **Unique opportunity for collaboration and data sharing**
- **The CAMD pCOA with ADCOMS provides a real-life glimpse into what is in this group's future**
- **There are many lessons learned to-date highlighting important issues that the TED Initiative will need to carefully consider**

**THANKS for the opportunity and your attention!**

# General Clinical Endpoint Considerations

- **Floor/Ceiling Effects:** high concentration of subjects scoring at bottom/top of scale (>15% of the patients obtain the lowest or highest possible score)

  Patients in these upper or lower ends cannot be distinguished from each other, and change cannot be measured
- **Interpretability:** extent to which one can assign qualitative (clinical) meaning to quantitative scores
- **Sensitivity:** ability of a clinical measure to identify those with a disease or problem
- **Specificity:** ability of a clinical measure to correctly state an individual does not have a disease when they are disease free
- **Positive Predictive Value (PPV):** Likeliness that a patient has a disease given positive test findings
- **Negative Predictive Value (NPV):** Likeliness that a patient does not have a disease given negative test results

# Composites: Psychometric Considerations

## Reliability

**Test-retest Reliability:** stability of the composite measure's component scores over time and correlation of them across testing sessions

**Alternate-Form Reliability:** correlation between alternative forms of the same composite measure

**Inter-rater Reliability:** extent that different raters agreement on scoring and classifying performance with composite

**Practice Effects:** what degree of improvement is seen with repeated administrations; related to test-retest reliability

# Composites: Psychometric Considerations

## Validity

**Construct Validity:** extent to which the composite measure reflects the construct of interest (e.g., to what extent is an IQ test actually measuring "intelligence“)

- **Convergent Validity:** extent to which two measures tap into similar or related constructs.
- **Discriminant Validity:** correlation between measures that are <u>not</u> expected to be related to one another or that assess dissimilar and unrelated constructs

**Criterion Validity:** correlation between the composite measure’s subcomponents and a criterion measure (or measures) considered representative of the construct (e.g., correlate composite with ‘gold standard’ measures)

**Content Validity:** evidence that the content of the composite’s subcomponents reflect the construct (e.g., IQ) or domain (e.g., memory) of interest

# Composites: Psychometric Considerations

## Validity

**Predictive Validity:** correlation of a composite at one point in time wither performance on another criterion measure at some future point.

**Ecological Validity (aka Face Validity):** extent to which a composite measure appears to assess the construct of interest (e.g., memory test of medication instructions)

**Concurrent Validity:** correlation of a composite measure with performance on another criterion measure at the same point in time (e.g., correlation between 2 memory tests)

# Composite Endpoint Considerations

- Subcomponents should derive from 'parent' measures with proper psychometric validation and empirical support
- Should tap into the aspects most affected in population under study
  - Medial temporal lobe functioning
- If first two considerations are met, then composite measure would be deemed suitable for research purposes
  - Applied to existing datasets
  - Not applicable for use in populations different from those derived
    - Unless validated in datasets from these population(s)
- However, the composite would still required to undergo
  - Prospective validation
    - Demonstration of external responsiveness
    - Demonstration of internal responsiveness
  - Demonstration of Clinical Meaningfulness
  - Qualification with regulatory authorities
    - Especially pertinent if composite will be used for earlier populations

**Diane Stephenson, PhD** is the Executive Director, Coalition Against Major Diseases at Critical Path Institute. She is a neuroscientist by training with 30 years combined experience in academic neuroscience and drug discovery. Diane has over 55 scientific publications and six patents in the neuroscience area. In her current role, Diane leads multidisciplinary teams comprised of academic experts, industry scientists, patient advocacy groups and regulatory experts collectively aimed at accelerating treatments for patients with neurodegenerative diseases.

# TBI Consensus Conference

Diane Stephenson, Ph.D., Executive Director, CAMD
Feb 2, 2015

CRITICAL PATH INSTITUTE

CRITICAL PATH INSTITUTE

## vision

Accelerating the Path to a Healthier World

## mission

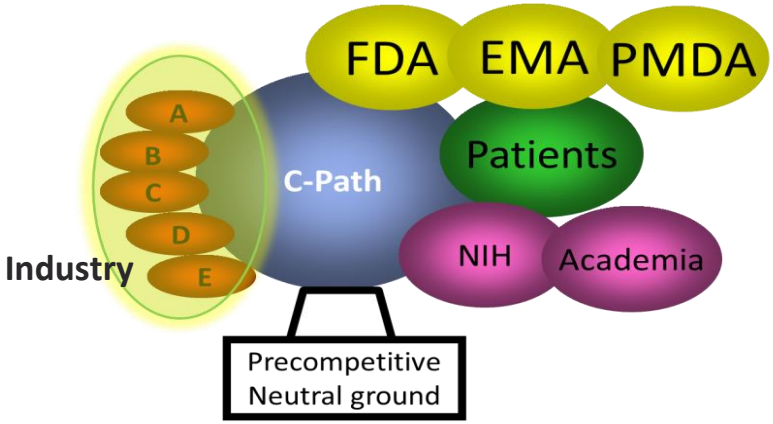
The Critical Path Institute is a catalyst in the development of new approaches to advance medical innovation and regulatory science. We achieve this by leading teams that share data, knowledge and expertise resulting in sound, consensus based science

## value

As an independent and trusted partner we value integrity, innovation and teamwork.

# C-Path: A Public Private Partnership

- Act as a trusted, neutral third party
- Convene scientific consortia of industry, academia, and government for pre-competitive sharing of data/expertise
  - ✓ The best science
  - ✓ The broadest experience
  - ✓ Active consensus building
  - ✓ Shared risk and costs




- Enable iterative EMA/FDA/PMDA participation in developing new methods to assess the safety and efficacy of medical products

- Official regulatory endorsement of novel methodologies and drug development tools

# Critical Path Institute Consortia

CRITICAL PATH INSTITUTE

## Eight global consortia collaborating with 1,300+ scientists and 61 companies

| | |
|---|---|
| CAMD | **Coalition Against Major Diseases**<br>Focusing on diseases of the brain |
| CPTR | **Critical Path to TB Drug Regimens**<br>Testing tuberculosis drug combinations |
| CRITICAL PATH INSTITUTE MS National Multiple Sclerosis Society | **Multiple Sclerosis Outcome Assessments Consortium**<br>Measuring drug effectiveness in MS |
| PKD CONSORTIUM CRITICAL PATH INSTITUTE | **Polycystic Kidney Disease Consortium**<br>New imaging biomarkers |
| PRO CONSORTIUM CRITICAL PATH INSTITUTE | **Patient-Reported Outcome Consortium**<br>Measuring drug effectiveness |
| ePRO CONSORTIUM CRITICAL PATH INSTITUTE | **Electronic Patient-Reported Outcome Consortium**<br>Electronic capture of drug effectiveness |
| PSTC CRITICAL PATH INSTITUTE | **Predictive Safety Testing Consortium**<br>Drug safety |
| CFAST | **Coalition For Accelerating Standards and Therapies**<br>Data standard |

- ✓ Biomarkers
- ✓ Clinical Outcome Assessment Instruments
- ✓ Clinical Trial Simulation Tools
- ✓ Data Standards
- ✓ In Vitro Tools

# C-Path Accomplishments

CRITICAL PATH INSTITUTE

- ✓ **First non-clinical safety biomarkers (7) qualified by the FDA, EMA, and PMDA**
- ✓ **First imaging biomarker for trial enrichment qualified by the EMA (Alzheimer's disease)**
- ✓ **First drug-disease-trial model for AD endorsed by the FDA & EMA**
- ✓ **First consortium (PSTC) to achieve letters of support with both FDA and EMA for biomarker use**
- ✓ **First Clinical Data Interchange Standards Consortium (CDISC) therapeutic area data standard (Alzheimer's disease), CFAST partnership for additional standards (MS, PD, PKD, TB, more)**
- ✓ **Unified clinical trial database of Alzheimer's disease (AD) placebo arm data provided by multiple pharmaceutical companies**

# Alzheimer's Disease: the High Unmet Need for New Therapies

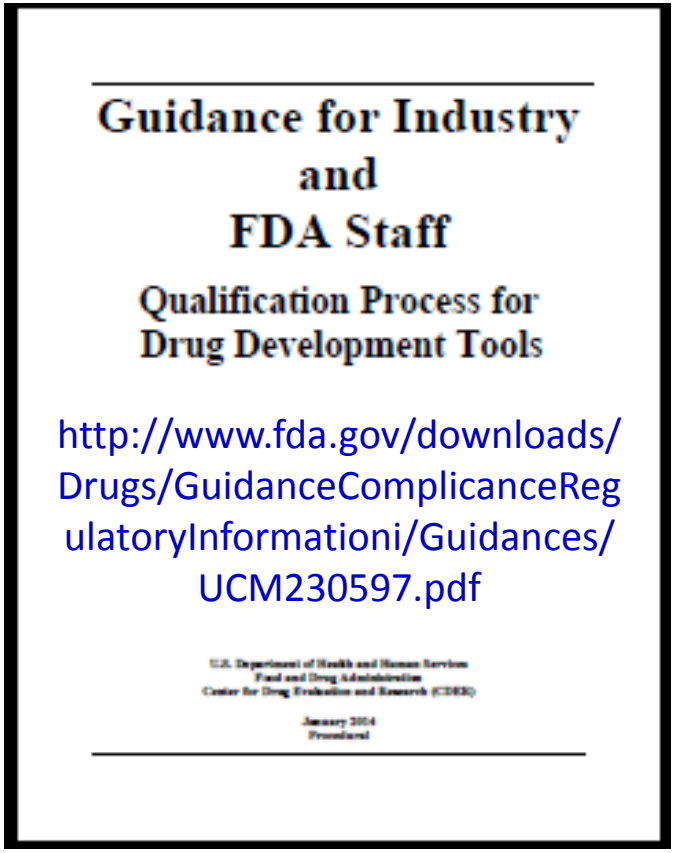
High risk and increasing cost for AD drug development

Lack of biomarkers for decision making

No effective therapy for modifying disease progression

| Gap | CAMD Approach |
| --- | --- |
| Huge uncertainty in design of clinical trials | Regulatory endorsed clinical trial simulation tool |
| Highly variable subpopulations recruited into randomized clinical trials | Regulatory biomarker qualification for enrichment in randomized clinical trials |
| Inadequate outcome measures for assessing efficacy of drugs in predementia stages | Innovative/sensitive clinical outcome assessment for efficacy of novel drug candidates |

# FDA Biomarker Qualification


Guidance for Industry
and
FDA Staff

Qualification Process for
Drug Development Tools

http://www.fda.gov/downloads/Drugs/GuidanceComplicanceRegulatoryInformationi/Guidances/UCM230597.pdf

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2004
Procedural

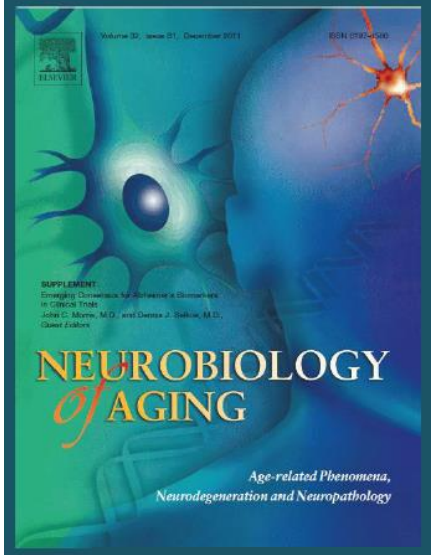
## Biomarker Qualification

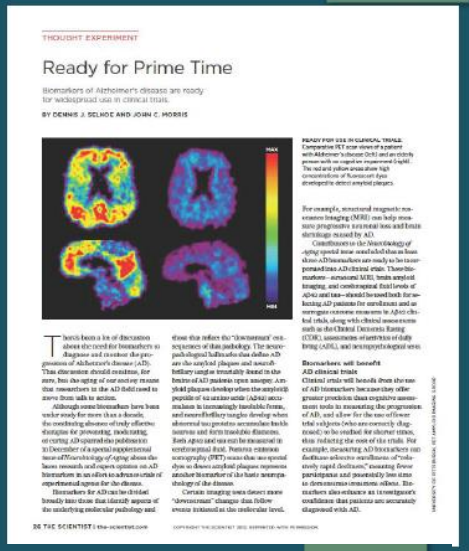
- Once qualified for a specific **context of use**, a biomarker can be used by drug developers for other applications without re-review
- **Incremental expansion** of the qualified context of use over time may be undertaken
- Biomarkers considered for qualification are conceptually **independent of the specific test or device** performing the measurement
- Biomarker qualification is a tool for drug development, and **not for approval/clearance of diagnostics or for companion diagnostics for use in clinical practice**

# Alzheimer's Disease
# Three top tier biomarkers identified, 2011

- Cerebrospinal Fluid biomarkers
  - Amyloid, tau, phosphotau
- Structural Neuroimaging
  - Volumetric MRI
- Molecular Neuroimaging
  - Amyloid PET

## Consensus Paper



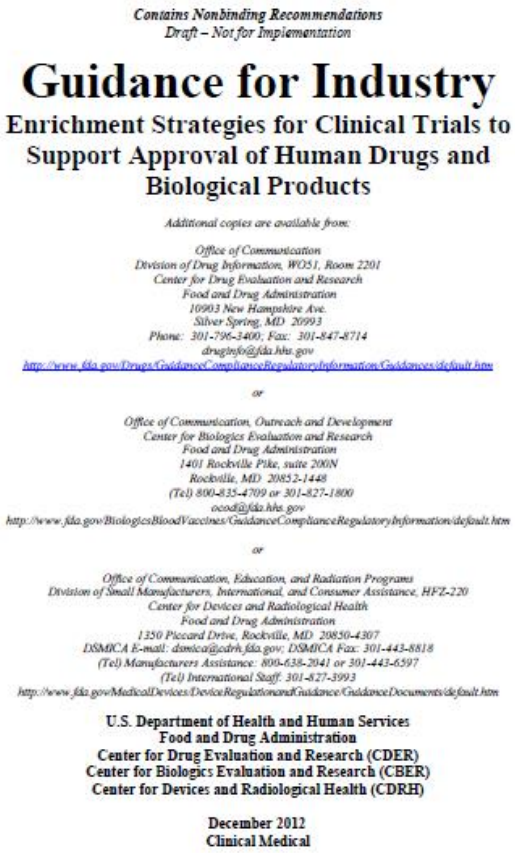

## AD Biomarkers Working Group

**CO-CHAIRS**
**John C. Morris, M.D.**, Washington University School of Medicine
**Dennis J. Selkoe, M.D.**, Brigham and Women's Hospital, Harvard Medical School

**MEMBERS**
**Paul S. Aisen, M.D.**, University of California San Diego
**Marilyn Albert, Ph.D.**, Johns Hopkins Alzheimer's Disease Research Center
**David M. Holtzman, M.D.**, Washington University School of Medicine
**Clifford R. Jack, M.D.**, Mayo Clinic
**William E. Klunk, M.D., Ph.D.**, University of Pittsburgh Physicians
**Richard Mayeux, M.D.**, Columbia University Medical Center
**Eric M. Reiman, M.D.**, Banner Alzheimer's Institute
**Reisa Sperling, M.D.**, Harvard Medical School , Brigham and Women's Hospital
**John Q. Trojanowski, M.D., Ph.D.**, Institute on Aging, Alzheimer's Disease Core Center, University of Pennsylvania

**NON-VOTING MEMBER**
**Marc Walton, M.D., Ph.D.**, U.S. Food and Drug Administration

# CAMD Biomarkers aiming for FDA Qualification
## *Prognostic Application, AD & PD*



*Contains Nonbinding Recommendations*
*Draft – Not for Implementation*

**Guidance for Industry**

**Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products**

*Additional copies are available from:*

*Office of Communication*
*Division of Drug Information, WO51, Room 2201*
*Center for Drug Evaluation and Research*
*Food and Drug Administration*
*10903 New Hampshire Ave.*
*Silver Spring, MD 20993*
*Phone: 301-796-3400; Fax: 301-847-8714*
*druginfo@fda.hhs.gov*
*http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm*

*or*

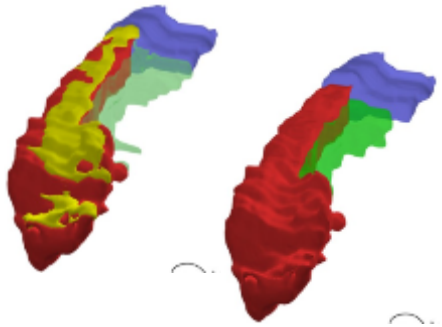
*Office of Communication, Outreach and Development*
*Center for Biologics Evaluation and Research*
*Food and Drug Administration*
*1401 Rockville Pike, suite 200N*
*Rockville, MD 20852-1448*
*(Tel) 800-835-4709 or 301-827-1800*
*ocod@fda.hhs.gov*
*http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm*

*or*

*Office of Communication, Education, and Radiation Programs*
*Division of Small Manufacturers, International, and Consumer Assistance, HFZ-220*
*Center for Devices and Radiological Health*
*Food and Drug Administration*
*1350 Piccard Drive, Rockville, MD 20850-4307*
*DSMICA E-mail: dsmica@cdrh.fda.gov; DSMICA Fax: 301-443-8818*
*(Tel) Manufacturers Assistance: 800-638-2041 or 301-443-6597*
*(Tel) International Staff: 301-827-3993*
*http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm*

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**
**Center for Biologics Evaluation and Research (CBER)**
**Center for Devices and Radiological Health (CDRH)**

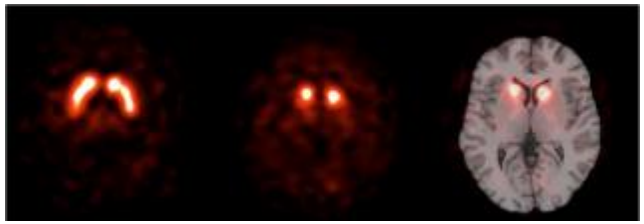
**December 2012**
**Clinical Medical**



Low Hippocampal Volume at baseline for enrichment in Pre-dementia trials

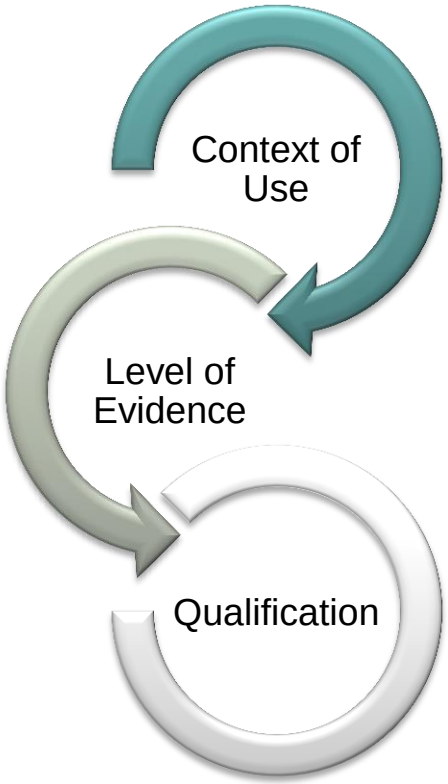
Baseline measures of β-amyloid protein, tau and phosphotau levels in CSF as biofluid biomarkers for enrichment in pre-dementia AD trials

Dopamine transporter neuroimaging as a prognostic biomarker to exclude those subjects termed as SWEDDs (scans without evidence of dopamine deficiency) for clinical trials in early motor PD subjects



*SPECT imaging of DAT in healthy and PD*

# Biomarker Qualification
## *Key learnings from CAMD experience*



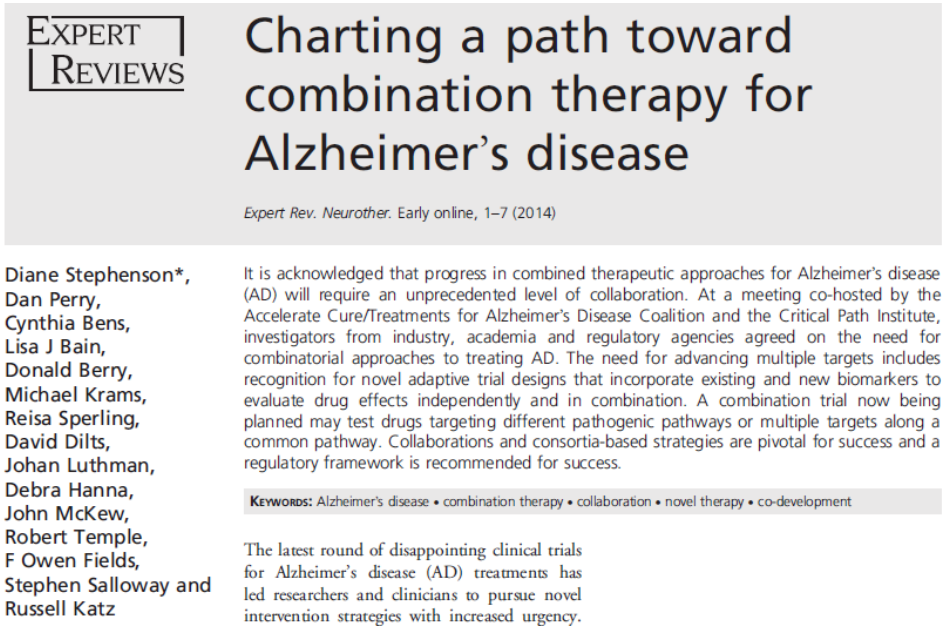

***Context of use drives everything*:**
- Start with the end game in mind
- Assure data exists (ideally in hand)
- Diagnostic ≠ prognostic ≠ surrogate
- Don't try to boil the ocean

***Biomarker validation:***
- Tried and true biomarkers may not be 'Regulatory ready'
- Test-retest data is important yet often unpublished

***Data and standards***
- What data supports your COU?
- Know your target population
- Be careful about retrofitting legacy data with future use of DDT for clinical trials
- Both observational and Clinical trial data are important
- Data standardization is key
- Do not underestimate challenges of data acquisition, remapping and analyses

***Champion multiple avenues for achieving regulatory impact***

# Multiple Avenues to Shape Regulatory Innovation



EXPERT REVIEWS

## Charting a path toward combination therapy for Alzheimer's disease

*Expert Rev. Neurother.* Early online, 1–7 (2014)

Diane Stephenson*, Dan Perry, Cynthia Bens, Lisa J Bain, Donald Berry, Michael Krams, Reisa Sperling, David Dilts, Johan Luthman, Debra Hanna, John McKew, Robert Temple, F Owen Fields, Stephen Salloway and Russell Katz

It is acknowledged that progress in combined therapeutic approaches for Alzheimer's disease (AD) will require an unprecedented level of collaboration. At a meeting co-hosted by the Accelerate Cure/Treatments for Alzheimer's Disease Coalition and the Critical Path Institute, investigators from industry, academia and regulatory agencies agreed on the need for combinatorial approaches to treating AD. The need for advancing multiple targets includes recognition for novel adaptive trial designs that incorporate existing and new biomarkers to evaluate drug effects independently and in combination. A combination trial now being planned may test drugs targeting different pathogenic pathways or multiple targets along a common pathway. Collaborations and consortia-based strategies are pivotal for success and a regulatory framework is recommended for success.

KEYWORDS: Alzheimer's disease • combination therapy • collaboration • novel therapy • co-development

The latest round of disappointing clinical trials for Alzheimer's disease (AD) treatments has led researchers and clinicians to pursue novel intervention strategies with increased urgency.

*Expert Rev Neurother.*
*2015 Jan;15(1):107-13*

## The Future Is Now: Model-Based Clinical Trial Design for Alzheimer's Disease

K Romero[1], K Ito[2], JA Rogers[3], D Polhamus[3], R Qiu[2], D Stephenson[1], R Mohs[4], R Lalonde[2], V Sinha[5], Y Wang[5], D Brown[6], M Isaac[6], S Vamvakas[6], R Hemmings[6], L Pani[6], LJ Bain[1], B Corrigan[2], for the Alzheimer's Disease Neuroimaging Initiative* for the Coalition Against Major Diseases**

*Clin Pharm Therap published online on 27th December 2014*

# Critical for Success: *Aligning across consortia*


alzheimer's association
Research Roundtable

ADNI

ALZHEIMER'S DISEASE
ADCS
COOPERATIVE STUDY

ACT-AD
Accelerate Cure/Treatments for Alzheimer's Disease

Banner
Alzheimer's
Institute

FNIH
Foundation for the
National Institutes of Health

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS
CLINICAL TRIALS AND METHODOLOGY

The New York
Academy of Sciences
*Building communities, advancing science since 1817*

imi
Innovative Medicines Initiative

CRITICAL PATH
INSTITUTE

PharmaCog

EMIF

PRO
CONSORTIUM
CRITICAL PATH INSTITUTE

CAMD
CRITICAL PATH INSTITUTE

GLOBAL
CEOINITIATIVE
–ON ALZHEIMER'S DISEASE–

# TBI Endpoints Development

*A Collaborative for Advancing Diagnosis and Treatment of TBI*

## CDISC, Data Aggregation, Landscape Analyses, and Expert Working Groups

**TED Contact Principal Investigator**
**Geoffrey T. Manley, MD, PhD**

Geoff Manley is Professor and Vice Chairman of Neurological Surgery at the University of California, San Francisco, and the Contact PI for the TED Initiative, as well as TRACK-TBI. He is an internationally recognized expert in neurotrauma, with a wide range of research interests from molecular aspects of brain injury to the clinical care of head trauma patients. He has helped to define new molecular mechanisms of injury to the nervous system that may lead to treatments for these devastating injuries. He is also considered a leader in the rapidly growing field of advanced neuromonitoring and clinical informatics for critical care.

# Data Standards, TBI-CDEs, and CDISC

NINDS Common Data Elements
Harmonizing information. Streamlining research.

TRACK-TBI
Transforming Research and Clinical Knowledge in Traumatic Brain Injury
International Traumatic Brain Injury Research Initiative

CDISC
CLINICAL DATA INTERCHANGE STANDARDS CONSORTIUM

*COMMENTARY*

**Common Data Elements for Research on Traumatic Brain Injury and Psychological Health: Current Status and Future Development**

*John Whyte, MD, PhD, Jennifer Vasterling, PhD, Geoffrey T. Manley, MD, PhD*

*SPECIAL COMMUNICATION*

**Common Data Elements in Radiologic Imaging of Traumatic Brain Injury**

*Ann-Christine Duhaime, MD, Alisa D. Gean, MD, E. Mark Haacke, PhD, Ramona Hicks, PhD, Max Wintermark, MD, Pratik Mukherjee, MD, PhD, David Brody, MD, Lawrence Latour, PhD, Gerard Riedy, MD, Common Data Elements Neuroimaging Working Group Members, Pediatric Working Group Members*

*SPECIAL COMMUNICATION*

**Common Data Elements for Traumatic Brain Injury: Recommendations From the Biospecimens and Biomarkers Working Group**

*Geoffrey T. Manley, PhD, Ramon Diaz-Arrastia, MD, PhD, Mary Brophy, MD, MPH, Doortje Engel, MD, PhD, Clay Goodman, MD, Katrina Gwinn, MD, Timothy D. Veenstra, PhD, Geoffrey Ling, MD, PhD, Andrew K. Ottens, PhD, Frank Tortella, PhD, Ronald L. Hayes, PhD*

**Position Statement: Definition of Traumatic Brain Injury**

*David K. Menon, MD, PhD, Karen Schwab, PhD, David W. Wright, MD, Andrew I. Maas, MD, PhD, on behalf of The Demographics and Clinical Assessment Working Group of the International and Interagency Initiative toward Common Data Elements for Research on Traumatic Brain Injury and Psychological Health*

Arch Phys Med Rehabil Vol 91, November 2010

CDISC
CLINICAL DATA INTERCHANGE STANDARDS CONSORTIUM

ONE MIND

## Objective 1.5

Collaborate with the Clinical Data Interchange Standards Consortium (CDISC) to conform TBI Common Data Elements (TBI-CDEs) to CDISC standards for FDA regulatory submission


Joanne Odenkirchen
Sureyya Dikmen
Joe Giacino
Lisa Wilde
Thomas DeGraba
Steve Broglio
Alex Valadka
TED Outcomes Core
TED Clinical Core

Amy Pamer
Bron Kisler
Dana Booth
Jon Neville
Rhonda Facile
Steve Kopko


TBI Endpoints Development

A Collaborative for Advancing Diagnosis and Treatment of TBI

CDISC
CLINICAL DATA INTERCHANGE STANDARDS CONSORTIUM

ONE MIND

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# Outcome Instruments

Dec. 2014

| Develop CDISC Standard (Y/N) | Outcome Instrument |
|---|---|
| y | Glasgow Outcome Scale – Extended (GOS-E) |
| y | Disability Rating Scale (DRS) |
| y | Expanded Disability Rating Scale - Postacute Interview (E-DRS-PI) -- Caregiver Version |
| y | Expanded Disability Rating Scale - Postacute Interview (E-DRS-PI) -- Survivor Version |
| ??? | Medical Outcomes Study 36-Item Short Form Health Survey (SF-36), v2 |
| y | Mayo-Portland Adaptability Inventory (MPAI) |
| | |
| y | Galveston Orientation and Amnesia Test (GOAT) |
| y | JFK Coma Recovery Scale–Revised (CRS-R) |
| | |
| y | Rey Auditory Verbal Learning Test (RAVLT) |
| y? | Trail Making Test (TMT) |
| y | Controlled Oral Word Association Test (COWAT) |
| | |
| y | PHQ-9 |
| y | GAD-7 |
| y | Alcohol Use Disorders Identification Test (AUDIT) |
| y | Alcohol Use Disorders Identification Test - Consumption Questions (AUDIT-C) |
| y | Substance Abuse questions from the TBI Model Systems data set |
| y | Posttraumatic Stress Disorder Check List-Civilian/Military/Stressor (PCL-C/M/S) |
| | |
| y | Rivermead Postconcussive Symptom Questionnaire (RPQ) |
| y | Neurobehavioral Symptom Inventory (NSI) |
| | |
| y | Neurological Outcome Scale for Traumatic Brain Injury (NOS-TBI) |
| | |

# Clinical Data

March 2015

**TBI Endpoints Development**

*A Collaborative for Advancing Diagnosis and Treatment of TBI*

# Curation and Harmonization of Data: The TED Metadataset

| STUDY | Mild/ Mod TBI Subjects | Controls | Years | Study Type | COAs[1] (number) | Biomarkers[2] (number) | Clinical Trials.gov |
|---|---|---|---|---|---|---|---|
| TRACK-TBI Pilot | 479 | 0 | 2010-2013 | Civilian | 10 | 4 | NCT01565551 |
| Army STARRS | 750 | >6000 | 2010-2014 | Military | 6 | 6 | |
| CRC | 761 | 240 | 1998-2014 | Sports | 16 | 2 | |
| Mission Connect | 102 | 72 | 2010-2014 | Military | 17 | 4 | |
| CNRM | 350 | 20 | 2010-2014 | Civilian | 5 | 5 | NCT01132937 |
| HTH-1 | 136 | 111 | 2007-2011 | Sports | 12 | 0 | NCT00545662 |
| COBRIT | 652 | 0 | 2007-2011 | Civilian | 9 | 3 | NCT00545662 |
| UW | 853 | 234 | 1981-2005 | Civilian | 3 | 1 | NCT00004730/4817 |

# Data Collection

QuesGen SYSTEMS, INC.

*Data Management for Clinical Research*

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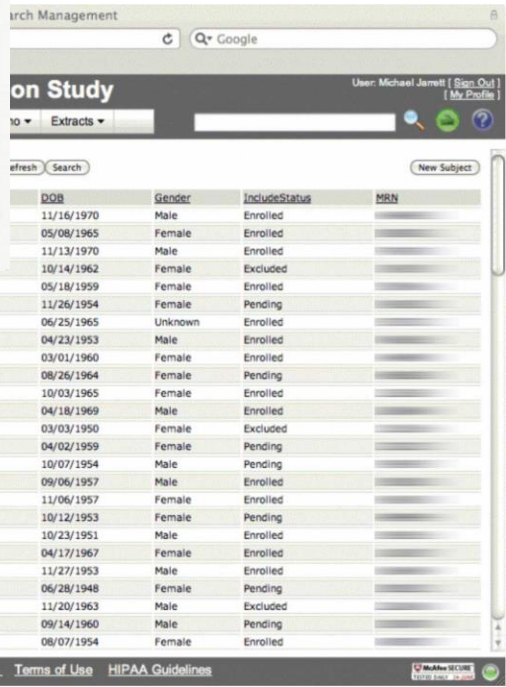
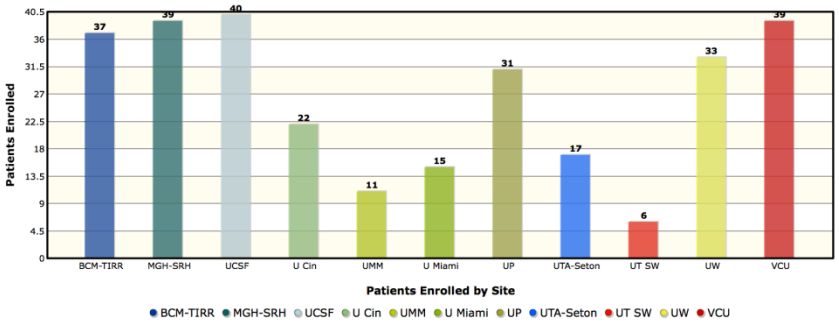
## TRACK TBI

*"The global aim of this project is to test and refine Common Data Elements (CDEs), neuroimaging standards, and best practices for genetics and proteomics in Traumatic Brain Injury (TBI) studies. The investigators anticipate that this project has the potential to substantially advance and revolutionize clinical research in TBI. Repositories for neuroimaging, proteomic, and genetic biomarkers will facilitate ..."*

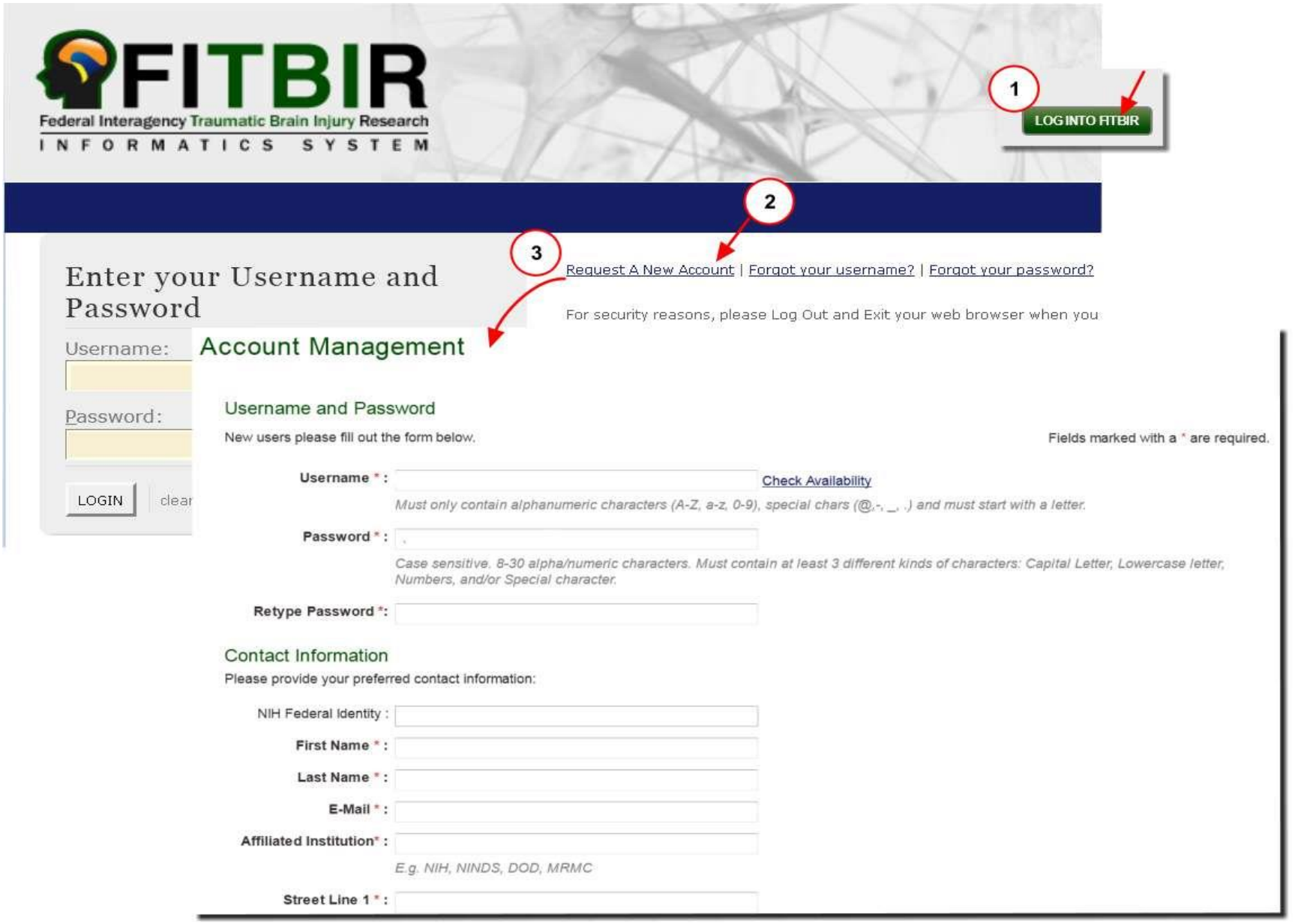
View This Page →

QuesGen SYSTEMS, INC.

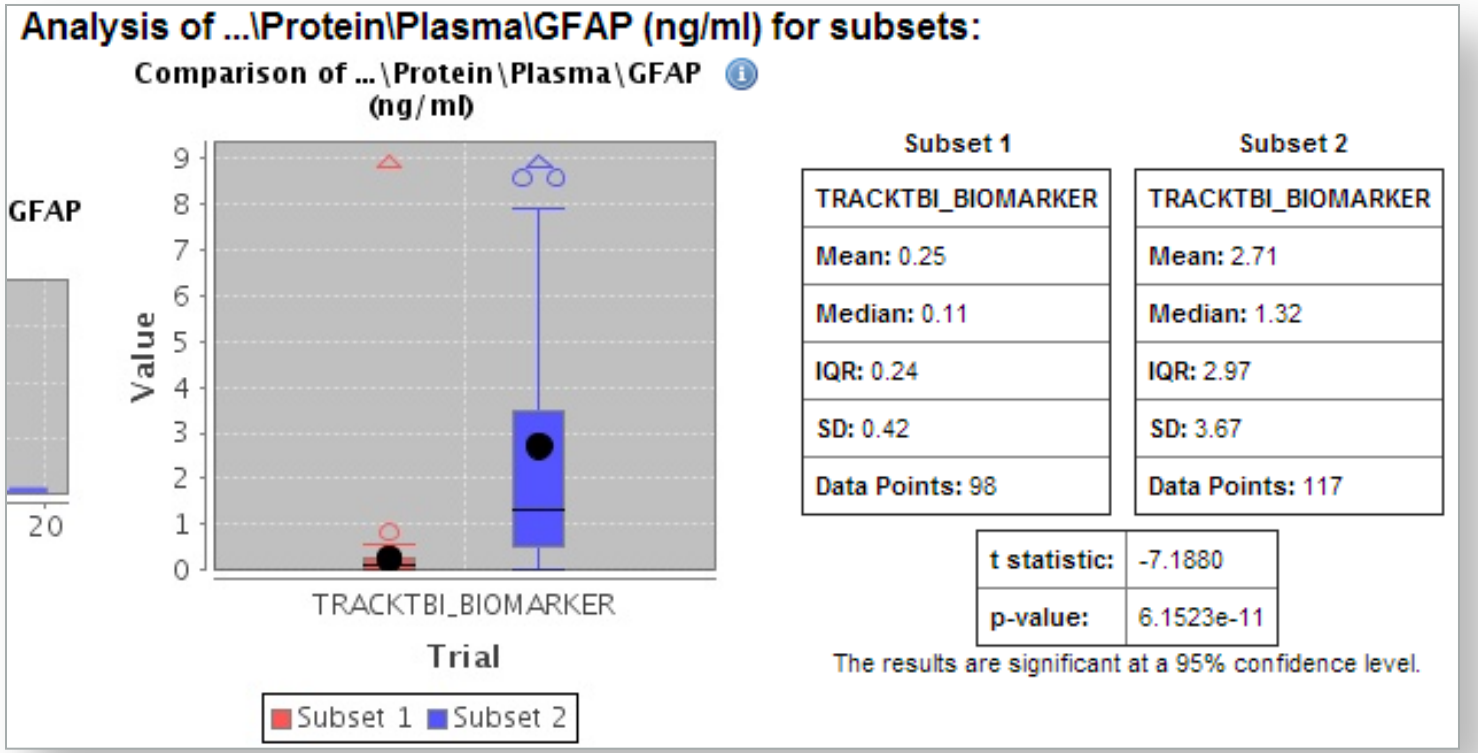


# Data Storage Platform

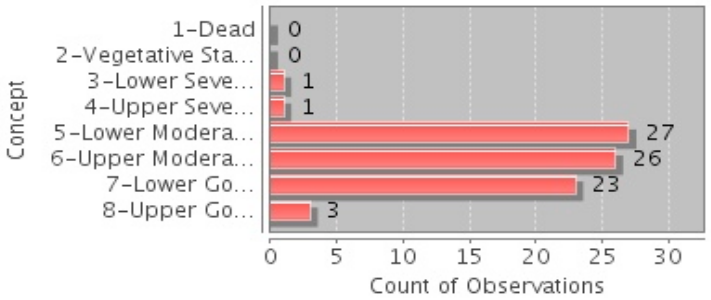


# Analytic Platform



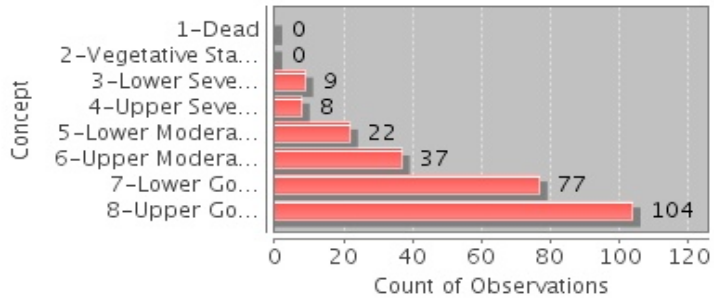
## Analysis of ...\6-Month Outcome Measurements\Glasgow Outcome Scale Extended\GOSE Score (categorical) (6 Month) for subsets:

**Subset 1**




| Category | Subset 1 (n) | Subset 1 (%n) |
|---|---|---|
| 1-Dead | 0 | 0% |
| 2-Vegetative State (VS) | 0 | 0% |
| 3-Lower Severe Disability (Lower SD) | 1 | 1.2% |
| 4-Upper Severe Disability (Upper SD) | 1 | 1.2% |
| 5-Lower Moderate Disability (Lower MD) | 27 | 33.3% |
| 6-Upper Moderate Disability (Upper MD) | 26 | 32.1% |
| 7-Lower Good Recovery (Lower GR) | 23 | 28.4% |
| 8-Upper Good Recovery (Upper GR) | 3 | 3.7% |
| **Total** | **81** | **100%** |

**Subset 2**




| Category | Subset 2 (n) | Subset 2 (%n) |
|---|---|---|
| 1-Dead | 0 | 0% |
| 2-Vegetative State (VS) | 0 | 0% |
| 3-Lower Severe Disability (Lower SD) | 9 | 3.5% |
| 4-Upper Severe Disability (Upper SD) | 8 | 3.1% |
| 5-Lower Moderate Disability (Lower MD) | 22 | 8.6% |
| 6-Upper Moderate Disability (Upper MD) | 37 | 14.4% |
| 7-Lower Good Recovery (Lower GR) | 77 | 30% |
| 8-Upper Good Recovery (Upper GR) | 104 | 40.5% |
| **Total** | **257** | **100%** |

| | |
|---|---|
| **Chi-Squared:** | 64.658 |
| **p-value:** | 1.3195e-12 |

The results are significant at a 95% confidence level.

## Summary Statistics

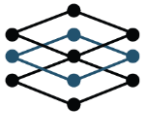
| Query Summary for Subset 1 | Query Summary for Subset 2 |
|---|---|
| (\\Internal Studies\Internal Studies\TRACK_TBI_PILOT\Outcome Data\6-Month Outcome Measurements\PTSD Checklist-Civilian\DSM-IV PTSD Qualification (6 Month)\Yes\ ) | (\\Internal Studies\Internal Studies\TRACK_TBI_PILOT\Outcome Data\6-Month Outcome Measurements\PTSD Checklist-Civilian\DSM-IV PTSD Qualification (6 Month)\No\ ) |

Palantir

ONE MIND™

## FLEXIBLE MODELING

Instead of rigid rows and columns, Palantir models data as a flexible graph of objects and relationships. Users are not locked into a single schema, but instead can evolve as needs change.



## KNOWLEDGE MANAGEMENT

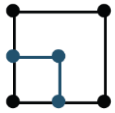
All data integrated into Palantir's products is stored in a version-controlled knowledgebase . Data provenance is recorded at granular levels to ensure that no matter where data travels or who uses it, it is clear from which study it originated.

## PRIVACY & SECURITY

Privacy-protective capabilities are built into our products' very architecture, which is designed to support precision data handling, multi-level security, and complete auditability.

## COLLABORATION

Enables multiple users, within and across organizations, to seamlessly, securely, collaboratively analyze the same data. As an open platform, data can be also exported out in its raw form for use in other tools.

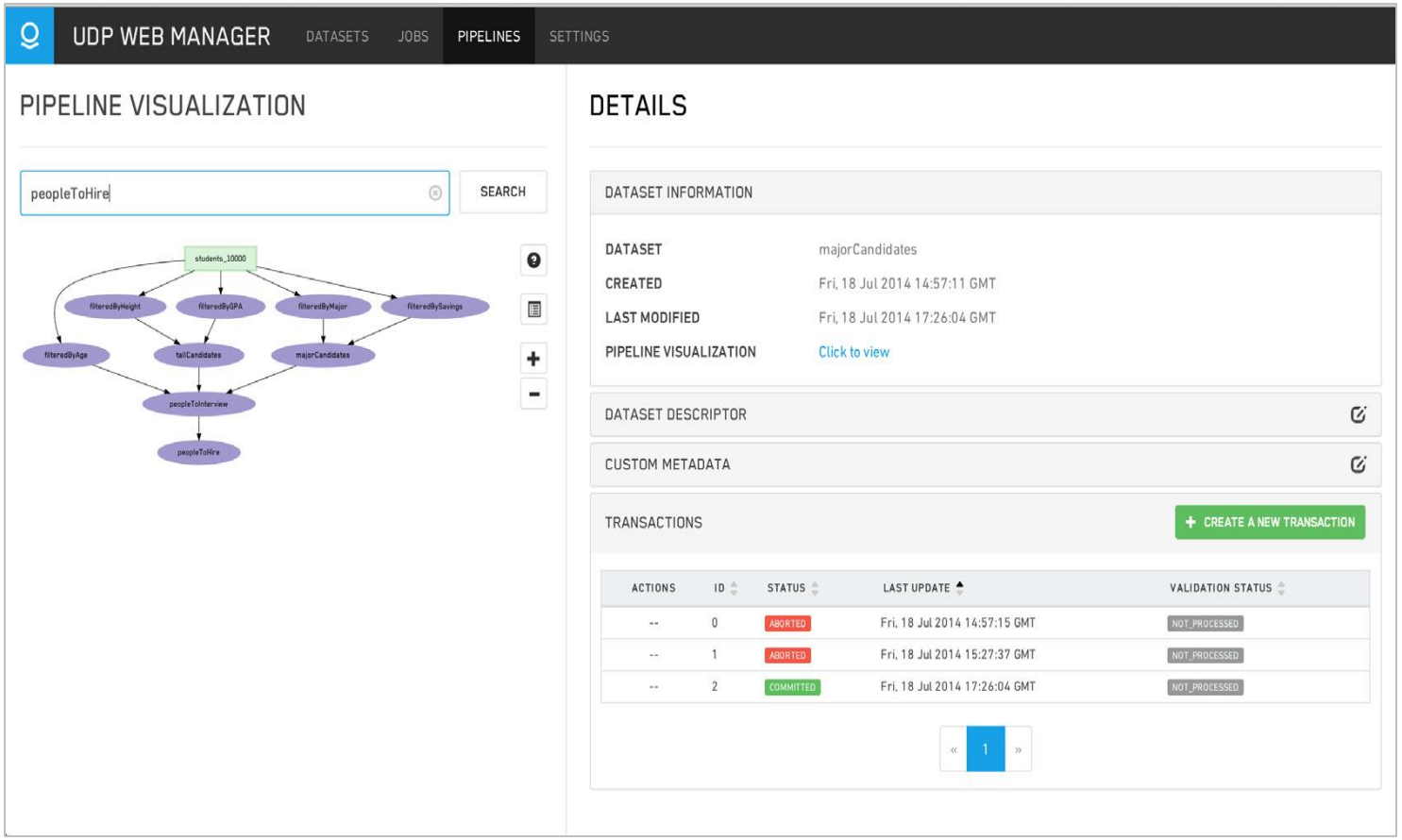


## EXTENSIBILITY

Palantir platforms are designed to be extensible at every pont, from low-level data integration, import pipeline customizations, to building custom user interfaces.

# Data Integration Layer

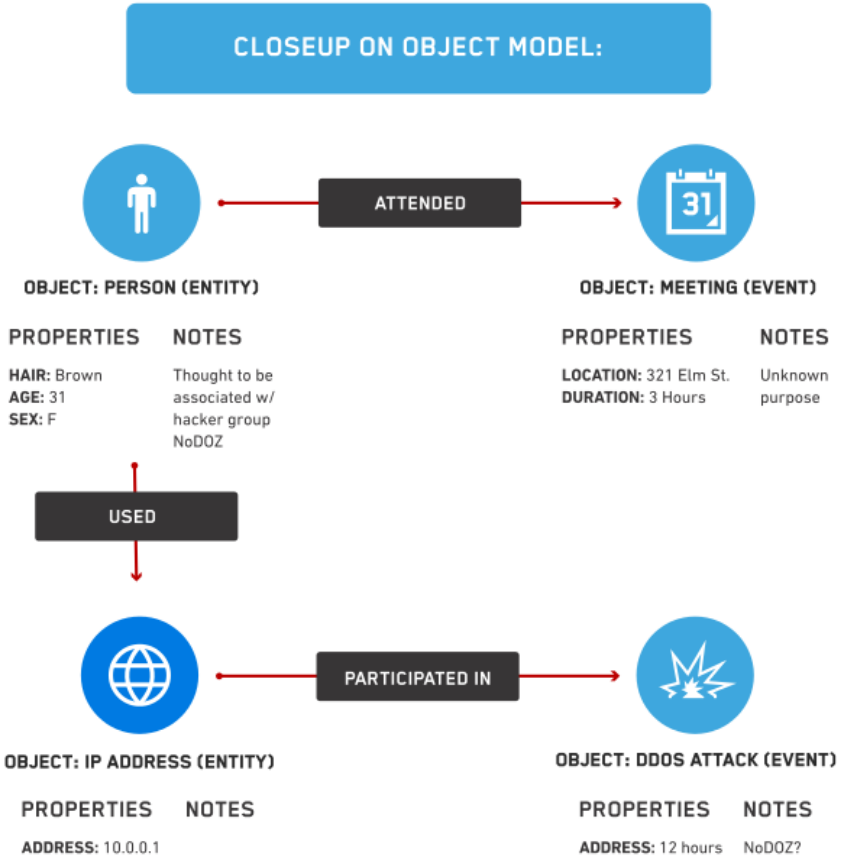
Palantir will act as end-to-end layer for landing, monitoring, querying, and transforming heterogeneous data at scale, while ensuring that data is not locked into a proprietary or closed store. This data reservoir allows organizations to create a single repository for all information, regardless of size, source, or format.



# Flexible Object Model

Dynamic Ontology provides a flexible framework that models data as objects, their properties, and the relationships between them.

Users are not locked in to one schema; instead, the ontology can be updated or modified as needed.



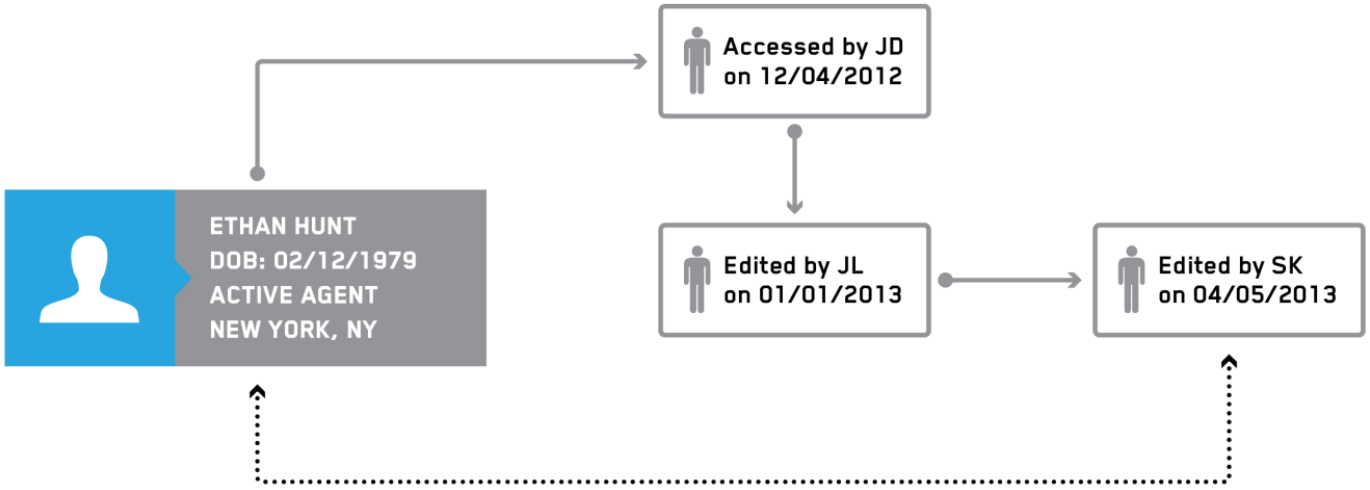
# Granular Access Controls

Palantir's security model allows organizations to assign users and groups specific access permissions to govern how they interact with their data. Information can be protected at the data source or property level, meaning that granular permissions can be set, as opposed to an "all-or-nothing" approach.

| DATA | SOURCE | BOB'S PERMISSIONS |
|---|---|---|
|  NAME = JOHN<br>AGE = 30 | .XLS SPREADSHEET | DISCOVER ACCESS |
|  ADDRESS=25 E ST.<br>COLOR=RED | .MSG E-MAIL | WRITE ACCESS |
|  MAKE=TOYOTA<br>MODEL=CAMRY<br>COLOR=SILVER | .HTML WEBSITE | NO ACCESS |

# Audit Logs

Palantir includes a full audit trail of all activity within the platform, keeping tabs on the data lifecycle. Data owners can keep up to date on how their data is being used within the community.



# Expert Working Groups:EWGs

**OUTCOMES EWG**
Lead | Michael McCrea, PhD
Co-Leads | Murray Stein, MD; Harvey Levin, PhD; Joseph Giacino, PhD; John Whyte, MD PhD
Rapporteurs | Yelena Guller Bodien, PhD and Sabrina Rose Taylor, PhD

**NEUROIMAGING BIOMARKER EWG**
Lead | Pratik Mukherjee, MD PhD
Co-Lead | Arthur Toga, PhD
Rapporteur | Christine Mac Donald, PhD

**BLOOD-BASED BIOMARKER EWG**
Lead | Ramon Diaz-Arrastia, MD PhD
Co-Lead | Kevin Wang, PhD
Rapporteur | John Yue, BS

**EMERGING TECHNOLOGIES EWG**
Lead | Jam Ghajar, MD PhD
Co-Lead | Mona Hicks, PhD
Rapporteur | Ethan Winkler, MD PhD

# Expert Working Groups:EWGs

- Landscape Analyses: Identify existing COAs and biomarkers to be analyzed - Survey Results and Consensus

- Define roles of EWGs' membership

- Develop work streams to achieve TED Stage I Aims

# Expert Working Groups:EWGs

**Develop work streams to achieve Stage I Aims:**

- Start with the end in mind. What does success look like?
- Create a plan with milestones and priorities
- What opportunities can be leveraged to increase the likelihood of success?
- What are the barriers or challenges? How can they be mitigated?
- How can seed projects contribute to success


BACK TO SQUARE ONE
SUCCESS
FAILURE