Multimodal Biomarkers for CNS Disorders: Session 4 - Regulatory Guidance and Decision Making

National Academies of Sciences, Engineering, and Medicine Workshop | March 14, 2023

NEUROSCIENCE PROGRAM

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CRITICAL PATH FOR RARE NEURODEGENERATIVE DISEASES
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Considerations for Multimodal CNS Biomarker Development and Clinical Trial Readiness

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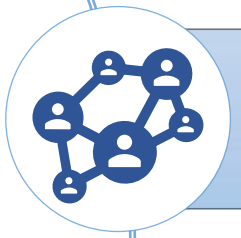
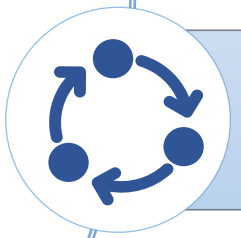
Strategic Adaptability

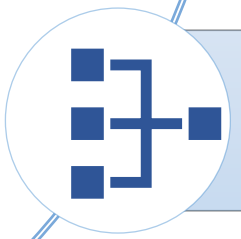
Explore opportunities for shared learnings from other disease areas and potential for common framework, study infrastructure, or normative databases across stakeholders and other related disease areas.



Biomarker development takes a village; leverage available resources and diverse collaborations – like consortia or public-private partnerships – to reduce risk, increase return on investment, and take more shots on goal.

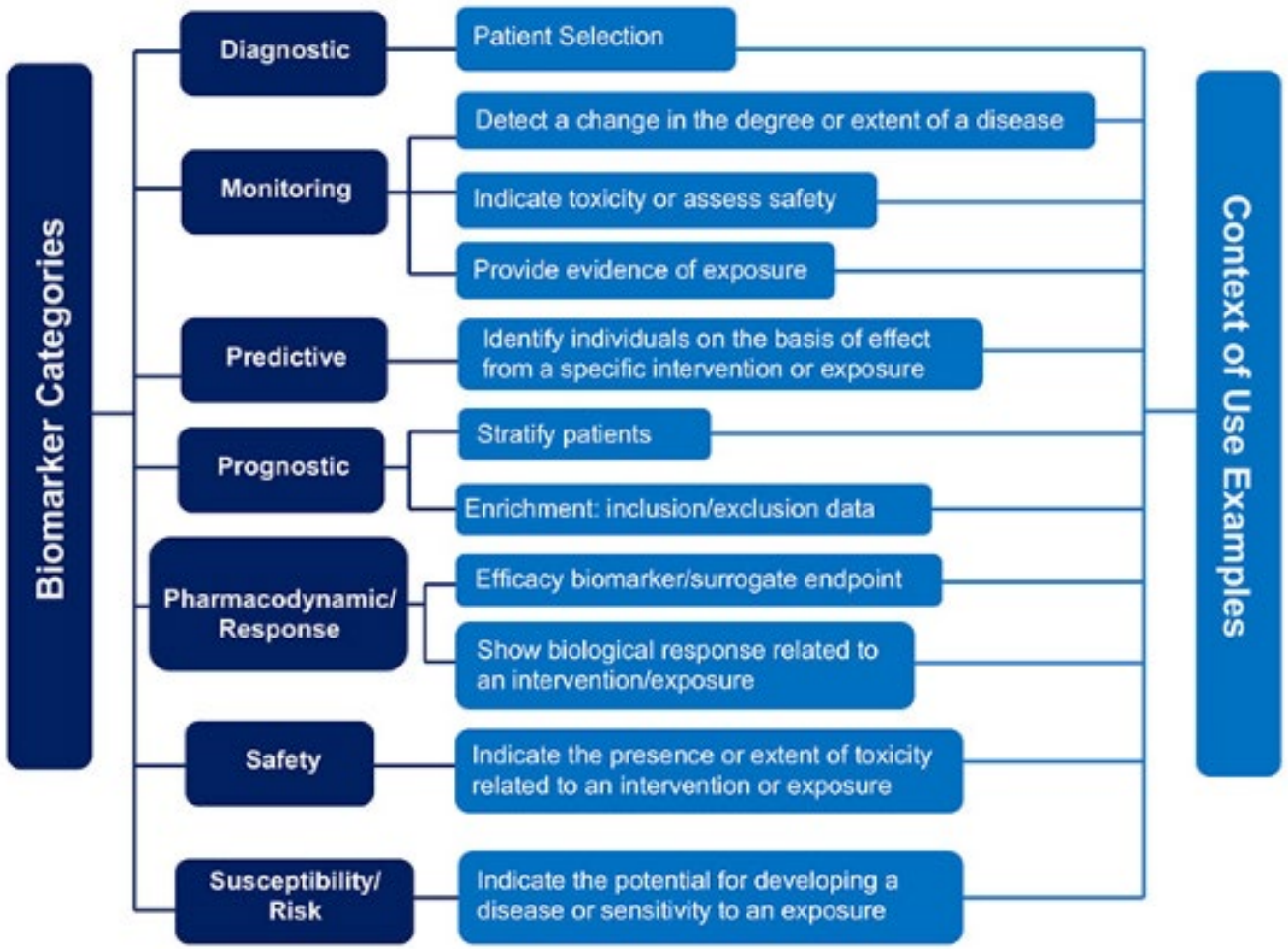


Consider biomarker applications across the full spectrum – i.e., diagnostic, prognostic, pharmacodynamic, safety, etc.. and how to optimally integrate multiple biomarkers or a single biomarkers with other outcome assessments across the disease continuum.



Iteratively evaluate what is being measured, and what the data is indicating; engage regulators early in the process; importance of data sharing to enhance discovery and validation efforts and address evidentiary burden.

Biomarker Categories & Applications



Ref.: https://www.fda.gov/drugs/biomarker-qualification-program/context-use

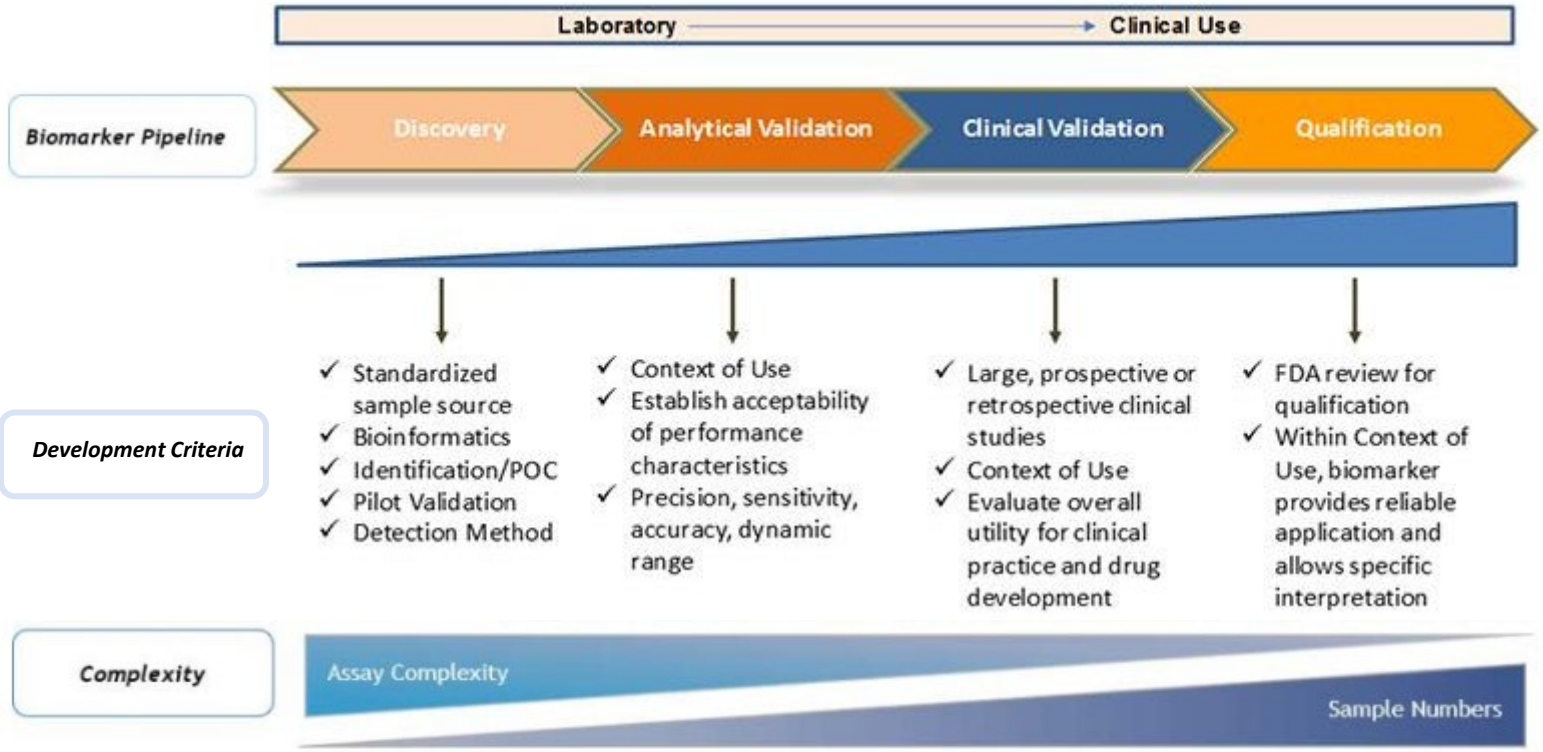
Biomarker integration in the drug development process:

- Investigational new drug (IND) pathway in the context of a specific drug devo program
- Scientifically-supported community implementation whereby a broadly used biomarker with appropriate scientific support, is generally accepted by experts in the field
- FDA's biomarker qualification program
- As a covariate within a clinical trial simulation model submitted via FDA's Drug Development Tools: Fit-for-Purpose Initiative

Biomarker Resourcing & Complexity

Biomarker development is highly resource intensive and time consuming

A collaborative, consortium approach can accelerate biomarker development and validation



C-Path is a non-profit, public-private partnership that serves as a unique neutral convenor

Image adapted from: https://www.ninds.nih.gov/current-research/focus-tools-topics/focus-biomarkers-research

C-Path's Consortium Approach to Biomarkers

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Core Competencies


Data Management and Standards


Biomarkers


Clinical Outcome Assessments


Modeling and Analytics


Regulatory Science

C-Path is evaluating biomarkers (fluid and imaging) across its various neurological disease consortia: Critical Path to Alzheimer's Disease, Critical Path to Parkinson's, Huntington's Disease Regulatory Science Consortium, and Critical Path to Therapeutics for the Ataxias

CPP's Digital Drug Development Tools (3DT)

An initiative launched in 2018 to leverage the unique role of CPP as a neutral convener, bringing stakeholders together in a pre-competitive space to collectively engage with regulatory agencies optimize the effective use of DHT in PD clinical trials.

Recommendations to Optimize the Use of Volumetric MRI in Huntington's Disease Clinical Trials

Front Neurol.. 2021. PMID: 34744964

Kirsi M Kinnunen [1], Ariana P Mullin [2 3], Dorian Pustina [4], Emily C Turner [2], Jackson Burton [2], Mark F Gordon [5], Rachael I Scahill [6], Emily C Gantman [4], Simon Noble [4], Klaus Romero [2], Nellie Georgiou-Karistianis [7], Adam J Schwarz [8]

A biological classification of Huntington's disease: the Integrated Staging System

Lancet Neurol.. 2022. PMID: 35716693

Sarah J Tabrizi [1], Scott Schobel [2], Emily C Gantman [3], Alexandra Mansbach [4], Beth Borowsky [5], Pavlina Konstantinova [6], Tiago A Mestre [7], Jennifer Panagoulias [8], Christopher A Ross [9], Maurice Zauderer [10], Ariana P Mullin [8], Klaus Romero [11], Sudhir Sivakumaran [11], Emily C Turner [11], Jeffrey D Long [12], Cristina Sampaio [13];
Huntington's Disease Regulatory Science Consortium (HD-RSC)

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Multimodal Biomarkers Applied to an Integrated Staging System Conceptual Framework to Inform Decision-Making

HD-RSC
HUNTINGTON'S DISEASE REGULATORY SCIENCE CONSORTIUM

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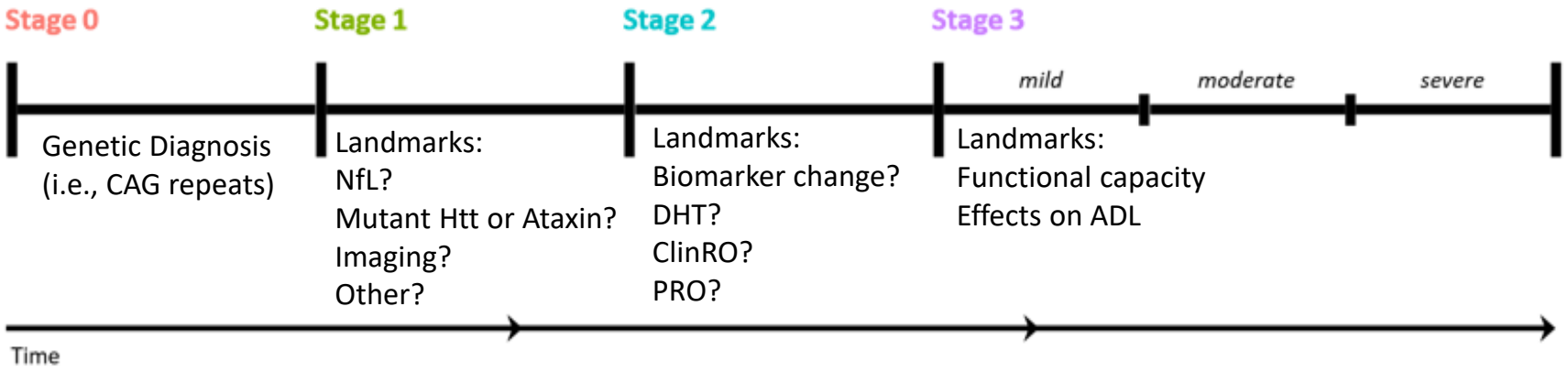
Precedence for biological-driven disease staging for neurological diseases:
Early Alzheimer's disease – FDA's "Early AD: Developing Drugs for Treatment - Guidance for Industry"
Huntington's disease – Sarah J. Tabrizi…HD-RSC et al., *Lancet Neurol.* July 2022. PMID: 35716693
Parkinson's disease and spinocerebellar ataxia – *development in progress*

Stage 0 mutation positive (no clinical sign of disease)

Stage 1 Biomarker of pathogenesis

Stage 2 Clinical sign(s) or symptom(s)

Stage 3 Functional changes



Key Questions:

What is/are the best biomarker(s) for each stage?

What concept of interest / concept of use is optimal for each stage?

What might be combined with NfL to provide disease area specificity across distinct neurological and neurodegenerative diseases?

Conserved vs. distinct considerations for rare vs. common neurological diseases?

Figure inspired from Ref.: Sarah J. Tabrizi…HD-RSC et al., *Lancet Neurol.* A biological classification of Huntington's disease: the integrated Staging System. July 2022 PMID: 35716693

Additional Resources

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FDA's BEST Resource for Biomarkers and More

BEST (Biomarkers, EndpointS, and other Tools) Resource

FDA-NIH Biomarker Working Group.

Silver Spring (MD): Food and Drug Administration (US); Bethesda (MD): National Institutes of Health (US); 2016-.

See FDA-NIH Biomarker Working Group

- Developed by the FDA-NIH Joint Leadership Council to provide harmonization of terms used in translational science and medical product development with an emphasis on endpoints and biomarkers
- The BEST glossary aims to capture distinctions between biomarkers and clinical assessments and to describe their distinct roles in biomedical research, clinical practice, medical product development, and in the regulation of products by the FDA

Ref.: https://www.ncbi.nlm.nih.gov/books/NBK326791/

Biomarker Consortia Overview (Non-encompassing)

CRITICAL PATH INSTITUTE

Foundation for NIH (FNIH) Identify, develop, and qualify potential biomarkers to improve drug development and regulatory decision-making; ~80 active projects across diverse disease areas

Critical Path Institute (C-Path) Biomarker development and qualification within the Predictive Safety Testing Consortium (PSTC) and other disease area-focused Consortia

Bluefield Project (The Neurofilament Surveillance Project longitudinal biomarkers study for frontal temporal lobe dementia (FTLD) genetic at-risk individuals (mutation in *C9orf72, MAPT, GRN*)

Parkinson's Progression Marker Initiative (PPMI, Longitudinal clinical study by The Michael J. Fox Foundation for Parkinson's Research)

Global Biomarker Standardization Consortium (GBSC, established by the Alzheimer's Association)

Examples from Europe: European Brain Research Area (EBRA, European Cluster Biomarkers (ECIB); European DLB Consortium – diagnostic biomarkers, a multicenter initiative; minor consortium efforts for biomarker development from legacy CORDIS, the repository for EU-funded research projects)

Critical Path Institute

- Predictive Safety Testing Consortium (PSTC) – pre-clinical and clinical safety biomarkers in six working groups: kidney, liver, pancreatic, skeletal muscle, vascular, and testicular injury.
- **Neuroscience Program** – includes Critical Path for Alzheimer's Disease (CPAD), Critical Path for Parkinson's (CPP), Duchenne Regulatory Science Consortium (D-RSC), Huntington's Regulatory Science Consortium (HD-RSC), and Critical Path to Therapeutics for the Ataxias (CPTA).
  - HD-RSC: Volumetric MRI-based biomarkers for HD
  - CPP: Digital health technology (3DT program)
  - **Multiple Neuro Consortia**: incorporation of biomarker data as covariates in disease progression models or in clinical trial simulation tools