CRITICAL PATH INSTITUTE

RARE AND ORPHAN DISEASE PROGRAMS

Rare Neurogenerative Disease Efforts Under the ACT for ALS

March 8, 2024

WELCOME

Building a rare disease community that works. Together.

c-path.org

Housekeeping

We will have an opportunity for Q&A after the presentations.

If you are joining us virtually, please place your questions in the Zoom chat.

Today's event is being recorded and may be photographed.

The recording will be made available on the C-Path website and YouTube channel after the event.

Restrooms

Please silence all cell phones

RARE AND ORPHAN DISEASE PROGRAMS
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Critical Path Institute is supported by the Food and Drug Administration (FDA) of the Department of Health and Human Services (HHS) and is 54% funded by the FDA/HHS, totaling $19,436,549, and 46% funded by non-government source(s), totaling $16,373,368. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement by, FDA/HHS or the U.S. Government..

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Opening Remarks

Jacqueline Corrigan- Curay, JD, MD

U.S. Food and Drug Administration (FDA)

Principal Deputy Center Director, Center for Drug Evaluation and Research (CDER)

ARC Website

- https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/accelerating-rare-disease-cures-arc-program

Support for clinical **T**rials **A**dvancing **R**are disease **T**herapeutics **(START)**

CBER's START Pilot Program
Industry.biologics@fda.hhs.gov

CDER's START Pilot Program
CDER.STARTProgram@fda.hhs.gov

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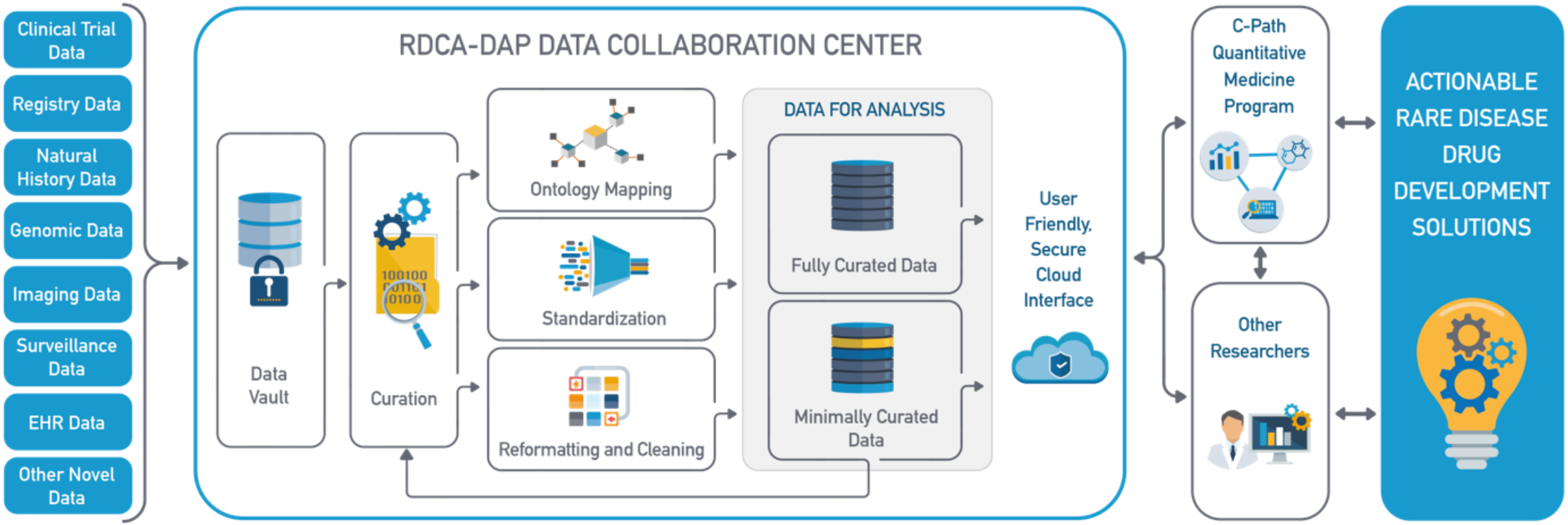
Opening Remarks

Klaus Romero, MD, MS, FCP

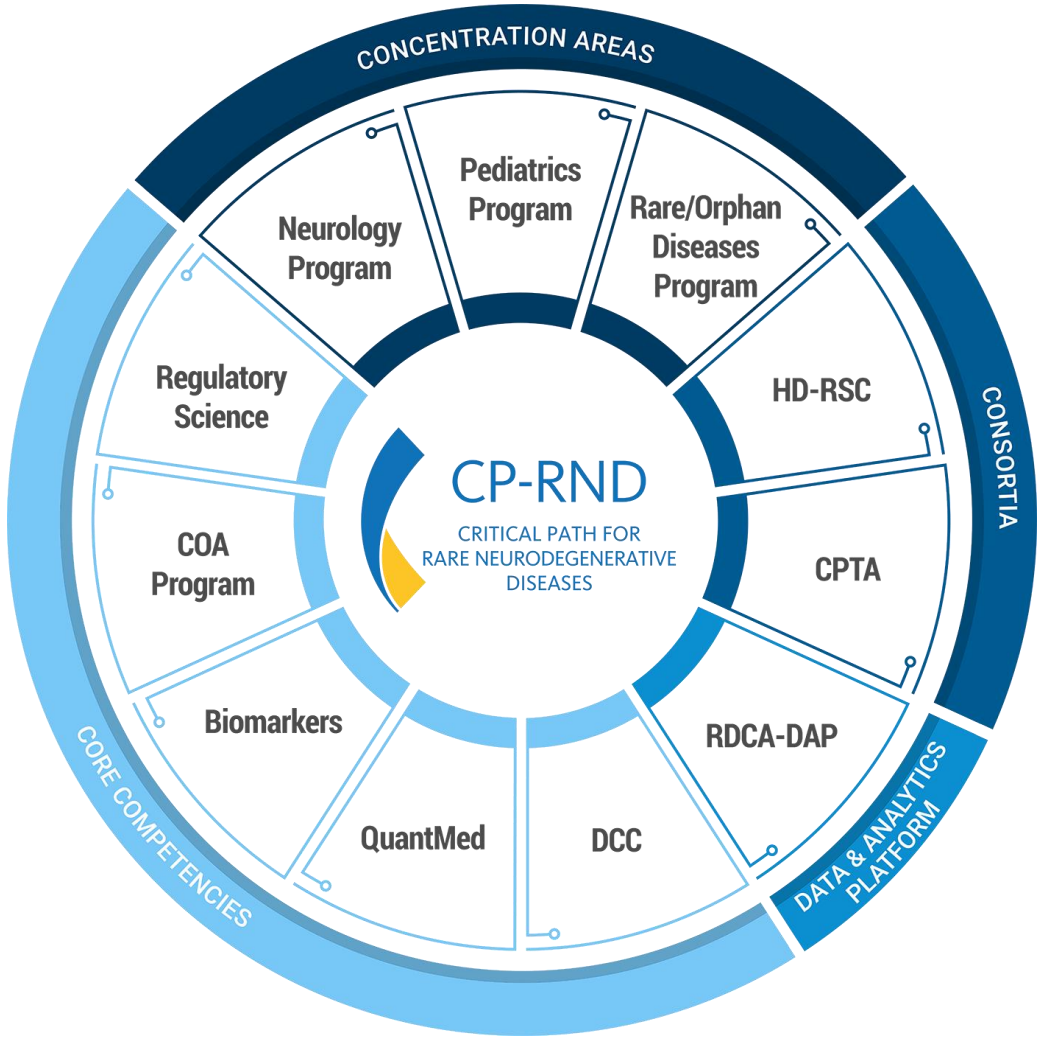
Critical Path Institute (C-Path)

Chief Executive Officer

From opportunities to solutions (data to insights)



CP-RND benefits from everything C-Path has to offer



OOPD's Efforts Relevant to Advancing Development of Medical Products for Rare Neurodegenerative Diseases

Katherine Needleman, MS, PhD, RAC

U.S. Food and Drug Administration
Director, Orphan Products Grants Program

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OOPD's Efforts Relevant to Advancing Development of Medical Products for Rare Neurodegenerative Diseases

Katherine Needleman, MS, PhD, RAC
Director, Orphan Products Grants Program
FDA/OOPD
March 8, 2024

Outline

- Brief Background
- Clinical Trial Grant Program
- Natural History Grant Program
- Rare Neurodegenerative Grant Program
  - What has been done
  - What FY24 brings

Office of Orphan Products Development

- The Office of Orphan Products Development (OOPD) provides incentives for sponsors to develop products for rare diseases.
- **Mission**: To promote the development of drugs, devices, biologics, and medical foods for patients with rare diseases and special populations.

DESIGNATION PROGRAMS	
1	Orphan Drug Designation & Exclusivity
2	Rare Pediatric Disease (RPD) Designation
3	Humanitarian Use Device Designation (HUD)

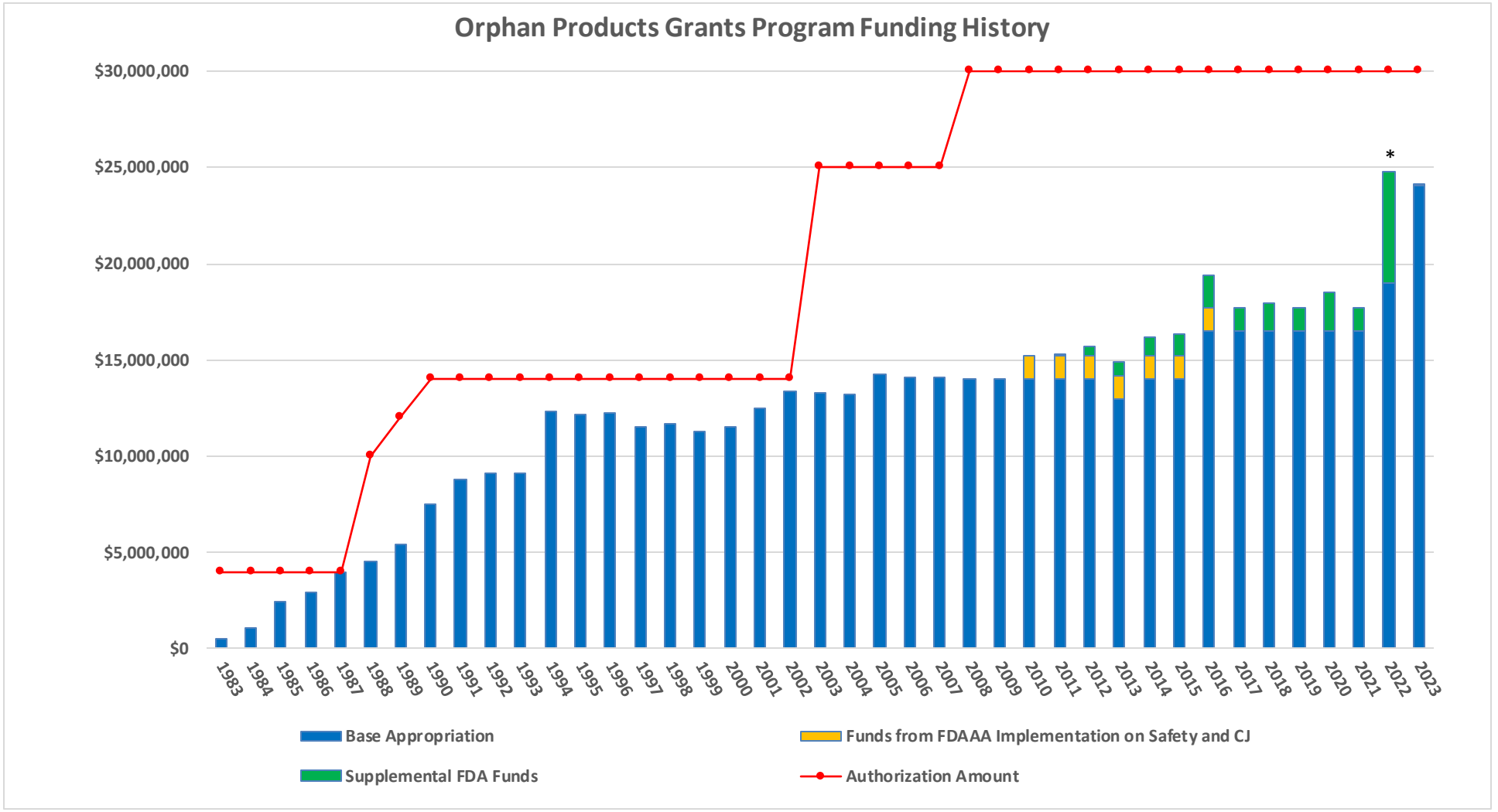
GRANT PROGRAMS	
1	Orphan Products Clinical Trials Grant Program
2	Orphan Products Natural History Grant Program
3	Pediatric Device Consortia Grant Program
4	Rare Neurodegenerative Disease Grant Program

Learn more about OOPD Grants programs:
Office of Orphan Products Development | FDA

Orphan Products Grants Program

- **Established:** 1983
- **Overall Budget**: ~$19M
- **Goal**: To advance the development of orphan products (drugs, biologics, devices, or medical foods) that demonstrate promise for the diagnosis or treatment of rare diseases or conditions
- **Clinical Trial Grants**
  - Funding ~ 75 ongoing studies
  - Focus on efficiency and innovative trial designs
  - Grants have led to over 85 product approvals
  - Publications, impact on field
- **Natural History (NH) Grants**
  - Launched Program in 2016
  - Currently funding 14 grants
  - Potential impact for clinical trial development and supporting regulatory decisions
  - Collaborations with industry and patient groups and publications

OOPD Grants Budget Still Below Authorization Amount for Years



* RNDD Grants Program Funding Began

OOPD Grant Statistics: Clinical Trial Grants

- Since 1983, FDA's OOPD:
  - Reviewed >3100 grant applications
  - Provided more than $530 million for more than 800 rare disease studies

- Over 85 FDA approved products were at least partially funded through the OOPD Grants Program for over 90 indications
  - ~10% of funded-studies have been used towards approval
  - Recent approval examples:

2020 APPROVED

3 Approvals
- Thyroid eye disease
- Long chain fatty acid oxidation disorders
- Hereditary Angioneurotic Edema

2021 APPROVED

1 Approval
- Prader Willi Syndrome

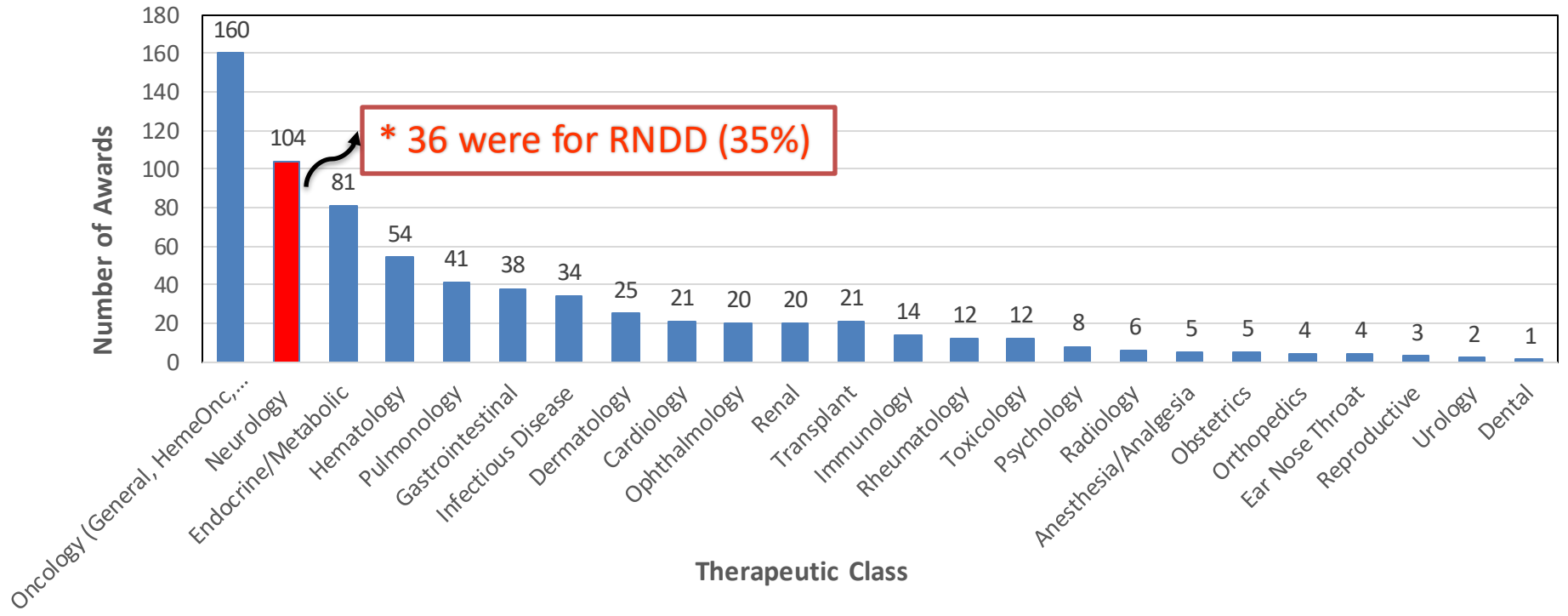
2022 APPROVED

5 Approvals
- Hepatorenal syndrome
- PEComa
- Active anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis
- GVHD
- Congenital Athymia

2023 APPROVED

1 New Approval &
3 Expanded Indications
- Neonatal seizures
- 2 products for Cystic Fibrosis
- Metastatic Melanoma

Therapeutic Classes represented from Clinical Trials awarded grants 1983-2023



RNDD Prior to 2022

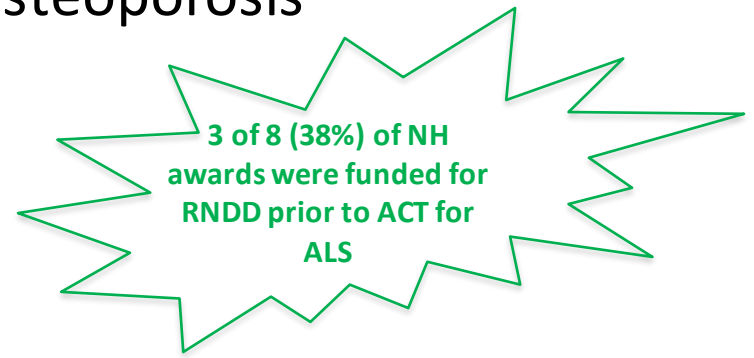
Prior to ACT for ALS, OOPD funded:

- 32 clinical trials totaling >$27M for RNDDs
  - >$4.5M of that was for ALS trials (6 grants)
- 3 natural history studies totaling >$5.6M
- 2 approvals partially supported by Orphan Products Grants Program
  - Tafamidis for familial amyloid polyneuropathy
  - Iduronate-2-Sulfatase for MPS II

OPD Natural History Grant Awards

FY2017

1. Angelman Syndrome
2. Friedreich Ataxia
3. Pregnancy & Lactation Associated Osteoporosis
4. Sarcoidosis
5. Sickle Cell Anemia
6. Myotonic Dystrophy Type 1



FY2019

1. Medullary Thyroid Cancer
2. Cardiac Disease in Duchenne Muscular Dystrophy

Rare Neurodegenerative Disease Grant Program

- **Established:** upon enactment of the ACT for ALS in December 2021.

- **Purpose**: Grants and contracts to public and private entities to cover costs of research on, and development of interventions intended to prevent, diagnose, mitigate, treat, or cure ALS and other rare neurodegenerative diseases in adults and children, including costs incurred with respect to the development and **critical evaluation of tools, methods, and processes**

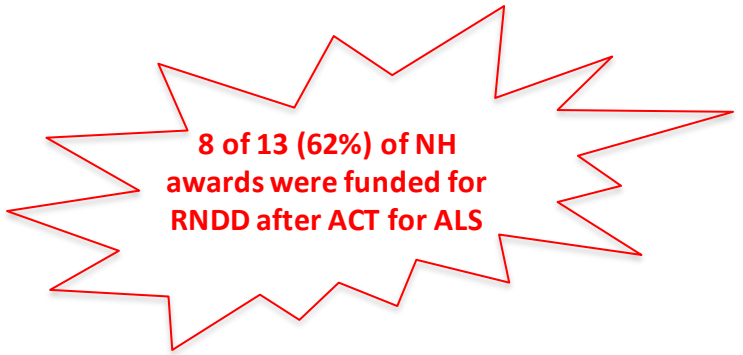
- To learn more about this program, see:

  Rare Neurodegenerative Disease Grant Program | FDA

OPD Natural History Grant Awards

FY2022

1. Autoimmune pulmonary alveolar proteinosis
2. Hypoparathyroidism
3. Ornithine aminotransferase (OAT) gene related ocular and systemic disease
4. Ataxia-telangiectasia
5. Amyotrophic lateral sclerosis
6. Castleman disease
7. Pulmonary arterial hypertension
8. Myotonic dystrophy type-1



FY2023

1. Amyotrophic Lateral Sclerosis
2. Familial Amyotrophic Lateral Sclerosis
3. Myotonic Dystrophy
4. Niemann-Pick Type C
5. Amyotrophic Lateral Sclerosis

FY2024

COMING SOON!

Rare Neurodegenerative Disease FY 22 Awards

Grants:

Institution	PI	Title	Budget
University of Minnesota	David Walk	Retrospective and prospective study in **amyotrophic lateral sclerosis** of clinic-based multicenter data collection	$1.6 million over four years
Johns Hopkins University	Howard Lederman	Prospective study in **ataxia-telangiectasia**	$1.6 million over four years
Virginia Commonwealth University	Nicholas Johnson	Prospective study in **myotonic dystrophy type-1** to establish biomarkers and clinical endpoints	$1.6 million over four years

Contracts:

Institution	Title	Budget
RTI International	ALS Functional Ratings Scale-Revised Clinical Outcome Assessment Remote-Use Equivalency Study	~$1.8 million over two years
RTI International	Landscape Analysis of Brain-Computer Interface Focused Patient Preference Studies in ALS Patients	~$330,000 over one year

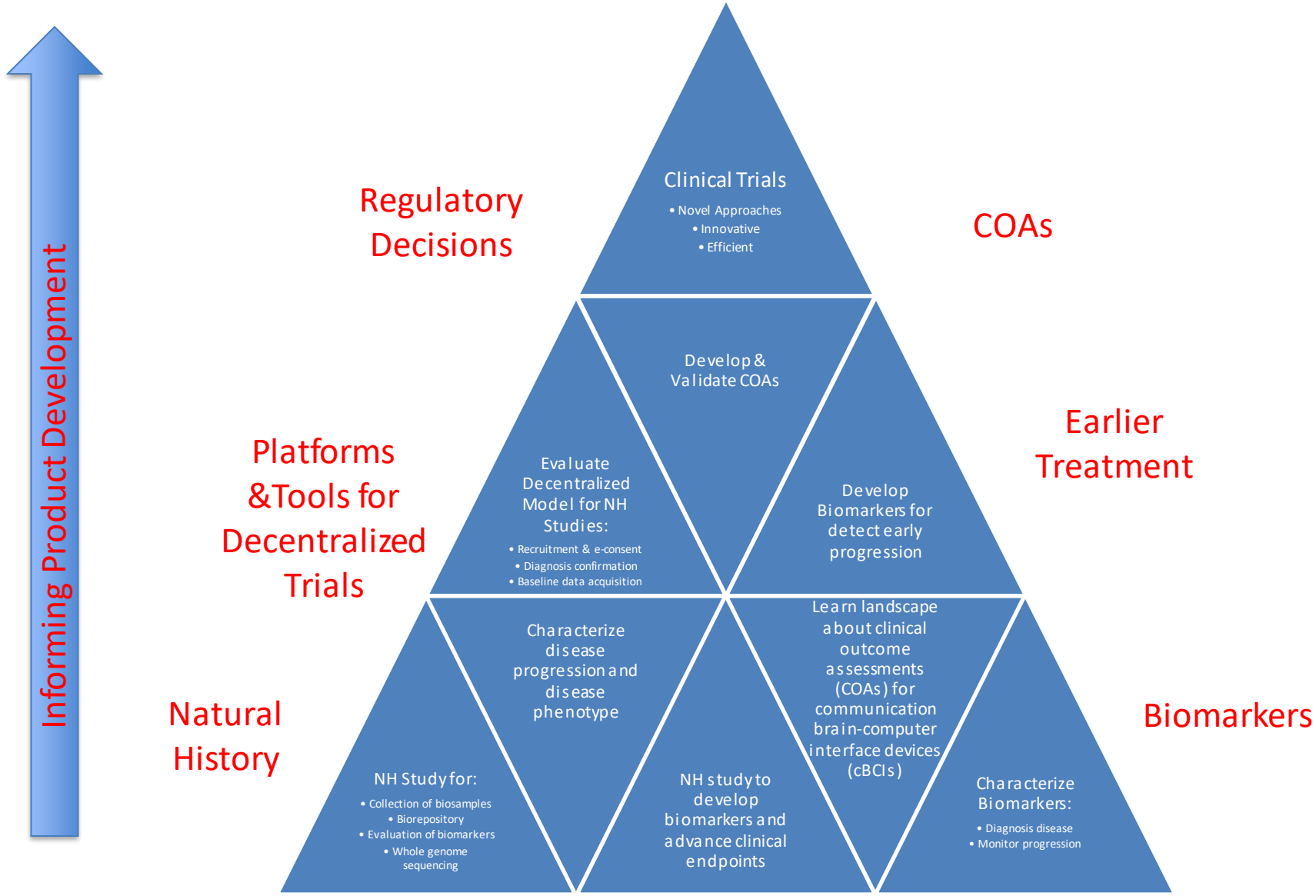
Intent to use $2.5M FY22 increase -> Leveraged and collaborated to use $5.8 M for these projects in FY22 with no effect on funding of other rare disease studies within Orphan Products Grants Program

Rare Neurodegenerative Disease Grant Program FY 23 Awards

Institution	PI	Title	Budget
Johns Hopkins University	Wong, Philip	Biomarker Study in **Amyotrophic Lateral Sclerosis (ALS)** to develop a diagnostic test for prodromal phase of ALS	$1.6 million over four years – FUNDING IN FULL
Massachusetts General Hospital	Wheeler, Thurman	Biomarker Study in **Myotonic Dystrophy** to Determine Extracellular RNA Biomarkers	$1.6 million over four years
University Of Illinois At Chicago	Cologna, Stephanie	Biomarker Study in **Niemann-Pick Type C** to determine clinically relevant Biomarkers	$1.6 million over four years
Massachusetts General Hospital	Sherman, Alexander	Prospective Natural History Study and Biomarker study in **Familial Amyotrophic Lateral Sclerosis (ALS)** and ultra-rare MNDs to Create a disease-agnostic scalable platform for decentralized observational and validation of digital biomarkers	$1.6 million over four years
University Of Minnesota	Pisharady, Pramod	Biomarker Study in **Amyotrophic Lateral Sclerosis (ALS)** to Optimize and Validate Multimodal Longitudinal Imaging of Brain and Cervical cord as an ALS disease biomarker using microstructure statistics and morphometry	$1.6 million over four years
Blackrock Microsystems	Melby, Shana	UH2/UH3 COAs for cBCI: Metrics for Brain Controlled Communication through a comprehensive review of clinical outcome assessments for communication brain computer interfaces in **amyotrophic lateral sclerosis (ALS)**	$500,000 over two years
University Of Minnesota	Walk, David	Retrospective and Prospective Study in **Amyotrophic Lateral Sclerosis (ALS)** of Clinic-based Multicenter Data Collection	$5.8 million over four years
New York University School Of Medicine	Gonzalez-Duarte Briseno, Maria Alejandra	Phase 2 Study of Dexmedetomidine Sublingual Film for the Ambulatory Treatment of Hyperadrenergic Autonomic Crisis in Patients with **Familial Dysautonomia**	$2.6 million over four years- Co-funded with OGP

FY 2023 awards announced in FDA Roundup

Rare Neurodegenerative Disease Grant Program Awards - Impact



FY24 Planning for Rare Neurodegenerative Disease Grants Program

- Used concept ideas obtained from stakeholders to establish a new FY 24 RFA to address unmet needs for rare neurodegenerative diseases

OOPD RNDD Funding Opportunities For FY24

- **Natural History and Biomarker Studies of Rare Neurodegenerative Diseases (U01)**
  - **Receipt Dates: May 6, 2024**
  - **FOA Number: RFA-FD-24-024**

Funding opportunities for rare disease research | FDA

RFA-FD-24-024: Natural History and Biomarker Studies for RNDD

The basics:

- **Purpose:**
  - To support efficient natural history studies alone or in conjunction with the development and validation of clinical outcome assessments (COAs) and/or biomarker studies to address the unmet needs in rare neurodegenerative diseases for children and adults
- **Eligibility:**
  - Foreign or domestic, public or private, for-profit or nonprofit entities (state and local units of government) are eligible; Federal agencies may not apply
  - The neurodegenerative diseases proposed to be studied meet the definition of a rare disease (prevalence of fewer than 200,000 persons in the US)
- **Budget:**
  - Not limited but time is limited to 4 years
- **Awards:**
  - Number of awards is contingent upon FDA appropriations and submission of a sufficient number of meritorious applications
  - Expect to fund up to 3 awards
  - Funding dependent on **quality of application** and **availability of Federal funds**

Conclusions

- OOPD has been very successful in contributing to:
  - product approvals
  - publications
  - regulatory decisions
  - standard of care changes
  - rare neurodegenerative disease product development
- High need for quality clinical trials and natural history studies for rare diseases
- OOPD continues to make changes to the grants program to increase its impact and continue to meet the Orphan Products Grants and RNDD Grants Programs missions
- Large need remains for funding in rare disease space – work together to bring products to rare disease patients!

OOPD Funding Opportunities

- Clinical Studies of Orphan Products Addressing Unmet Needs of Rare Diseases (R01)
  - Receipt Dates: October 22, 2024
  - Resubmission Only Receipt Dates: June 4, 2024; June 3, 2025
  - FOA Number: RFA-FD-23-001
- Natural History and Biomarker Studies of Rare Neurodegenerative Diseases (U01)
  - Receipt Dates: May 6, 2024
  - FOA Number: RFA-FD-24-024

Funding opportunities for rare disease research | FDA

OOPD Contact Information

For more information on OOPD programs go to:

www.fda.gov/orphan

Still have questions?

Email us at orphan@fda.hhs.gov
Email: katherine.needleman@fda.hhs.gov

Call us at 301-796-8660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Critical Path for Rare Neurodegenerative Diseases (CP-RND) Efforts and Vision

Collin Hovinga, PharmD, MS, FCCP

Critical Path Institute (C-Path)
Vice President, Rare and Orphan Disease Programs

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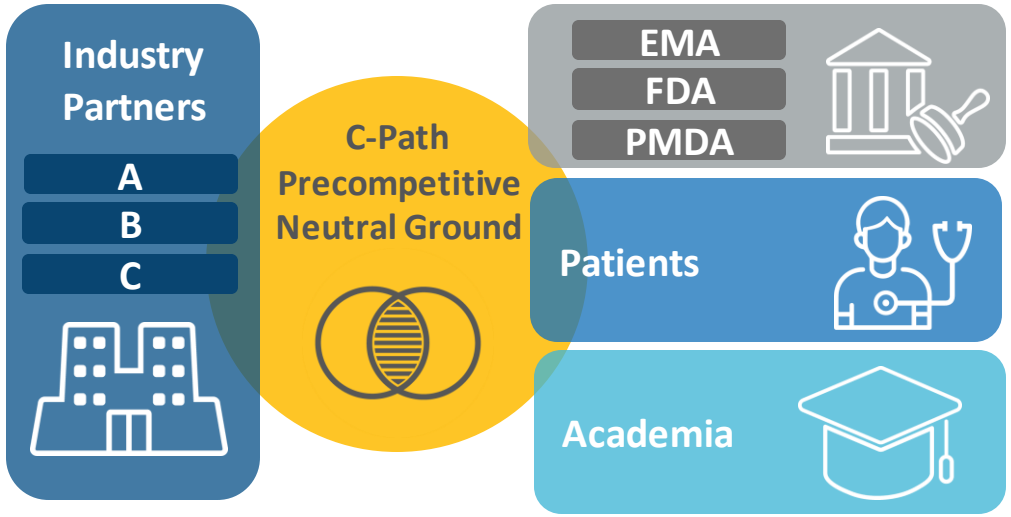
C-Path's Public-Private Partnership Model

- Foster development of new evaluation tools to inform medical product development and regulatory decision-making
- Convene scientific consortia of industry, academia, and government for sharing of data/expertise
  - ✓ The best science
  - ✓ The broadest experience
  - ✓ Active consensus building
- Enable iterative EMA/FDA/PMDA participation in developing new methods to assess the safety and efficacy of medical products
- Obtain official regulatory endorsement of novel methodologies and drug development tools to address unmet needs



Creating Solutions to Address Unmet Needs in Drug Development

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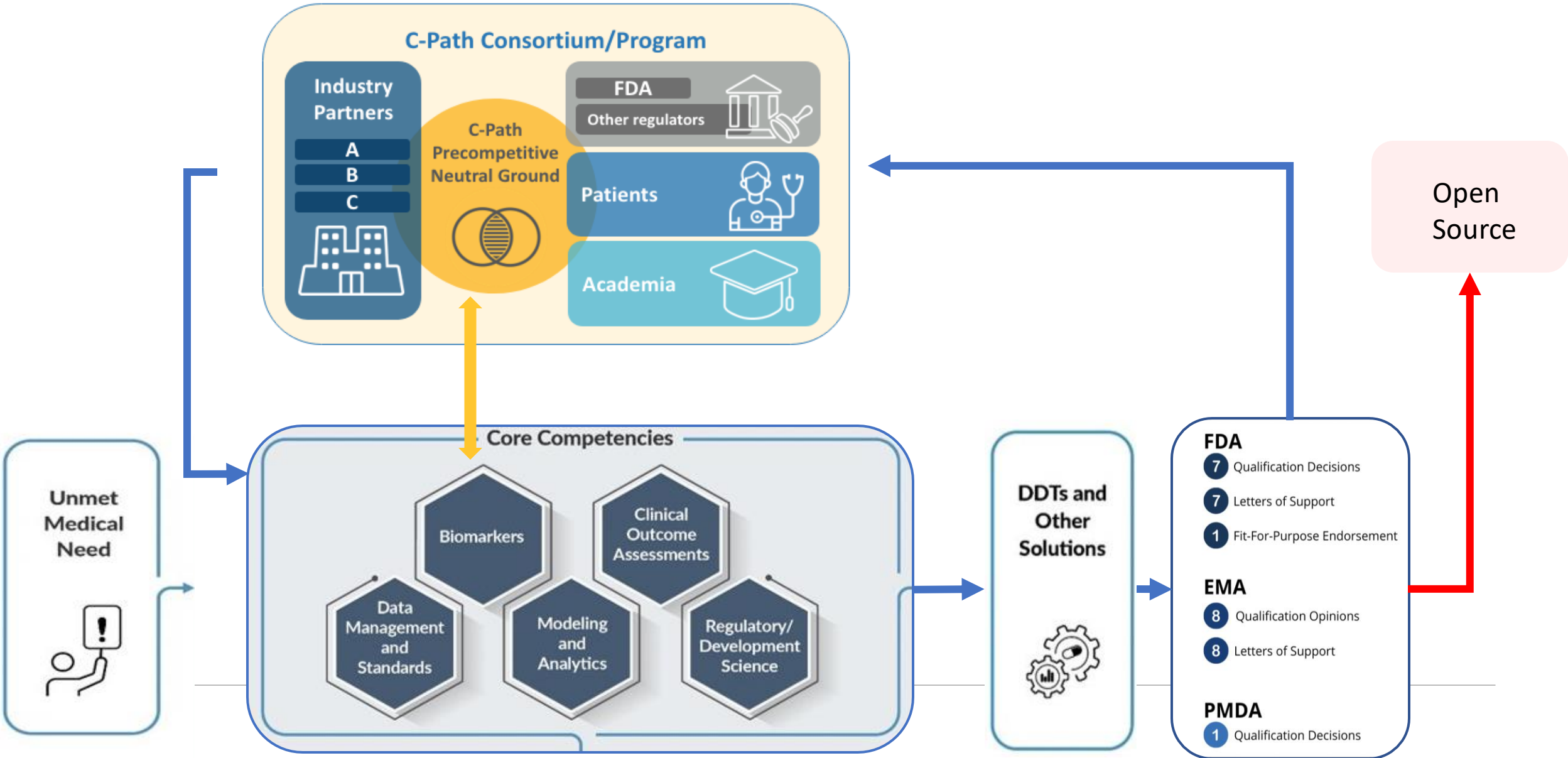

Critical Path for Rare Neurodegenerative Diseases (CP-RND)

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Accelerating Access to Critical Therapies for ALS Act (ACT for ALS):

C-Path selected to establish a PPP involving FDA/NIH, persons with lived experience/advocates, researchers and industry aimed at advancing research in ***ALS and other rare neurodegenerative diseases***.

- ✓Ataxias- CPTA
- ✓Huntington's Disease-HD-RSC
- ✓Amyotrophic lateral sclerosis (ALS)
- ✓Others being developed through Task Forces

Consistent input from persons with lived experience, caregivers and the advocacy community is *critical for the success*.

Key advantages comes from the opportunity for *shared learnings* among RNDs and among stakeholder communities

Programs under Section 3 of the ACT for ALS

Public Law 117.79
Accelerating Access to Critical Therapies for ALS Act (ACT for ALS) Section 3

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Critical Path for Rare Neurodegenerative Diseases (CP-RND)

- Accelerate efficiencies in RND drug development through creation of tool (DDTs).
- Focus on RWD/RWE-clinical data, biomarkers, DHTs, COAs, clinical trial simulation and regulatory science/endorsement to bridge scientific discoveries to implementable solutions

AMP®ALS

Accelerated Medicines Partnership® in ALS

- Molecular analyses of ALS biospecimens and clinical research to develop validated ALS biomarkers for early diagnosis & treatment assessment, and to discover new therapeutic targets and risk factors for ALS

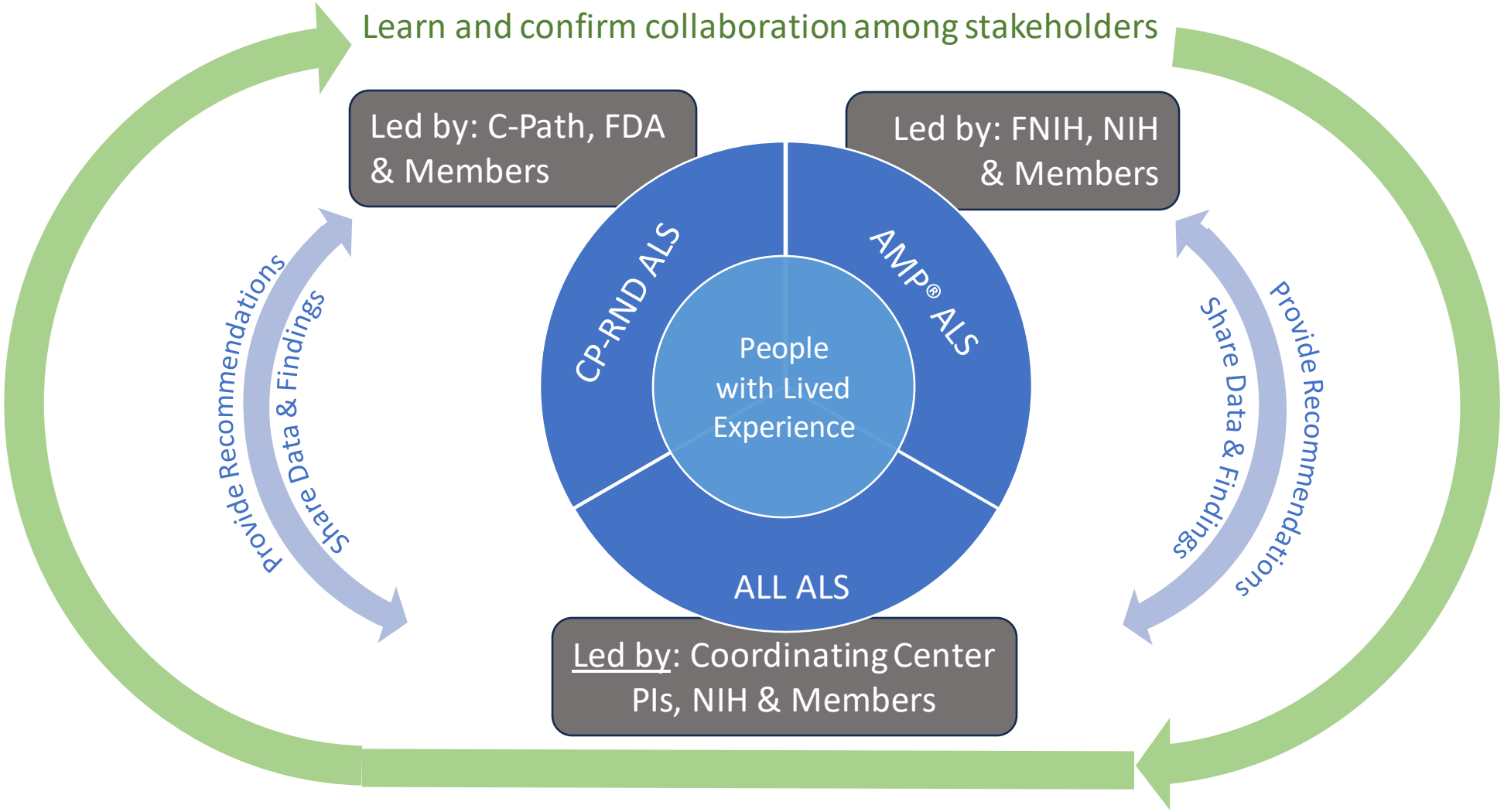
ALL ALS

ALLALS
Access for ALL in ALS

Access for ALL in ALS Clinical Research Consortium

- Clinical research infrastructure to support the collection of COAs/PROs and longitudinal biospecimens from people living with ALS, at genetic risk for ALS, and controls

ACT for ALS Collaborations



Foundation for the Future: CP-RND Completed Pre-consortium ALS Efforts

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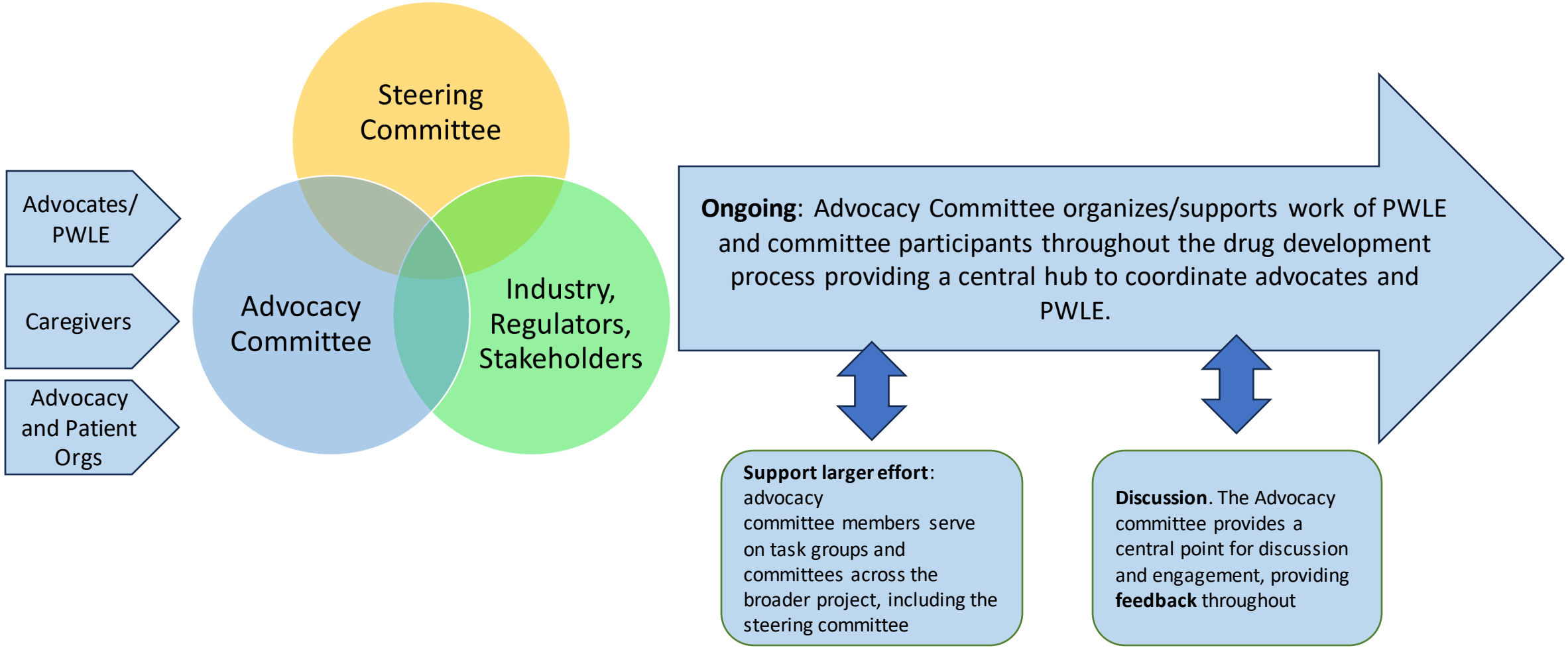
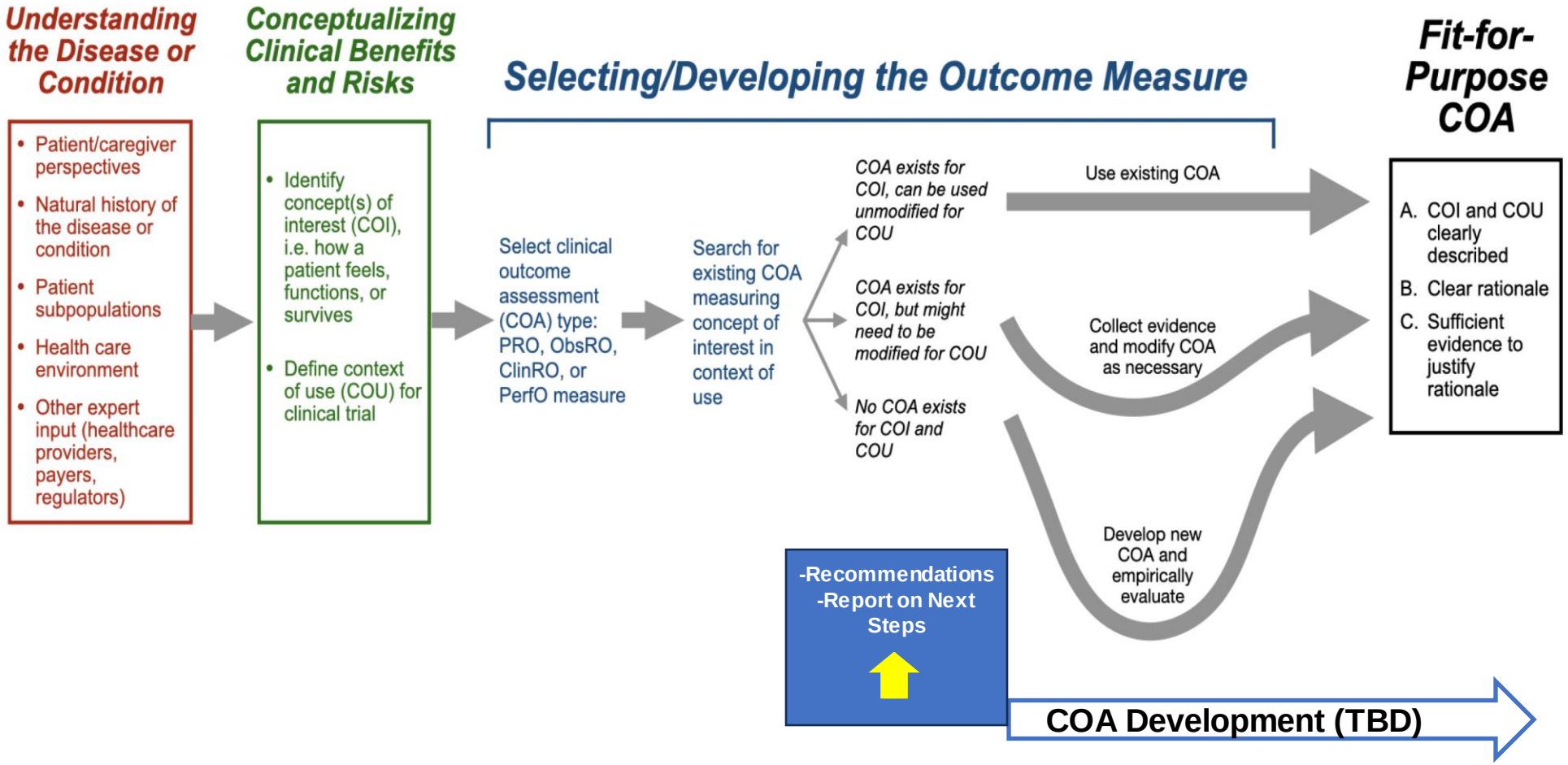
PFDD process	Data Landscape	Biomarkers	COAs	Modeling	Digital Health Technologies
• Active and ongoing engagement with people with lived experience and their advocacy organizations. • Coordinating with AMP efforts, reducing burden • Formation of a PWLE group to give/get feedback on ALS related projects/WGs	• 70+ larger databases reviewed; priority listing created and shared with AMP®ALS WG • Summarized results of clinicaltrials.gov search of >700 studies • Data dictionary collection and data share agreements for priority data sets underway	• Reviewed efforts to-date and spoke with KOLs regarding NfL/TDP43 and other potential biomarkers for use in ALS clinical trials • Conducted survey of biospecimens available for researchers, summary shared with AMP® ALS WG	• Discussed challenges and gaps in current COAs with KOLs • Initiated early efforts to evaluate to examine important concepts for PWLE and COAs following FDAs Roadmap for Patient-Focused Outcome Measures	• Existing models were reviewed and discussed with KOLs, including models for survival, longitudinal, stratification/staging , severity metrics from DHTs	• Landscaping efforts on DHT for ALS based on high priority concepts (literature review) • Interviews with programs performing DHT ALS research and applicability for specific COU • Identified data sets for curation in the data warehouse.

Model for PFDD in CP-RND

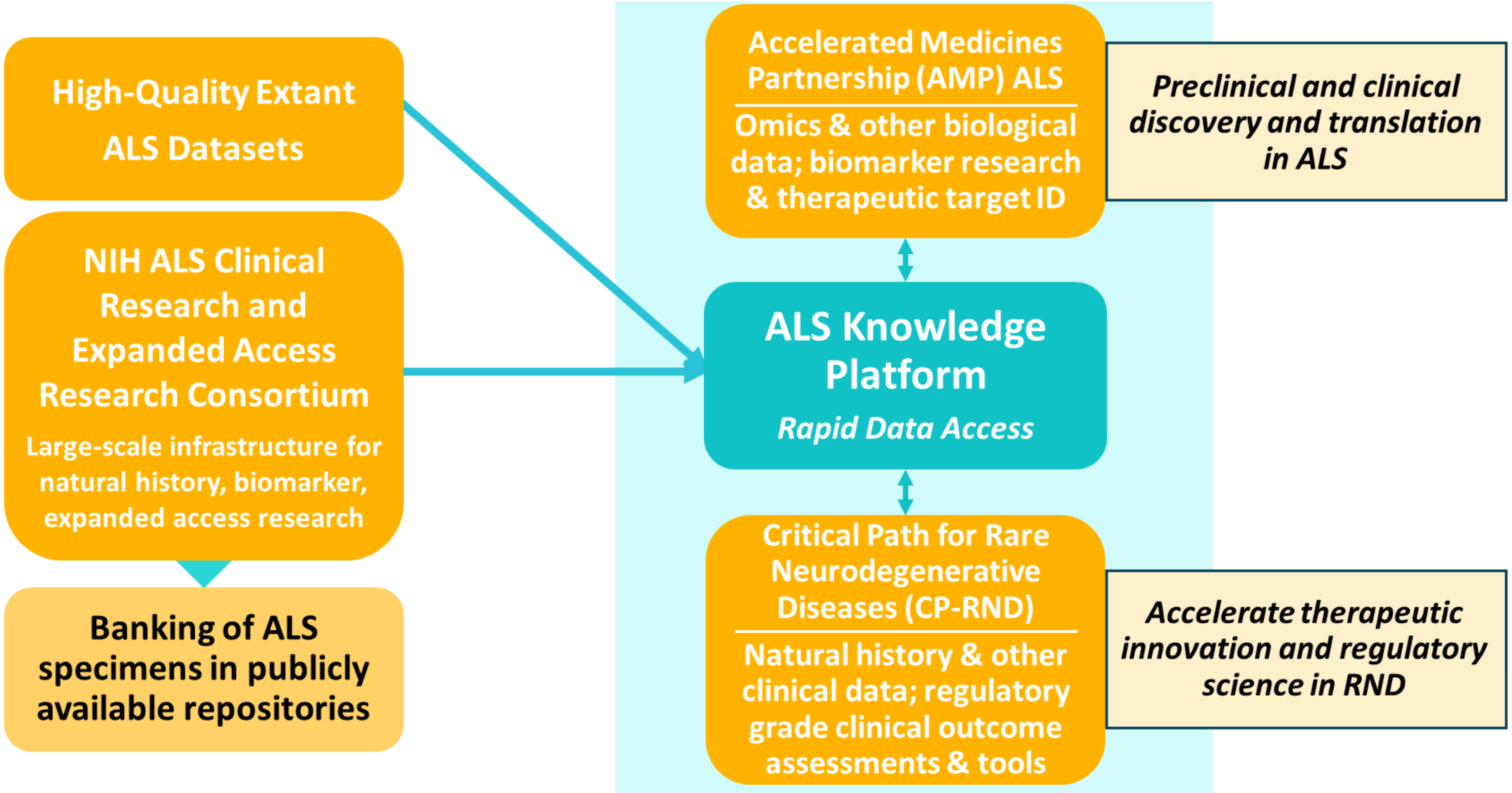


Advancing CoAs focusing on Meaningful Outcomes for People Living with ALS

- ***How do we get to a well-developed COA meaningful to PWLE?***



ALS Knowledge Platform: CP-RND/RDCA-DAP + AMP-ALS



CP-RND Program Updates: Data Collaboration Agreements (DCAs)

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Targeting

10

extant datasets annually into the ALS knowledge portal

25+

extant datasets identified for tier 1 priority review

15+

industry sponsored clinical trials identified for tier 1 priority review

14*

Data Contribution Agreements (DCA) under review

1

Data Contributor Agreement (DCA) Signed

2

Data Use Agreements (DUA) Signed

2

Extant datasets accessed and under review with C-Path team

Actionable Solutions for Rare Diseases Drug Development

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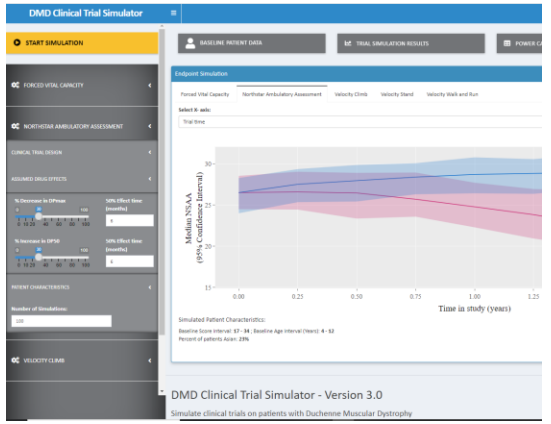
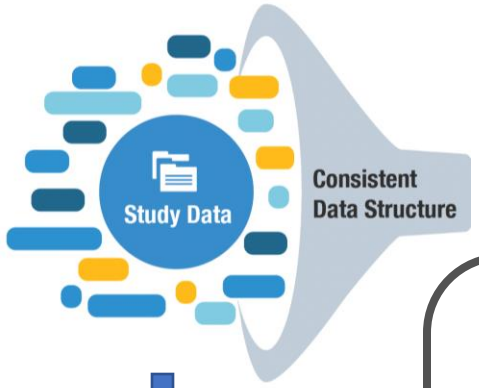
Toward Clinical Trial Simulation Tools

Input: Clinical trial data, Observational study data

Output: CTS Tool





Model Training and Validation

Disease Progression
- Demographics - Omics
- Clinical Assessments
- Biomarkers

+

Clinical Trial Components
- Placebo Effect
- Trial Design
- Dropout

+

Candidate Drug Effects
- Dose Response
- Disease-modifying
- Symptomatic

Example: Clinical Trial Simulation Tool- Duchenne Muscular Dystrophy

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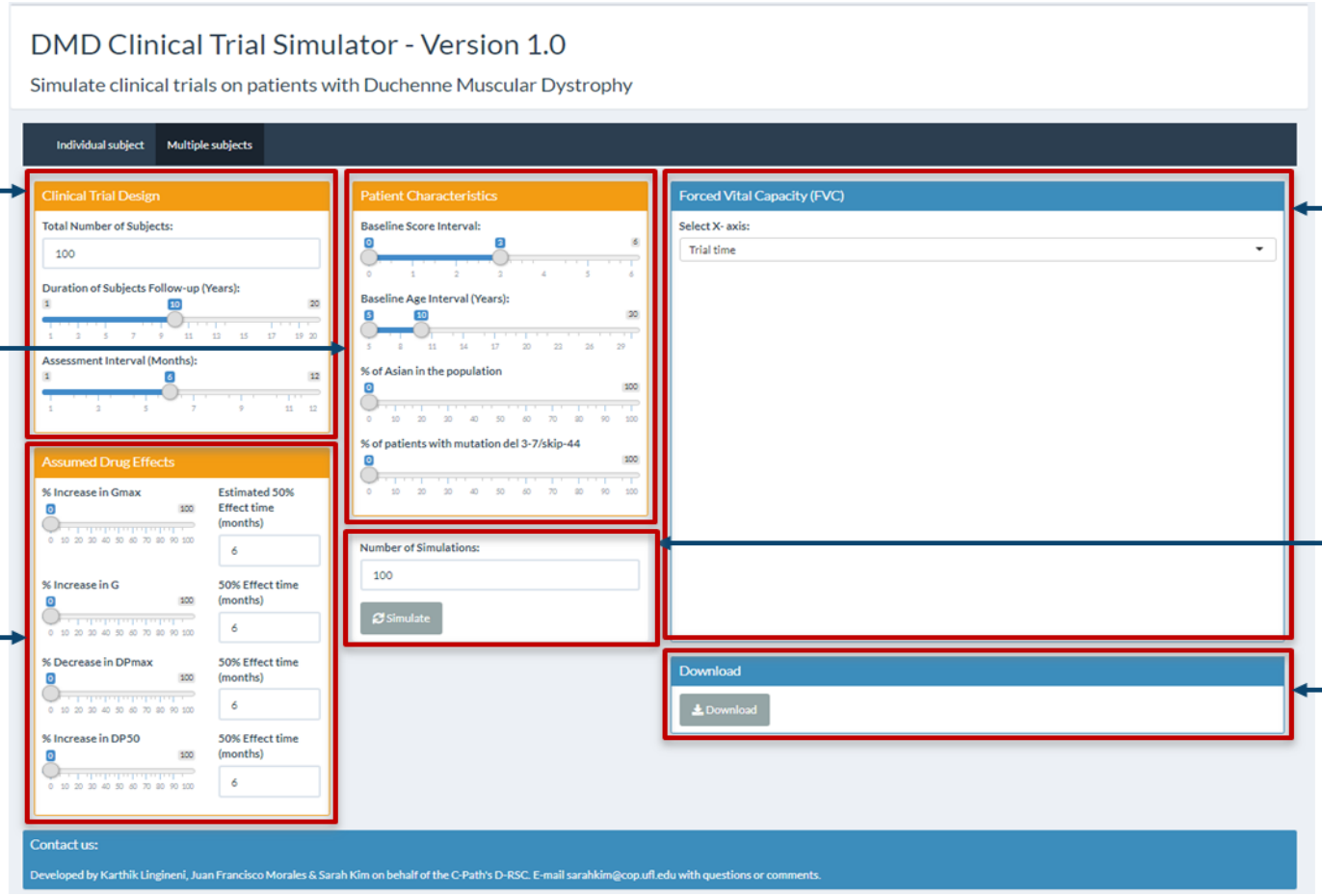
Trial design parameters:
- Study duration
- Assessment frequency

Baseline Patient features:
- FVC
- Age
- Race
- del 3-7/skip-44 mutation

Assumed drug effects:
- % changes to model parameters to mimic drug effects
- Adjustable times to effect



Plotting window by user chosen time metric:
- Plots by age groups
- Plots by time in study
- Provides mouse-over quantitative values

Number of trials to simulate

Simulation output export feature:
- Export virtual patient data
- Export plots
- Export power estimates

A Model-based Clinical Trial Simulation Tool to Optimize Clinical Trial Design of Studies to Investigate Efficacy of Potential Therapies for Duchenne Muscular Dystrophy Briefing Document submitted to the FDA's Fit-for-Purpose Initiative Consultation and Advice pathway. Revisions submitted to FDA/EMA

Biomarkers and Digital Health Technologies (DHTs)

- Survey performed to identify biospecimens that might be available for biomarker work done under FNIH/AMP-ALS
- Active review and intake of extant data to assess the suitability of a regulatory submission under specific context of use for key fluid biomarkers and DHTs
- Early focus is on DHTs addressing accelerometry and speech
- Gaps in existing data will be provided to AMP-ALS/NIH and FDA for further support

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Advancing Drug Development.
Improving Lives. Together.

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Huntington's Disease/Ataxias Efforts

Terina Martinez, PhD

Critical Path Institute

Executive Director, CP-RND

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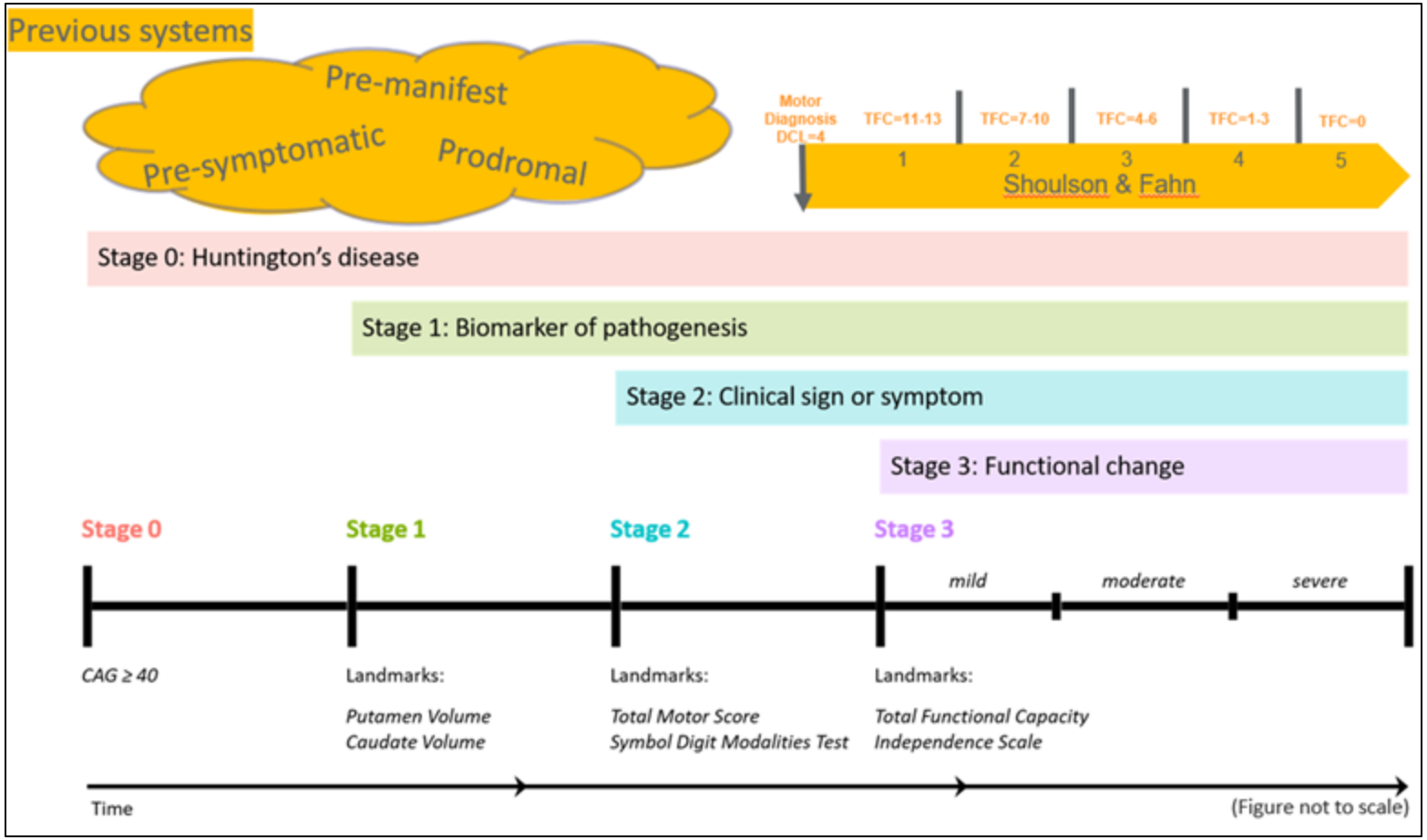
The overall goal of the Huntington's Disease Regulatory Science Consortium (HD-RSC) is to **create a regulatory science strategy for HD** that helps de-risk drug development. **HD-RSC provides a neutral forum and collaborative framework to bring together the essential participants from the HD community** to aggregate data, identify solutions, and develop regulatory-grade tools.

HD-RSC has embarked on the **next stage of its evolution** by focusing our research plan on **optimizing drug development tools for earlier stages of the disease continuum.**

Leveraging the **Huntington's Disease Integrated Staging System (HD-ISS) as a foundation**, HD-RSC incorporates the voice of individuals with lived experience and utilizes data modelling/analytics, the characterization of actionable clinical biomarkers, clinical outcome assessments, and digital health technologies to develop tools with regulatory rigor and clinical meaningfulness to capture what matters most to people living with HD, their families, and caregivers.

The HD-ISS as a conceptual framework for HD-RSC working groups: incorporating genetic, biomarker, clinical and functional endpoints



- The HD-ISS is a biology-based, data-driven framework derived from extensive published evidence
- Clinical trial enrichment using stage landmarks may help to identify pwHD closer and/or farther from stage transitions
- Slowing progression across any Stage boundary could lead to long-term decreases in morbidity and mortality

Ref.: Modified from Tabrizi *et. al.*, 2022, *Lancet Neurology;* PMID: 35716693

Impact Potential for HD-RSC Tools & Solutions

Drug Development Tool Solution	Impact
HD Integrated Staging System	Clinical trial enrichment, enable prevention trials
Clinical Trial Simulation Tool	Optimize clinical trial design
Neuroimaging and Fluid Biomarkers	Improve ability to detect onset; sensitively measure progression
Novel outcome measures / endpoints	Improve ability to detect onset and changes in meaningful symptoms

Recent Publications & Regulatory Submissions

Review > Lancet Neurol. 2022 Jul;21(7):632-644. doi: 10.1016/S1474-4422(22)00120-X.

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

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)

Review > Front Neurol. 2021 Oct 22:12:712565. doi: 10.3389/fneur.2021.712565. eCollection 2021.

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

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]

Review > Front Neurol. 2021 Sep 21:12:712555. doi: 10.3389/fneur.2021.712555. eCollection 2021.

Volumetric MRI-Based Biomarkers in Huntington's Disease: An Evidentiary Review

Kirsi M Kinnunen [1], Adam J Schwarz [2], Emily C Turner [3], Dorian Pustina [4], Emily C Gantman [4], Mark F Gordon [5], Richard Joules [1], Ariana P Mullin [3 6], Rachael I Scahill [7], Nellie Georgiou-Karistianis [8]; Huntington's Disease Regulatory Science Consortium (HD-RSC)

HD Clinical Trial Simulation Tool Submitted to EMA and FDA

CPTA
CRITICAL PATH TO THERAPEUTICS FOR THE ATAXIAS
CRITICAL PATH INSTITUTE

Critical Path to Therapeutics for the Ataxias (CPTA)

Founded in 2021, CPTA is a consortium focused on accelerating therapeutic development for spinocerebellar ataxia (SCA).

The overall goal of the Critical Path to Therapeutics for the Ataxias (CPTA) is to be **a neutral convenor for the ataxia community** to collaboratively aggregate and analyze data, identify solutions, and develop regulatory-grade tools, **to accelerate development of novel therapeutics for rare inherited ataxias**.

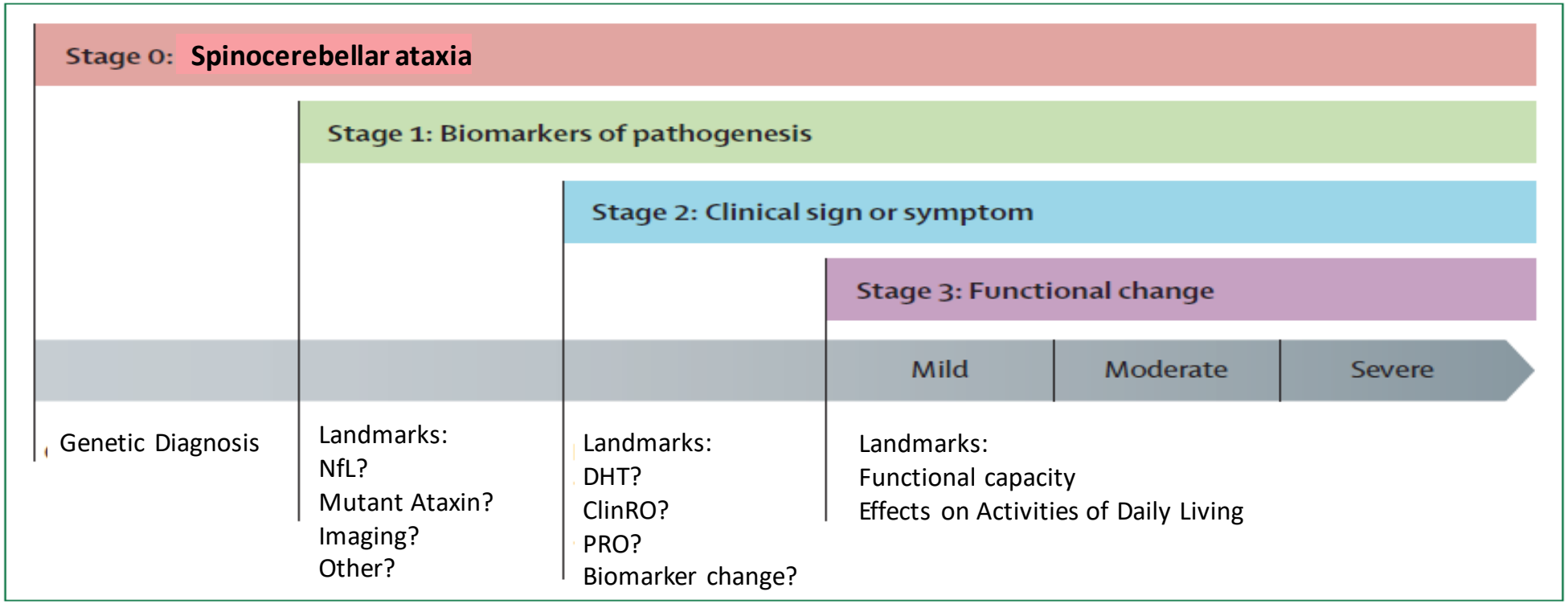
To inform and enable implementation of its Research Strategy, **CPTA has built an Aggregated Ataxia Database** hosted on C-Path's Rare Disease Cures Accelerator – Data and Analytics Platform (RDCA-DAP); representing >1,600 patients and spanning 7 SCA types, **it is the largest publicly accessible SCA database**.

Leveraging its database as a foundation, CPTA endeavors to optimize clinical endpoints and develop a biology-driven integrated staging system for the SCAs that **captures clinical relevance/meaningfulness and what matters most to people living with SCA, their families, and caregivers**.

Considerations for Ataxia Disease Staging

What concept of interest is optimal for each disease stage?

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



Modified from Ref.: Sarah J. Tabrizi…HD-RSC et al., *Lancet Neurol.* July 2022 PMID: 35716693

Abbreviations:
NfL = neurofilament light chain
DHT = digital health technology
ClinRO = clinician reported outcome
PRO = patient reported outcome

Impact Potential for CPTA Tools & Solutions

Drug Development Tool Solution	Impact
SCA Integrated Staging System	Clinical trial enrichment, enable prevention trials
Integrated Ataxia Database	Inform research plan and regulatory decision making
Novel outcome measures / endpoints	Improve ability to detect onset and changes in meaningful symptoms

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INSTITUTE

Advancing Drug Development.
Improving Lives. Together.

c-path.org

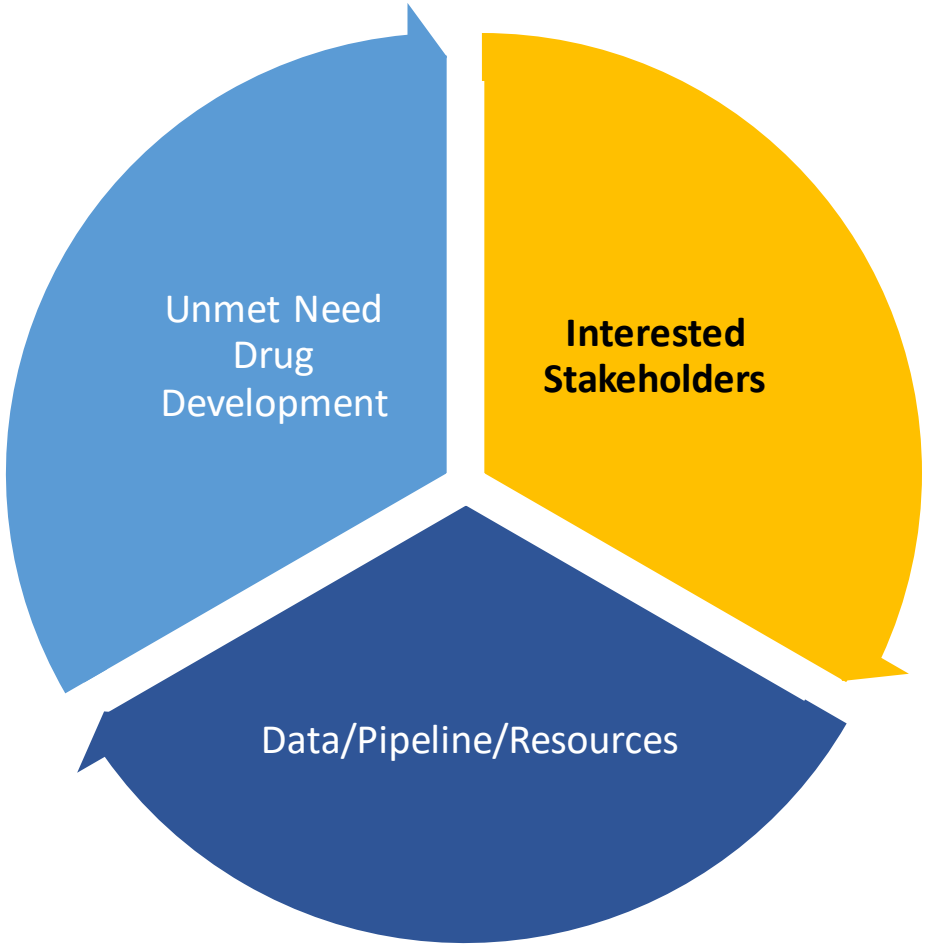
CP-RND Next Steps and How to Get Involved

Collin Hovinga, PharmD, MS, FCCP

Critical Path Institute (C-Path)
Vice President, Rare and Orphan Disease Programs

CRITICAL PATH INSTITUTE

Other Rare Neurodegenerative Diseases



Progressive subnuclear palsy (PSP)- trial simulation tool

Frontotemporal dementia (FTD)-ongoing discussions regarding biomarkers and data

Developmental epileptic encephalopathies (DEE)-non-seizure endpoints and data standards

Spastic paraplegia (HSP, PLS)-early conversations underway to identify unmet needs and action steps

Get in touch with us!

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CRITICAL PATH
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NINDS: Translational Efforts to Advance Therapies for RNDs

Amir Tamiz, PhD

National Institute of Neurological Disorders and Stroke (NINDS)

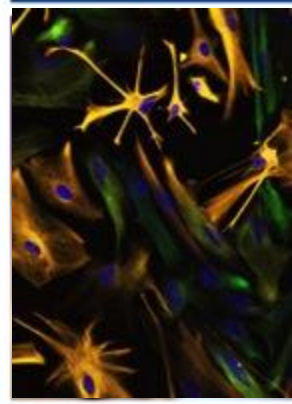
Director, Division of Translational Research

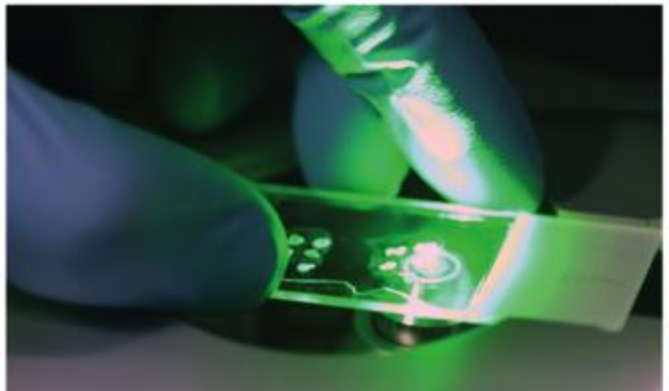
National Institute of Neurological Disorders and Stroke

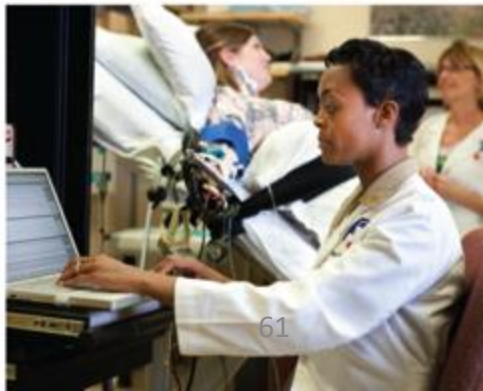
National Institute of Neurological Disorders and Stroke

NINDS Translational Efforts to Advance Therapies for RNDs

Amir Tamiz, PhD
Associate Director,
NINDS





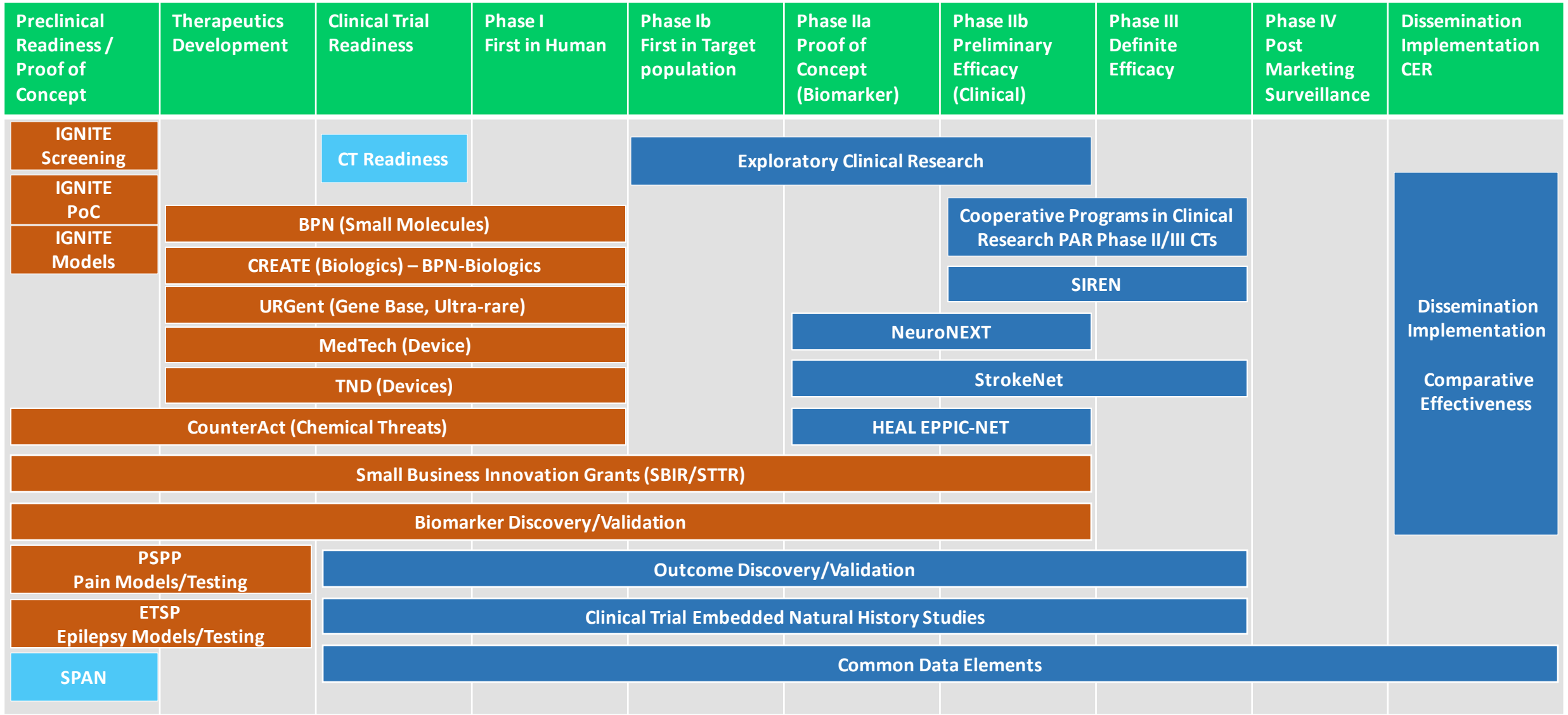


Mission of NINDS

The mission of NINDS is to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease

- ✓ Support and perform basic, translational, and clinical neuroscience research
- ✓ Fund and conduct research training and career development programs and ensure a vibrant, talented, and diverse work force
- ✓ Promotes the timely dissemination of scientific discoveries and their implications for neurological health to the public

NINDS Programs Across the Translational and Clinical Spectrum



National Institute of Neurological Disorders and Stroke

Division of Neuroscience

Division of Translational Research

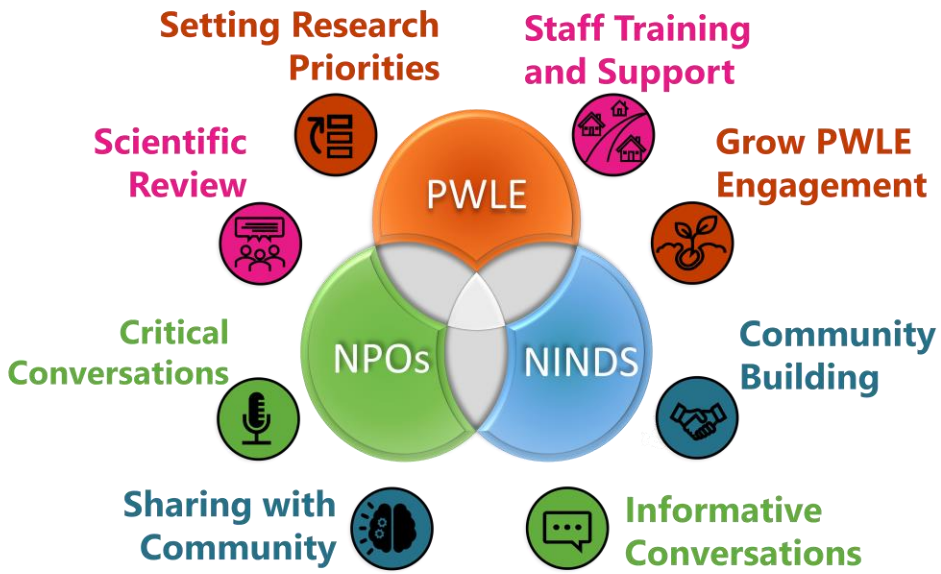
Division of Clinical Research

NINDS Translational Strategy

The Right Care for the Right Patients at the Right Time

1. Measure
   - Support discovery and development of biomarkers
2. Intervene
   - Support therapy development
   - Pursue early interventions and rare diseases
   - Consider ethical consequences
3. Validate
   - Implement clinical measures in preclinical design
   - Support first in human trials
   - Support advanced strategies to evaluate efficacy of interventions

NINDS Strategic Plan emphasizes significant increase in our engagement with PWLE



Lived Experience Engagement Strategist rebekah.corlew@nih.gov

NINDS Translational Biomarker Program

Facilitate fit-for-purpose validation of biomarkers ready for use in clinical trials, to accelerate therapeutic development, and improve patient care.

- ✓ Launched in 2018
- ✓ Supports neurological and NINDS neuromuscular disorders
- ✓ Supports validation studies for specific context of use
- ✓ Over 30 awarded projects

Program	Grant Mechanism	Entry Criteria	Scope	
Discovery/Development PAR-22-089	R61/R33 Up to 5 years	• Biological rational • Context of use	• Detection method	• Initial proof of concept
Analytical Validation: PAR-24-095 PAR-24-098	U01/U44 Up to 4 years	• Detection method • Proof of concept	• Optimize measurement • Study site variability • Outcome variability	
Clinical Validation: PAR-24-097 PAR-24-096	U01/U44 Up to 5 years	• Multi site analytical validation in hand	• Specify context of use • Large multisite prospective studies	

Clinical Trial Readiness Program

- Funding for prospective, longitudinal, observational, multi-site clinical studies aimed at *clinical outcome assessment (COA) and biomarker* validation for upcoming clinical trials
- Only for rare diseases that will have candidate therapeutics ready to test in clinical trial(s) in the near future (PAR-22-184, 5-7 years)
- Requires preliminary data on COA and analytical validation of candidate biomarkers
- Two application receipt dates per year through Feb 2025
- Support for up to 5 years, up to $750,000/yr direct cost

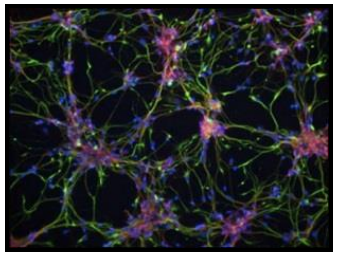
Innovation Grants to Nurture Initial Translational Efforts

Advance projects to the point where they can move into preclinical development

PAR-21-124: Assay Development and Therapeutic Agent Identification

PAR-21-123: Development and Validation of Model Systems to Facilitate Neurotherapeutic Discovery

PAR-21-122: Neurotherapeutic Agent Characterization and In vivo Efficacy Studies

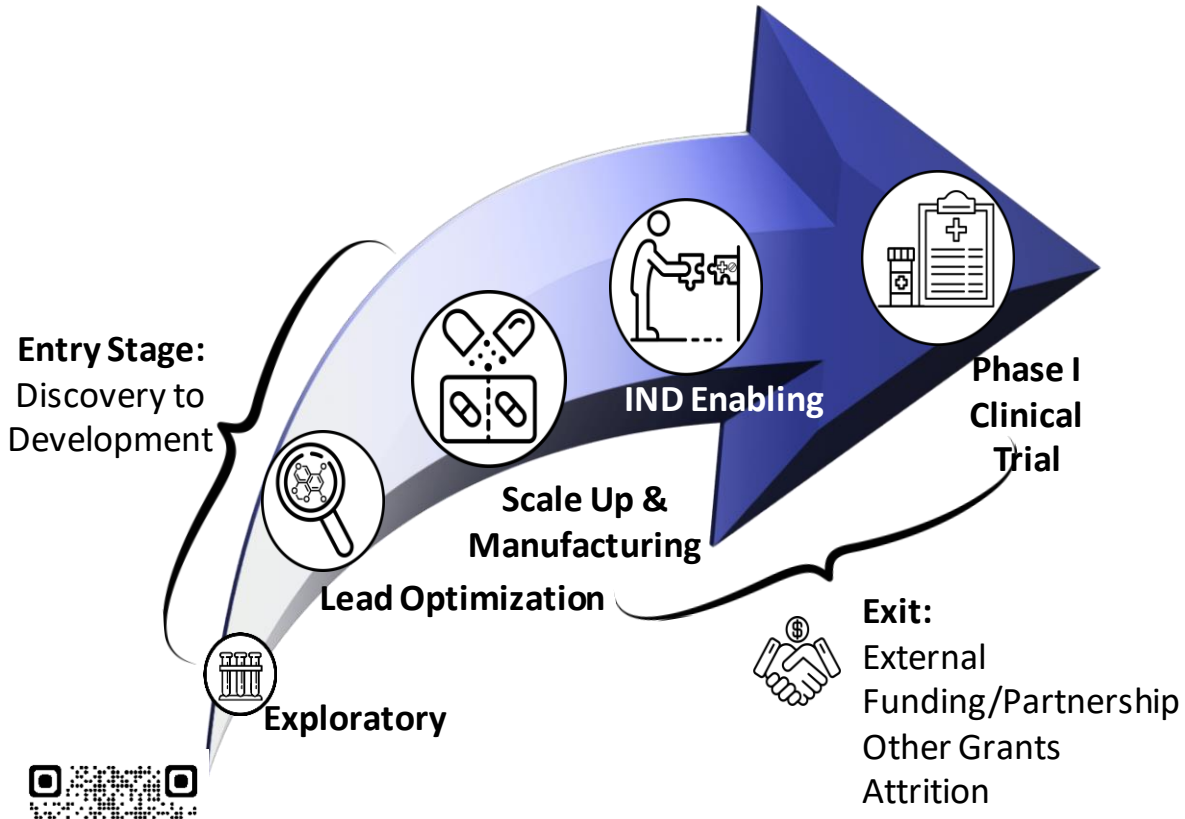


Timeline: 3 years *Budget: ≤ $499,000/Year; ≤ $750,000 for Project*

Blueprint Neurotherapeutics Network

Grand Challenge to Provide Grant Funding and Resources to Facilitate Drug Discovery and Development to Treat Nervous System Disorders

1. Identify the best ideas for translation in the NIH research community.
2. Provide non-dilutive grant (PAR) funding and necessary resources (contracts, consultants, etc.)
3. Preserve PI/Institution's Intellectual Property (IP) to facilitate licensing.
4. De-risk potential therapeutics to the point that industry will invest in them.
5. Project scope: NCCIH, NEI, NIA, NIAAA, NIBIB, NIDA, NIDCR, NIEHS, NIMH, NINDS, OBSSR
6. Work in partnership with CDER and CBER to navigate the regulatory path

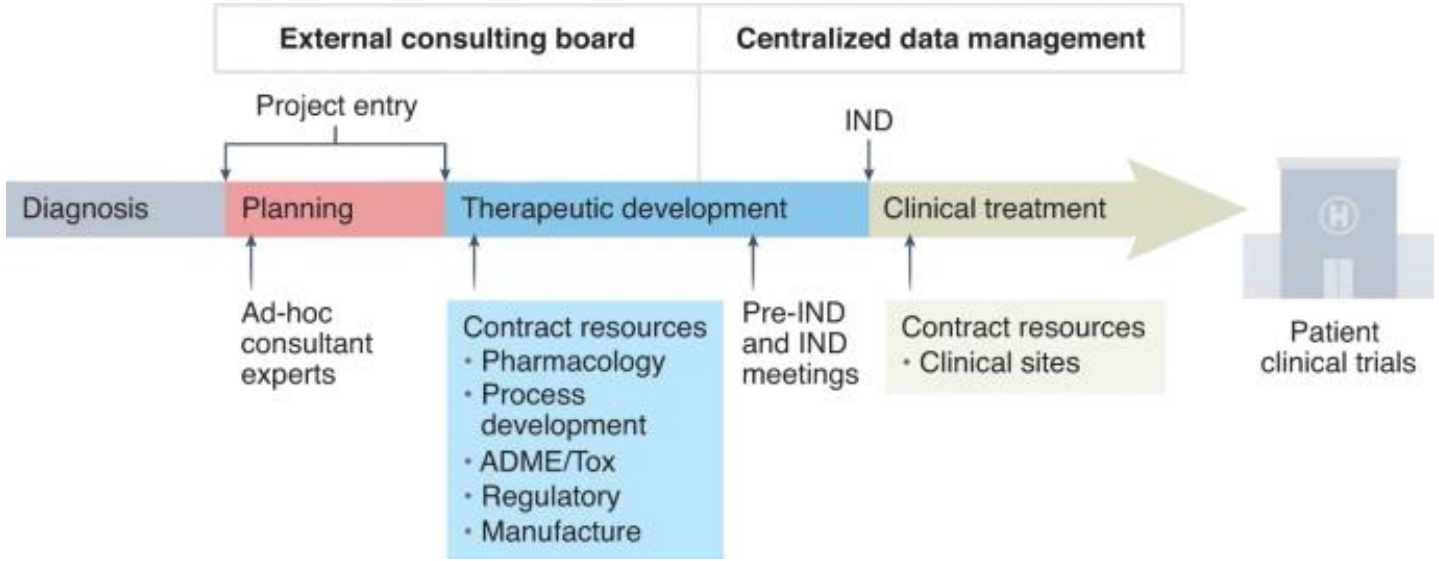


Neurotherapeutics Course

URGenT Network for Ultra-Rare Neurological Diseases

Support development of **gene-based therapies for ultra-rare neurological diseases**, which affect as few or fewer than 1:50,000 people.

- ✓ Phased program with **multiple entry points**
- ✓ Funding and resources to advance gene-based therapies - **nonclinical clinical studies**
- ✓ Accelerated development timeline **(3 years start to finish)**
  - PAR-22-030 (U01)
  - PAR-22-028 (X01)
  - OTA-24-002
  - OTA-24-003



Correspondence | Published: 04 November 2021

NINDS launches network to develop treatments for ultra-rare neurological diseases

Nina F. Schor, Amir P. Tamiz, Walter J. Koroshetz, NINDS Ultra-Rare Gene-based Therapy (URGenT) Working Group & Ann-Marie Broome

Nature Biotechnology **39**, 1497–1499 (2021) | Cite this article

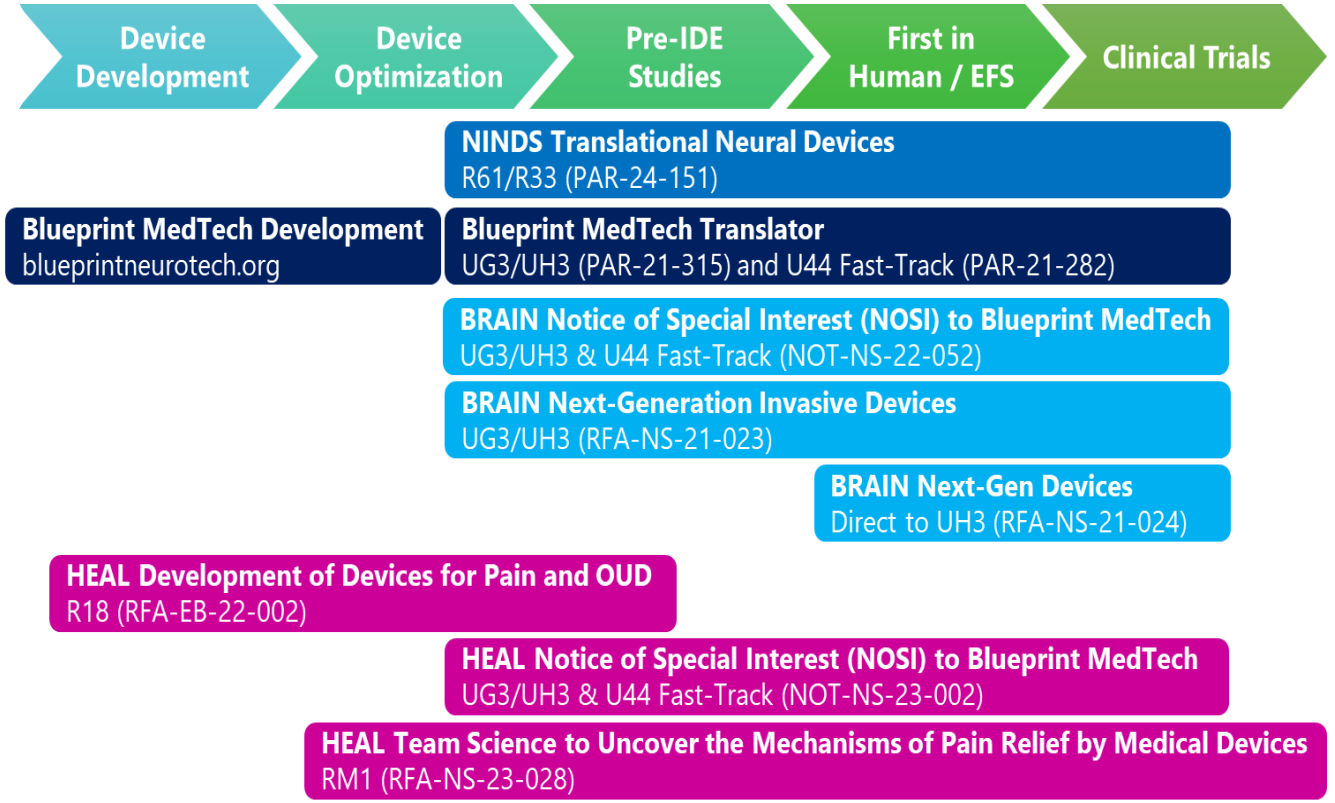
882 Accesses | **15** Altmetric | Metrics

NINDS Translational Devices Program

Mission: To support the development, optimization, translation, and early clinical testing of therapeutic and diagnostic devices for disorders that affect the nervous or neuromuscular systems.

Funding: Over 10 funding opportunities and notices managed by our team span the translational pipeline from Device Development through early-stage Clinical Trials.

- ✓ Blueprint MedTech program which provides funding as well as access to in-kind resources and mentorship
- ✓ Special programs that leverage congressional initiatives with set-aside funds, including BRAIN and HEAL
- ✓ Trans-NIH training course to educate innovators
- ✓ Common Fund SPARC program to support development of open-source technologies for neuromodulation



Contact: NINDS-Devices@nih.gov

Thank you

NINDS' New Podcast

Amir Tamiz, PhD: amir.tamiz@nih.gov

@NINDStranslate

https://www.ninds.nih.gov/

FNIH: ALS Efforts

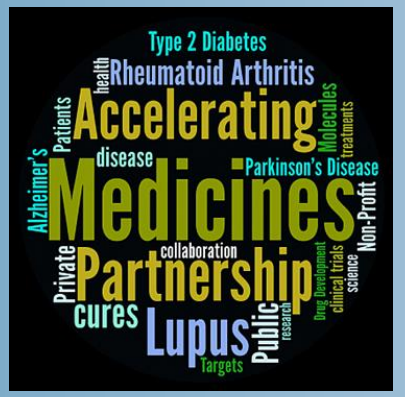
Shubhangi Lal, B.Pharm, MS, MBA

Foundation for the National Institutes of Health (FNIH)

Project Manager, Translational Science

Accelerating Medicines Partnership®

Amyotrophic Lateral Sclerosis (ALS)



Shubhangi Lal, B.Pharm, MBA - Project Manager, Translation Science, Neuroscience, FNIH

FNIH
Foundation for the National Institutes of Health

Foundation for the NIH
Building Bridges to Breakthroughs

The FNIH is an independent 501(c)(3) non-profit organization founded by the U.S. Congress to support the mission of the NIH.

We connect the world's leading public and private organizations

We accelerate new therapies, diagnostics, and potential cures.

We advance global health and seek equity in care.

600+

programs supported since inception

$1.5B

raised to date

18

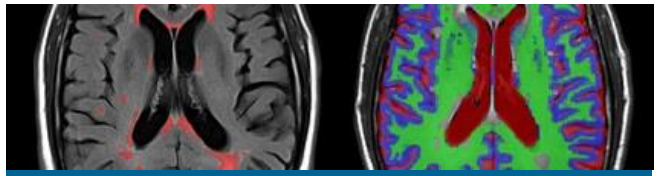
years of outstanding Charity Navigator ratings

FNIH

https://fnih.org/

Major partnerships at the FNIH

Largest organization to manage public-private partnerships



Alzheimer's Disease Neuroimaging Initiative (ADNI)

$206 Million

NIA, NIBIB, 25+ companies, 3 not-for-profit organizations

Accelerating COVID 19 Therapeutic Interventions and Vaccines (ACTIV)

$1+ Billion

NIH (OD), BARDA, CDC, DOD, VA, EMA, OWS, FDA, 20 companies, 4 not-for-profit organizations

Accelerating Medicines Partnership (AMP®)

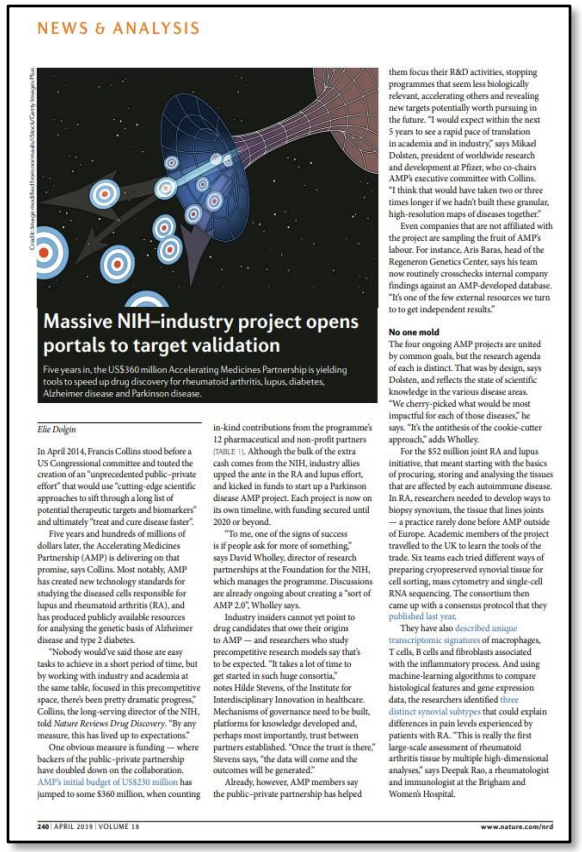
$783 Million

NIH (OD), BARDA, CDC, DOD, VA, EMA, OWS, FDA, 20 companies, 4 not-for-profit organizations

+ more additional partnerships such as the Biomarkers Consortium, PACT, GCGH and Lung-MAP

FNIH

The Accelerating Medicines Partnership® (AMP®) Program



NEWS & ANALYSIS

Massive NIH–industry project opens portals to target validation

Five years in, the US$360 million Accelerating Medicines Partnership is yielding tools to speed up drug discovery for rheumatoid arthritis, lupus, diabetes, Alzheimer disease and Parkinson disease.

Elie Dolgin

In April 2014, Francis Collins stood before a US Congressional committee and touted the creation of an "unprecedented public–private effort" that would use "cutting-edge scientific approaches to sift through a long list of potential therapeutic targets and biomarkers" and ultimately "treat and cure disease faster".

Five years and hundreds of millions of dollars later, the Accelerating Medicines Partnership (AMP) is delivering on that promise, says Collins. Most notably, AMP has created new technology standards for studying the diseased cells responsible for lupus and rheumatoid arthritis (RA), and has produced publicly available resources for analysing the genetic basis of Alzheimer disease and type 2 diabetes.

"Nobody would've said those are easy tasks to achieve in a short period of time, but by working with industry and academia at the same table, focused in this precompetitive space, there's been pretty dramatic progress," Collins, the long-serving director of the NIH, told *Nature Reviews Drug Discovery*. "By any measure, this has lived up to expectations."

One obvious measure is funding — where backers of the public–private partnership have doubled down on the collaboration. AMP's initial budget of US$230 million has jumped to some $360 million, when counting in-kind contributions from the programme's 12 pharmaceutical and non-profit partners (TABLE 1). Although the bulk of the extra cash comes from the NIH, industry allies upped the ante in the RA and lupus effort, and kicked in funds to start up a Parkinson disease AMP project. Each project is now on its own timeline, with funding secured until 2020 or beyond.

"To me, one of the signs of success is if people ask for more of something," says David Wholley, director of research partnerships at the Foundation for the NIH, which manages the programme. Discussions are already ongoing about creating a "sort of AMP 2.0", Wholley says.

Industry insiders cannot yet point to drug candidates that owe their origins to AMP — and researchers who study precompetitive research models say that's to be expected. "It takes a lot of time to get started in such huge consortia," notes Hilde Stevens, of the Institute for Interdisciplinary Innovation in healthcare. Mechanisms of governance need to be built, platforms for knowledge developed and, perhaps most importantly, trust between partners established. "Once the trust is there," Stevens says, "the data will come and the outcomes will be generated."

Already, however, AMP members say the public–private partnership has helped them focus their R&D activities, stopping programmes that seem less biologically relevant, accelerating others and revealing new targets potentially worth pursuing in the future. "I would expect within the next 5 years to see a rapid pace of translation in academia and in industry," says Mikael Dolsten, president of worldwide research and development at Pfizer, who co-chairs AMP's executive committee with Collins. "I think that would have taken two or three times longer if we hadn't built these granular, high-resolution maps of diseases together."

Even companies that are not affiliated with the project are sampling the fruit of AMP's labour. For instance, Aris Baras, head of the Regeneron Genetics Center, says his team now routinely crosschecks internal company findings against an AMP-developed database. "It's one of the few external resources we turn to to get independent results."

No one mold

The four ongoing AMP projects are united by common goals, but the research agenda of each is distinct. That was by design, says Dolsten, and reflects the state of scientific knowledge in the various disease areas. "We cherry-picked what would be most impactful for each of those diseases," he says. "It's the antithesis of the cookie-cutter approach," adds Wholley.

For the $52 million joint RA and lupus initiative, that meant starting with the basics of procuring, storing and analysing the tissues that are affected by each autoimmune disease. In RA, researchers needed to develop ways to biopsy synovium, the tissue that lines joints — a practice rarely done before AMP outside of Europe. Academic members of the project travelled to the UK to learn the tools of the trade. Six teams each tried different ways of preparing cryopreserved synovial tissue for cell sorting, mass cytometry and single-cell RNA sequencing. The consortium then came up with a consensus protocol that they published last year.

They have also described unique transcriptomic signatures of macrophages, T cells, B cells and fibroblasts associated with the inflammatory process. And using machine-learning algorithms to compare histological features and gene expression data, the researchers identified three distinct synovial subtypes that could explain differences in pain levels experienced by patients with RA. "This is really the first large-scale assessment of rheumatoid arthritis tissue by multiple high-dimensional analyses," says Deepak Rao, a rheumatologist and immunologist at the Brigham and Women's Hospital.

240 | APRIL 2019 | VOLUME 18 www.nature.com/nrd

For an overview of the AMP Initiative, see:
Nature Reviews Drug Discovery - February 27, 2019
https://www.nature.com/articles/d41573-019-00033-8

Precompetitive public-private collaboration started in 2014

- **Unite resources of NIH and private partners to improve our understanding of disease pathways and transform current models for developing new treatments by:**
  - Identifying new targets, biomarkers and development paradigms
  - Developing leading-edge tools and technologies
  - Collecting large scale datasets and supporting analytics for open analysis by the public
  - Generating consensus platforms and procedures

FNIH

AMP® ALS: Design Phase Partners

Steering Committee Co-Chairs:

Dan Doctoroff, Target ALS Stephanie Fradette, Biogen Amelie Gubitz, NINDS

PUBLIC SECTOR

National Institute of Neurological Disorders and Stroke

U.S. FOOD & DRUG ADMINISTRATION

Ex-Officio Members

CRITICAL PATH INSTITUTE
collaborate · innovate · accelerate

FNIH

FNIH

PRIVATE SECTOR

9 Pharma, 8 NPOs

abbvie

ALS ASSOCIATION

ALS THERAPY DEVELOPMENT INSTITUTE

alsFINDINGaCURE

ANSWER ALS

Biogen

EVERYTHINGALS
CARE TO CURE

GSK

I AM ALS

Lilly

MDA

Mitsubishi Tanabe Pharma

NOVARTIS

QurAlis

REGENERON

Takeda

TARGET ALS

AMP® ALS Design Phase Working Groups and Scope

People with Lived Experience (PWLE) Engagement
Scope: Support the meaningful participation of PWLE in all aspects of AMP ALS

Portal and Data Architecture
Scope: Determine appropriate ALS Knowledge Portal provider and define technical requirements to support data architecture

Extant Data
Scope: Identify high-value existing clinical & molecular datasets for integration into the ALS Knowledge Platform

Biomarkers & New Clinical Data
Scope: Develop research aims related to the discovery, development, and validation of new and/or optimized biomarkers for ALS

Clinical Endpoints
Scope: Identify gaps and opportunities for patient-informed Clinical Outcome Assessment (COA) development

FNIH

AMP® ALS Provides Solutions for Challenges in ALS Research

Challenges	How will AMP® ALS help?
Decentralized data storage; need for data harmonization to allow comparisons between datasets	Establish an ALS Knowledge Platform
Low inventory of well-annotated longitudinal biospecimens	Launch of "ALL ALS" Clinical Research Consortium
Delayed diagnosis	Develop/validate diagnostic biomarkers
Difficulties in assessing treatment response	Develop/validate monitoring biomarkers
Clinical and statistical limitations, insufficient standardization Clinical Outcome Assessments (COAs)	Optimize Clinical Outcome Assessments (COAs) and address regulatory requirements

FNIH

Key AMP® ALS Deliverables

Largest harmonized, longitudinal ALS clinical dataset comprising all stages of ALS, including pre-symptomatic in familial ALS

Multimodal molecular analyses of longitudinal biofluid samples and post-mortem tissue, including whole genome, gene expression, targeted and untargeted proteomics data

New biofluid-based and digital biomarkers to aid in early diagnosis, monitor disease progression, as well as response to treatment

New patient-informed Clinical Outcome Assessments

Thank you!

FNIH

Panel Discussion/Question and Answer

Building a rare disease community that works. Together.

Klaus Romero, MD, MS, FCP
Critical Path Institute
Chief Executive Officer

Michelle Campbell, PhD
U.S Food and Drug Administration
Associate Director, Office of Neuroscience, CDER

Gumei Liu, MD, PhD
U.S. Food and Drug Administration
Associate Director for Policy

Collin Hovinga, PharmD, MS, FCCP
Critical Path Institute
Vice President, Rare and Orphan Disease Programs

Teresa Buracchio, MD
U.S. Food and Drug Administration
Director, Office of Neuroscience, CDER

Amir Tamiz, PhD
NINDS
Director, Division of Translational Research

Closing Remarks

Collin Hovinga, PharmD, MS, FCCP
Critical Path Institute
Vice President, Rare and Orphan Disease Programs

Teresa Buracchio, MD
U.S. Food and Drug Administration
Director, Office of Neuroscience, CDER

CRITICAL PATH INSTITUTE

Questions?

Email RODadmin@c-path.org

THANK YOU!

Building a rare disease community that works. Together.

c-path.org

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