Natural History Studies and Registries in the Development of Rare Disease Treatments

Hybrid Public Workshop

May 13, 2024 | 10am-4pm *(eastern)*

The public meeting will begin shortly

A workshop prepared in collaboration with the Food and Drug Administration and the NIH National Center for Advancing Translational Sciences

REAGAN-UDALL FOUNDATION FOR THE FDA

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This activity is supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of an award of $97,915 in federal funds (100% of the project). 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. For more information, please visit FDA.gov.

REAGAN-UDALL FOUNDATION FOR THE FDA

Welcome

Susan C. Winckler, RPh, Esq.
Chief Executive Officer
Reagan-Udall Foundation for the FDA

Hybrid Meeting

REAGAN-UDALL FOUNDATION FOR THE FDA

Joining online:
Microphone and video will remain off during the meeting
Share your questions using the Zoom Q&A function

Joining in-person:
Please write your questions on the index cards provided

This public meeting is being recorded
The slides, transcript, and video will be available at www.ReaganUdall.org

Today's Agenda (Eastern Time)

REAGAN-UDALL FOUNDATION FOR THE FDA

10am	Welcome & Opening Remarks
10:15am	"What Are Registries and Natural History Studies" "Why Registries and Natural History Studies are Critical to Rare Disease Treatment Development"
10:30am	Getting Started: Developing Registries and Designing Natural History Studies
11:25am	Addressing Challenges in Registry and Natural History Data Collection
12:25pm	Funding Opportunities
12:40pm	Lunch
1:35pm	Collecting Fit for Purpose Data to Inform Regulatory Decision Making
2:35pm	Case Examples
3:45pm	Closing Remarks & Adjourn

REAGAN-UDALL FOUNDATION FOR THE FDA

Opening Remarks

Patrizia Cavazzoni, MD
Director
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

"What Are Registries and Natural History Studies?"

Dominique Pichard, MD, MS
National Center for Advancing Translational Sciences, NIH

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NCATS

COLLABORATE. INNOVATE. ACCELERATE.

What are registries and natural history studies?

Dominique C. Pichard, MD, MS

Director

Division of Rare Diseases Research Innovation, NCATS

NIH National Center for Advancing Translational Sciences

Definitions

- **Natural history of a disease**: the course a disease takes in the absence of intervention in individuals with the disease, from disease onset until either the disease's resolution or death.

- **Natural history study**: a preplanned observational study intended to track the course of a disease over time.

- **Registry**: a collection of information about a specified group of people
  - Ex. Contact registry, disease registry, population registry

Examples of registries

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

National Amyotrophic Lateral Sclerosis (ALS) Registry

NATIONAL CANCER INSTITUTE
Surveillance, Epidemiology, and End Results Program

Rett Syndrome Registry™

National Center for Advancing Translational Sciences

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National Center for Advancing Translational Sciences

“What Are Registries and Natural History Studies?”

Kerry Jo Lee, MD
Center for Drug Development and Research, FDA

REAGAN-UDALL FOUNDATION FOR THE FDA

Accelerating Rare disease Cures (ARC) Program

NATURAL HISTORY STUDIES AND REGISTRIES IN THE DEVELOPMENT OF RARE DISEASE TREATMENTS

Kerry Jo Lee, M.D.

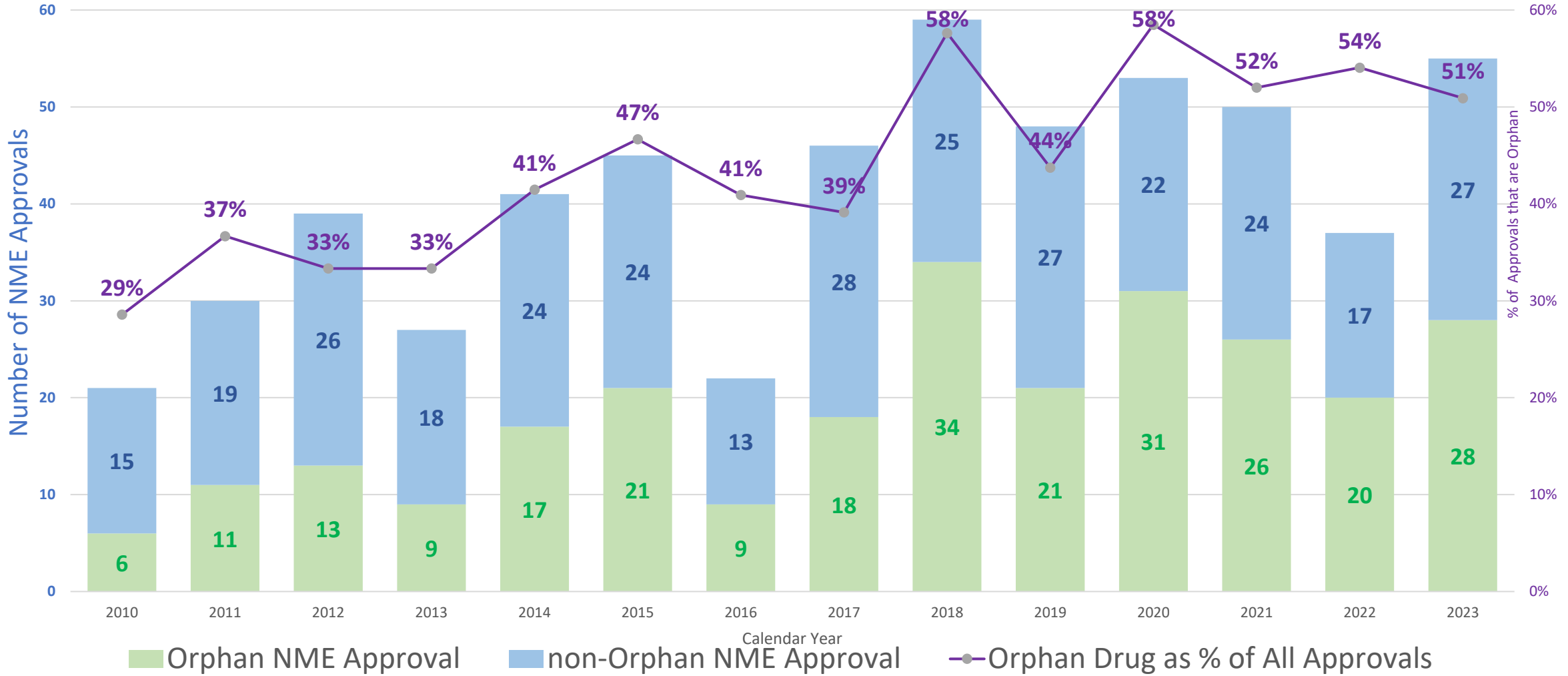
Associate Director for Rare Diseases

Rare Diseases Team

DRDMG | ORPURM | CDER | US FDA

FDA U.S. FOOD & DRUG ADMINISTRATION

Proportion of CDER Novel Drug Approvals that are Orphan



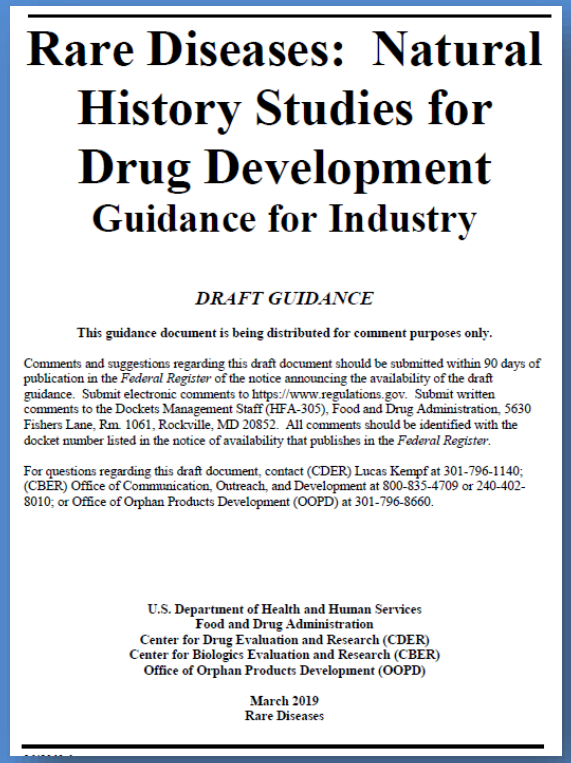
We Face Common Challenges in Rare Disease Drug Development

- **Natural history** is often poorly understood
- Diseases are progressive, **serious**, **life-limiting** *and* often lack adequate **approved therapies – urgent needs,** many have **pediatric onset**
- **Small populations** often restrict study design options
- **Phenotypic and genotypic** diversity within a disorder
- **Development programs often lack solid translational background**
- **Drug development tools** - **outcome measures** and **biomarkers** often **lacking**
- Lack of **precedent**, including **clinically meaningful endpoints**, for drug development in many rare diseases

Supporting the Design and Conduct of Clinical Trials for Rare Diseases

Search for Selected FDA Guidance Documents by Topic Relevant to Rare Disease Drug Development

https://www.fda.gov/drugs/guidances-drugs/guidance-documents-rare-disease-drug-development



Rare Diseases: Natural History Studies for Drug Development
Guidance for Industry

DRAFT GUIDANCE

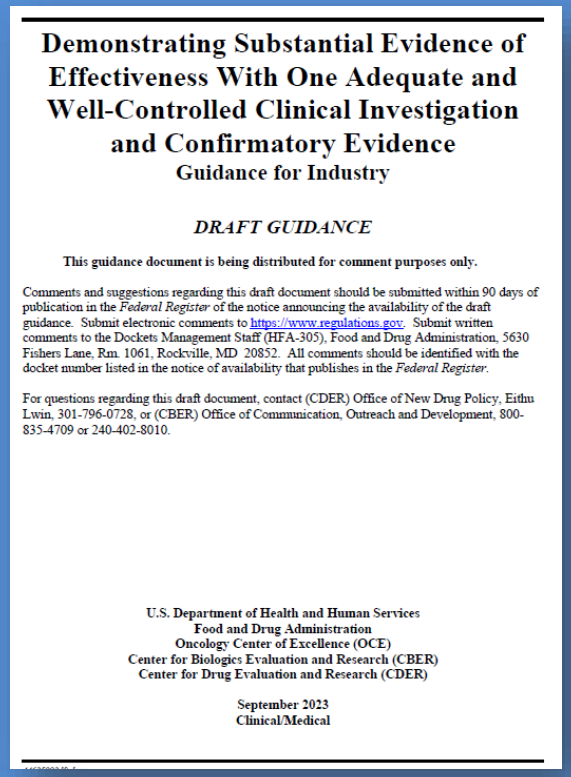
This guidance document is being distributed for comment purposes only.

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 https://www.regulations.gov. Submit written comments to the Dockets Management Staff (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 (CDER) Lucas Kempf at 301-796-1140; (CBER) Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010; or Office of Orphan Products Development (OOPD) at 301-796-8660.

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)
Office of Orphan Products Development (OOPD)

March 2019
Rare Diseases



Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence
Guidance for Industry

DRAFT GUIDANCE

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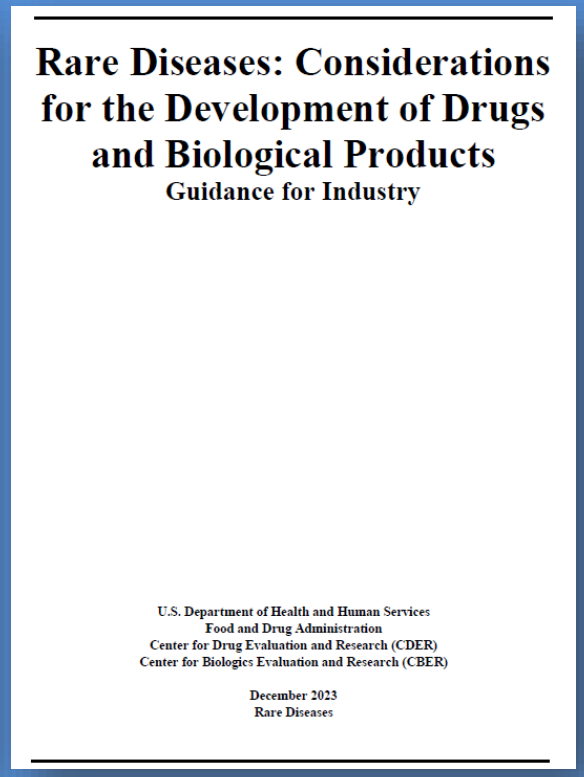
For questions regarding this draft document, contact (CDER) Office of New Drug Policy, Eithu Lwin, 301-796-0728, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Biologics Evaluation and Research (CBER)
Center for Drug Evaluation and Research (CDER)

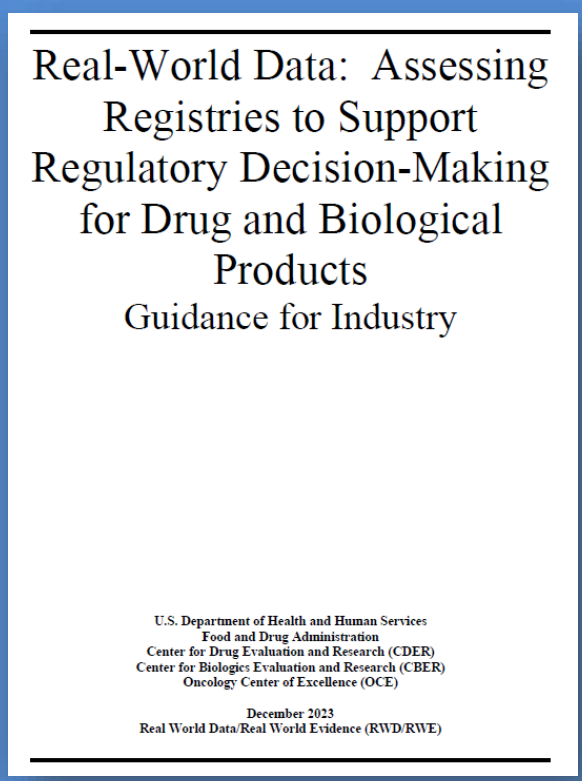
September 2023
Clinical/Medical



Rare Diseases: Considerations for the Development of Drugs and Biological Products
Guidance for Industry

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)

December 2023
Rare Diseases



Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products
Guidance for Industry

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)
Oncology Center of Excellence (OCE)

December 2023
Real World Data/Real World Evidence (RWD/RWE)

Visit the ARC website for conference recordings and other resources

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

Getting Started: Developing Registries and Designing Natural History Studies

Presenters

Leslie Gordon, MD, PhD
The Progeria Research Foundation

Eileen King, PhD
Cincinnati Children's Hospital Medical Center

Michael Wagner, PhD
University of Cincinnati College of Medicine

Kristen Wheeden, MBA
United Porphyrias Association

REAGAN-UDALL FOUNDATION FOR THE FDA

Getting Started: Developing Registries and Designing Natural History Studies

Photo Courtesy of PRF

Leslie B. Gordon, MD, PhD
The Progeria Research Foundation
Hasbro Children's Hospital & Alpert Medical School of Brown U.
Boston Children's Hospital Boston and Harvard Medical School

Reagan-Udall Foundation For The FDA

May 13, 2024

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Families sign consents for PRF to permit use of their photographs. To respect those families and children's wishes, please do not use the photos in this presentation.

Please contact The Progeria Research Foundation for image use permissions.

Thank you very much.

Together We *WILL* Find The Cure!

www.progeriaresearch.org

Learning From Each Other:
PRF Road to the Cure Using Registry, Database, Natural History Studies

Photo Courtesy of PRF

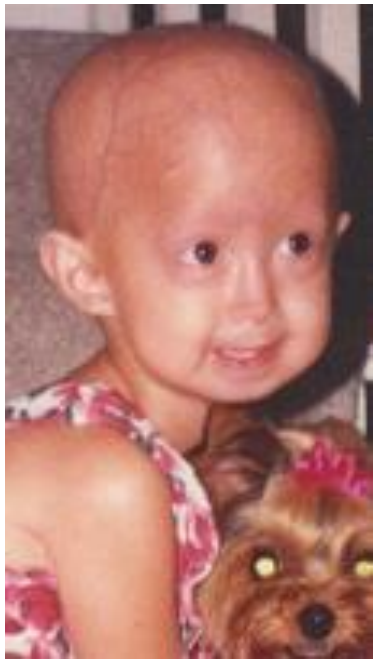
Provide you with some of the key thematic lessons learned through our journey with progeria, so that we can all become better, faster and stronger towards curing our patients.

Because TIME is not on our side…

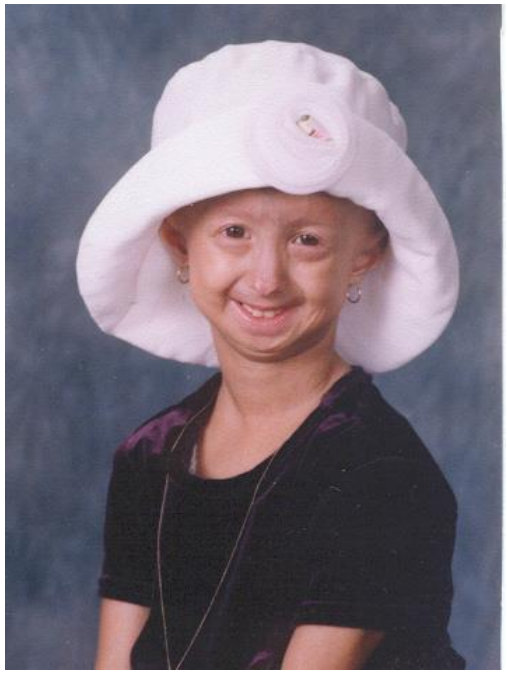
This Is Progeria (HGPS)

Rachel: Newborn

Toddler



2nd grade



9 years old

- Segmental Premature Aging
- Autosomal Dominant
- Lifespan Ave. 14.6 yrs. (5-21y) without treatment
- Premature atherosclerosis, CV failure

1998 - There Was No Hope…

Photo Courtesy of PRF

- 2 or 3 scientists working on Progeria
- No Research Funding
- Was this a genetic disease?
- No Central Source of Clinical Information
- Clinical Disease Poorly Defined
- No Treatment Prospects
- No Place for Families and Physicians to go for Help

The Progeria Research Foundation - 1999

Photo Courtesy of PRF

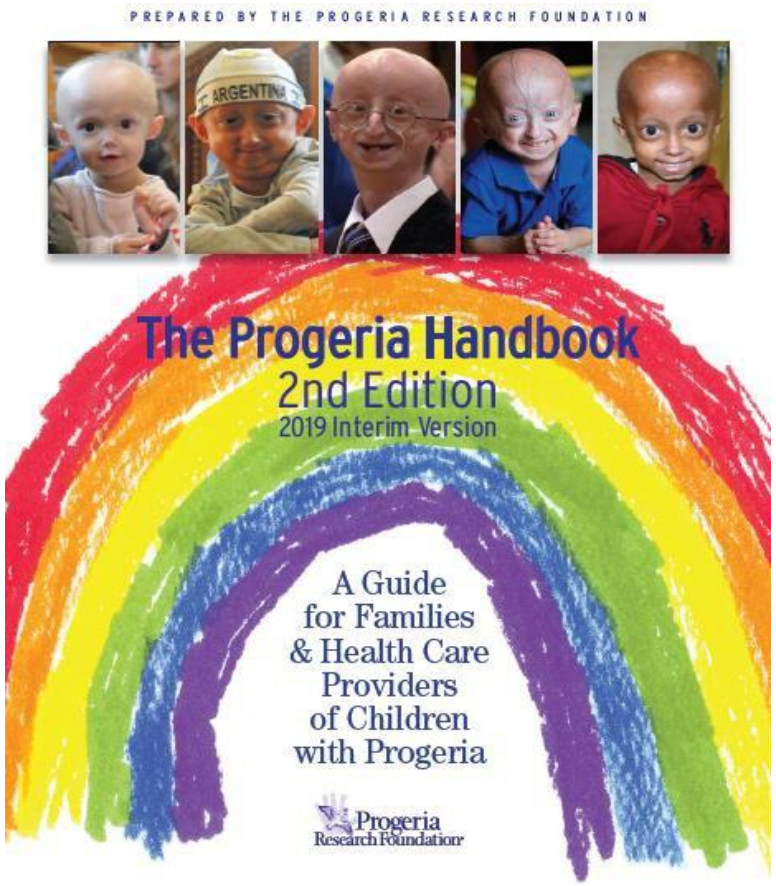
Mission

- ❑ Cause
- ❑ Treatment
- ❑ Cure

Together We *WILL* Find The Cure!

www.progeriaresearch.org

A Few Milestones



- Gene Mutations Discovered and Defined (Nature, 2003)
- CV-faithful Progerin-producing Mouse Models Developed
- Natural History Study at NIH Clinical Center (NEJM, 2008)
- 4 Clinical Treatment Trials – fully enrolled months after initiation – 107 children from 42 countries
- World's Progeria Experts at Boston Children's Hospital
- 130-Page Clinical Care Handbook
- Plasma Progerin Biomarker in Validation (Circulation, 2021)

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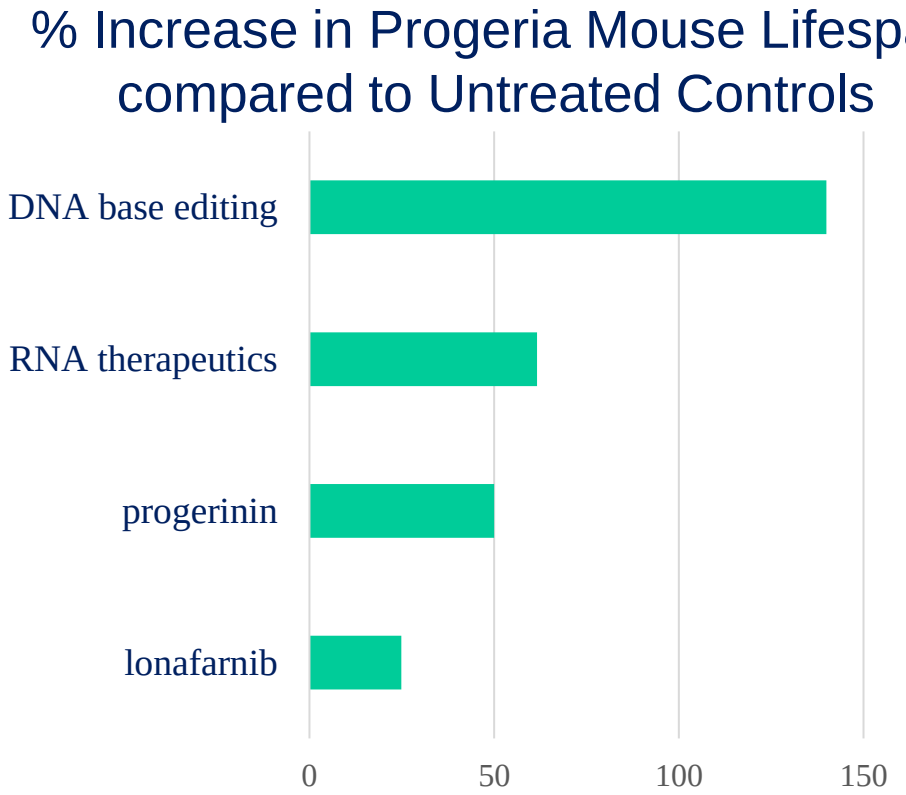
FOR THE CHILDREN ♥ FOR THE CURE

Nov 30, 2020: PRF Joins only 5% of Rare Diseases with an Approved Drug

Photo Courtesy of PRF

- 21 years from Registry initiation to approval
- 13 y. of continuous clinical trials with lonafarnib
- Lifespan Extension Avg. 4.2 yrs (JAMA, 2023)

What's Next?



NONE of These Accomplishments Would Be Possible Without the PRF International Registry, Database, & Natural History Studies

Photos Courtesy of PRF

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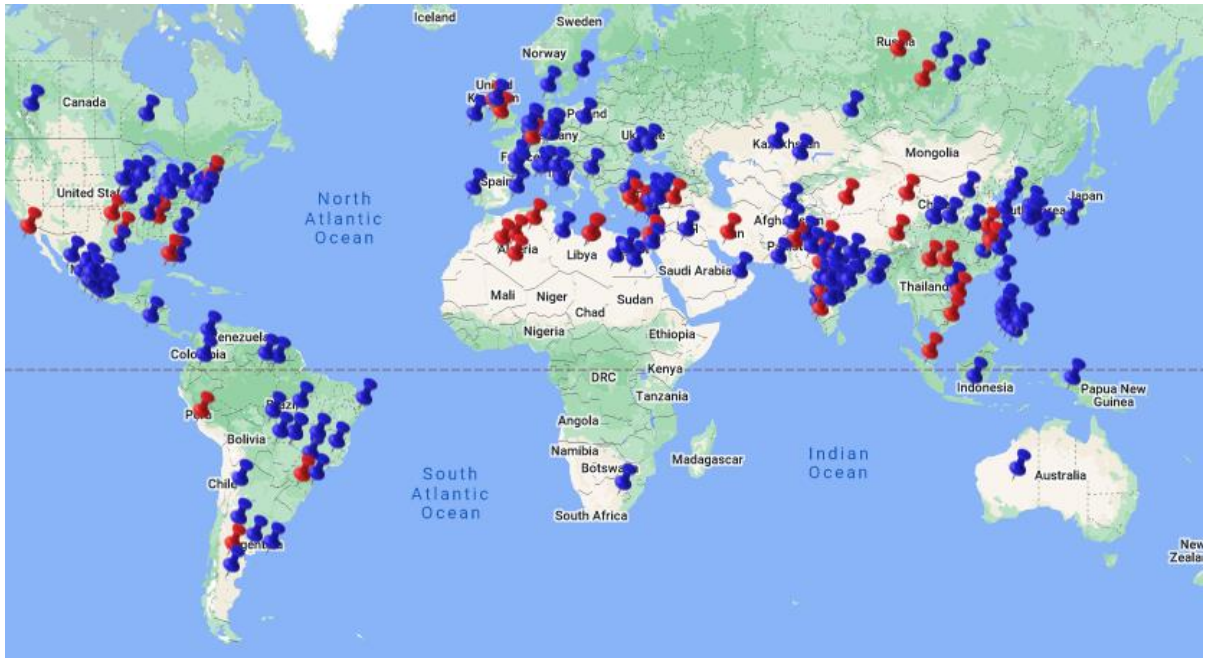
PRF Progeria International Registry:
~40% of World's Population Living With Progeria

- **Top Priority Upon Contact with MD or Patient Family**
- **Unconsented**
- **Longitudinal Communication → Trust,Education → Program, Trial Participation**
- **Info packets sent to MD and Family Immediately**



149 Patients
51 Countries
35 Languages

Photo Courtesy of PRF

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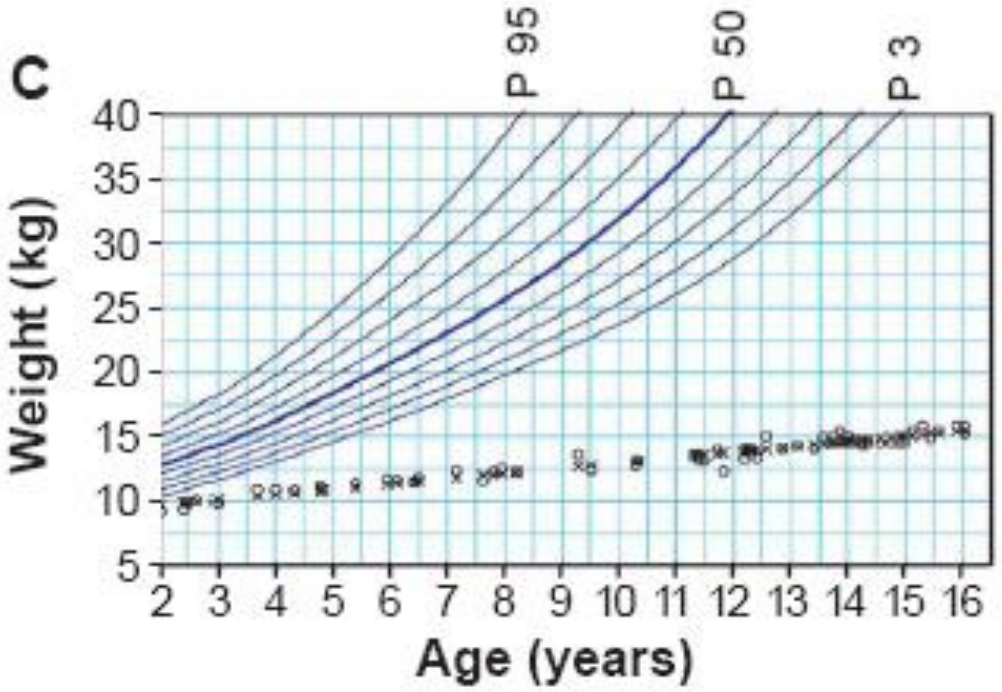
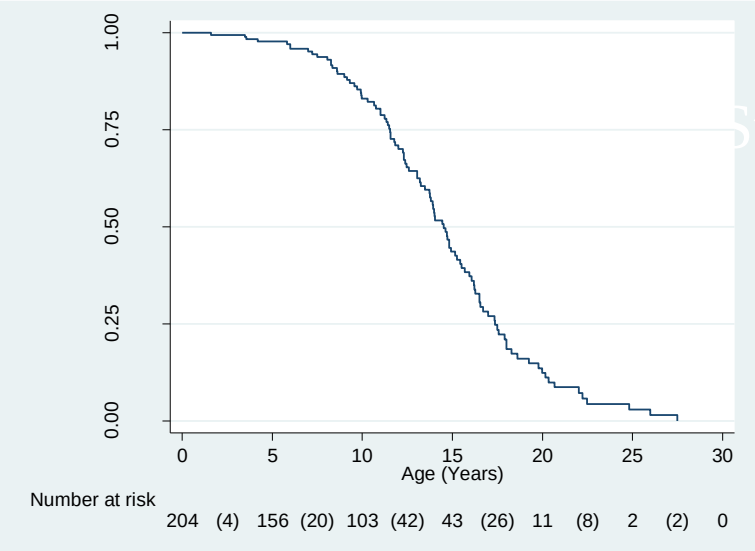
Medical & Research Database

- **Consented Program (IRB-approved)**
- **Longitudinal Collection of Clinical Data**
- **Outcomes must be objectively evaluable, statistically abnormal, affecting how a patient feels, functions or survives**



- ✓ **Primary Outcome for the Natural History Study at NIH and First 2 Clinical Trials came from Database Weight Analysis**
- ✓ **This outcome did not show improvement, but the evaluation gave us our first trials, an important gateway**
- ✓ **34 Peer-reviewed Publications**

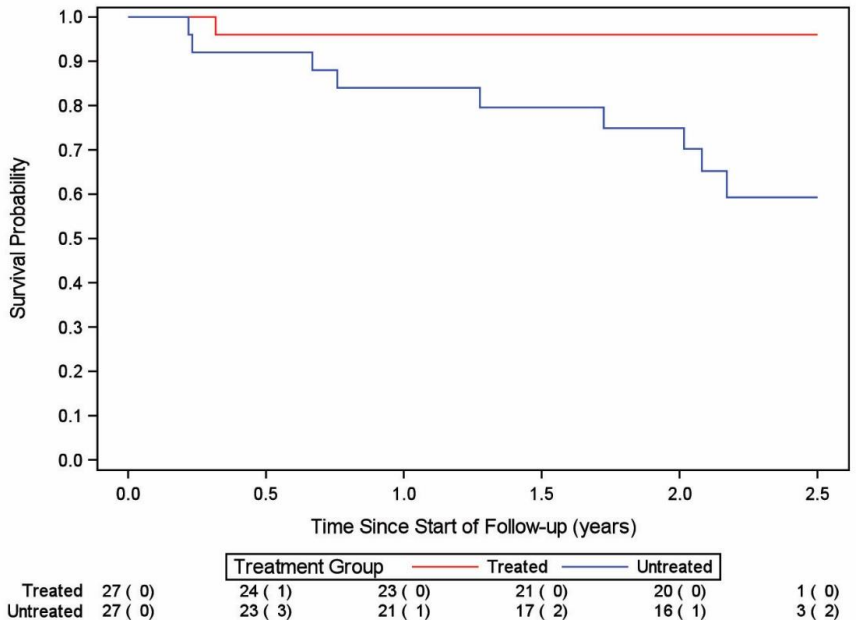
PRF Registry and Database Survival Data, With Time On Therapy, Was The Primary Outcome Used for Drug Approval



Circulation

American Heart Association

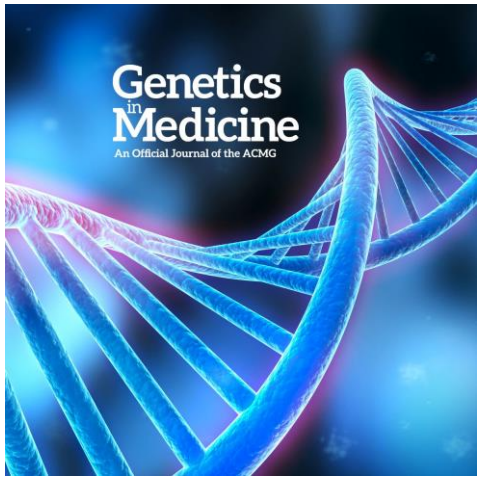
Impact of Farnesylation Inhibitors on Survival in Hutchinson-Gilford Progeria Syndrome
Leslie B. Gordon, Joe Massaro, Ralph B. D'Agostino, Sr., Susan E. Campbell, Joan Brazier, W. Ted Brown, Monica E. Kleinman and Mark W. Kieran



JAMA | Preliminary Communication

Association of Lonafarnib Treatment vs No Treatment With Mortality Rate in Patients With Hutchinson-Gilford Progeria Syndrome

FDA Special Report



Suzuki, et al, 2022

Long-term Survival Benefit of Lonafarnib Also Came From The Registry and Database: 2.2→4.3 years…

Dual Purpose: Progeria Treatment Trials Also Serve As Natural History Studies

Photo Courtesy of PRF

- **29 Scientific articles published from BCH Progeria clinical trial data**
- **Now that lonafarnib is the standard of care, a new "natural history" on this medication must be defined, to use as comparison to any new drug added to lonafarnib in a trial**
- **We are continually working to define a primary outcome measure for future trials**

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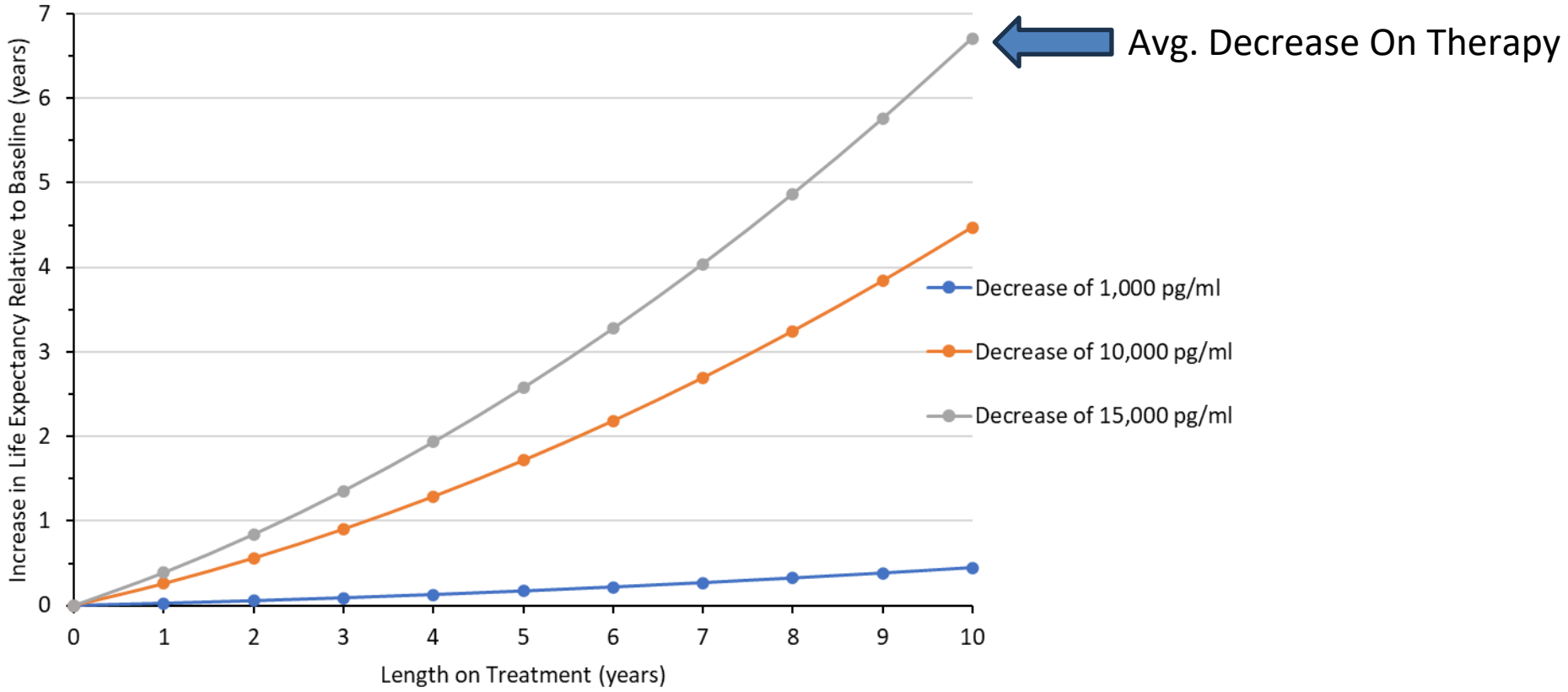
FOR THE CHILDREN ♥ FOR THE CURE

Registry and Database Survival Data Essential for Defining Plasma Progerin Biomarker Being Validated as our Primary Trial Biomarker Outcome Measure



- Lonafarnib Therapy: Lifespan Benefit with Decreased Progerin
- The lower you go, the longer you stay low, the greater the benefit

A Few Take-home Messages

Photo Courtesy of PRF

- **Patient families are passionate <u>partners</u>.**
- **Always assume your data will be used for drug approval, so use RedCap or similar database system**
- **Raw data will be useful many times over, so safeguard your source data.**
- **Patient Registries and Nature History Studies are critical foundational tools for the Cure.**

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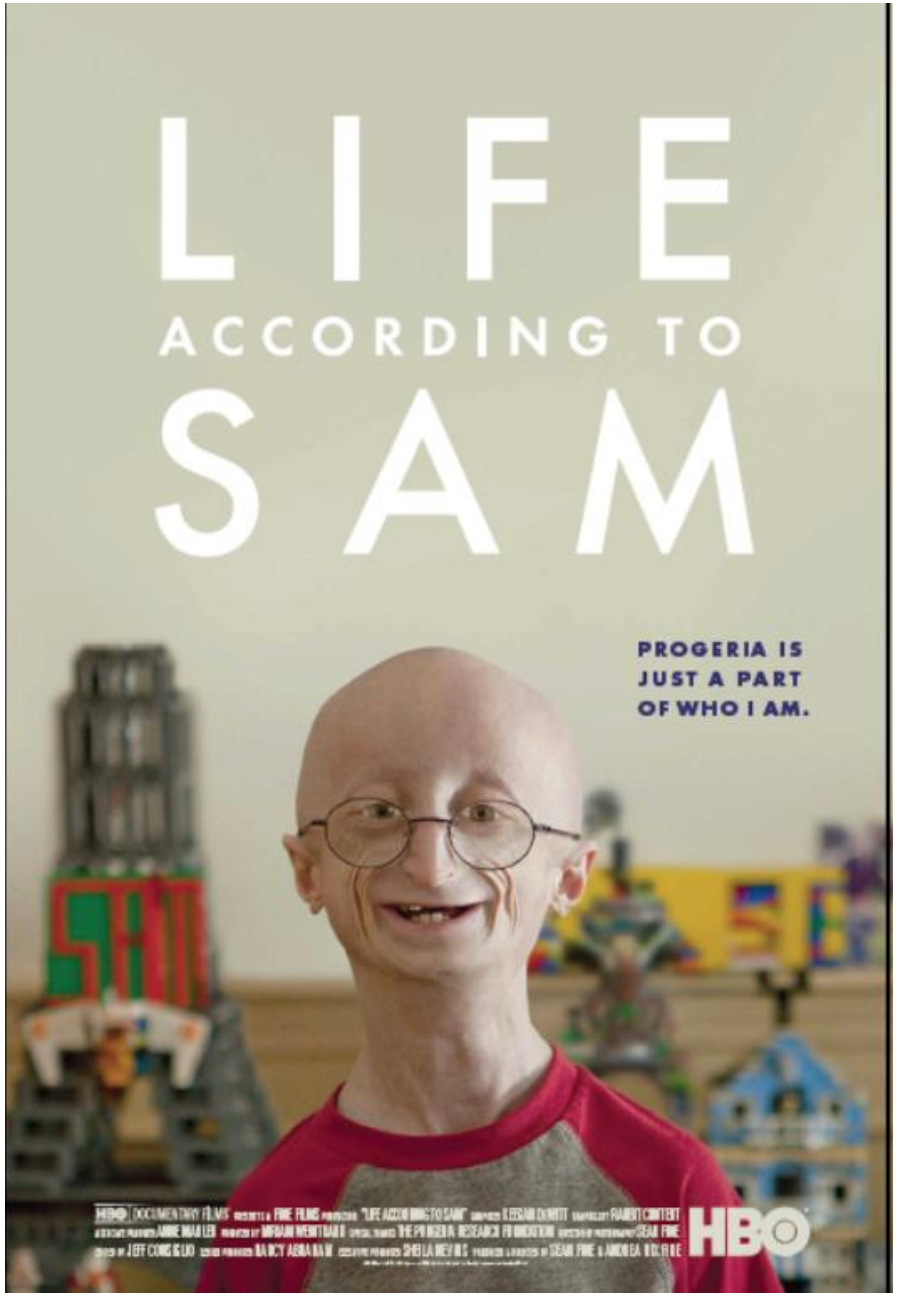


Thank You!

Reagan-Udall Organizers

Many Talented Collaborators

Progeria Research Foundation
FOR THE CHILDREN ♥ FOR THE CURE

Together We *WILL* Find The Cure!

Getting Started: Developing Registries and Designing Natural History Studies

Eileen King, Ph.D.
Michael Wagner, Ph.D.
Data Management and Coordinating Center
Rare Diseases Clinical Research Network
Cincinnati Children's Hospital Medical Center

May 13, 2024

RARE DISEASES
CLINICAL RESEARCH NETWORK

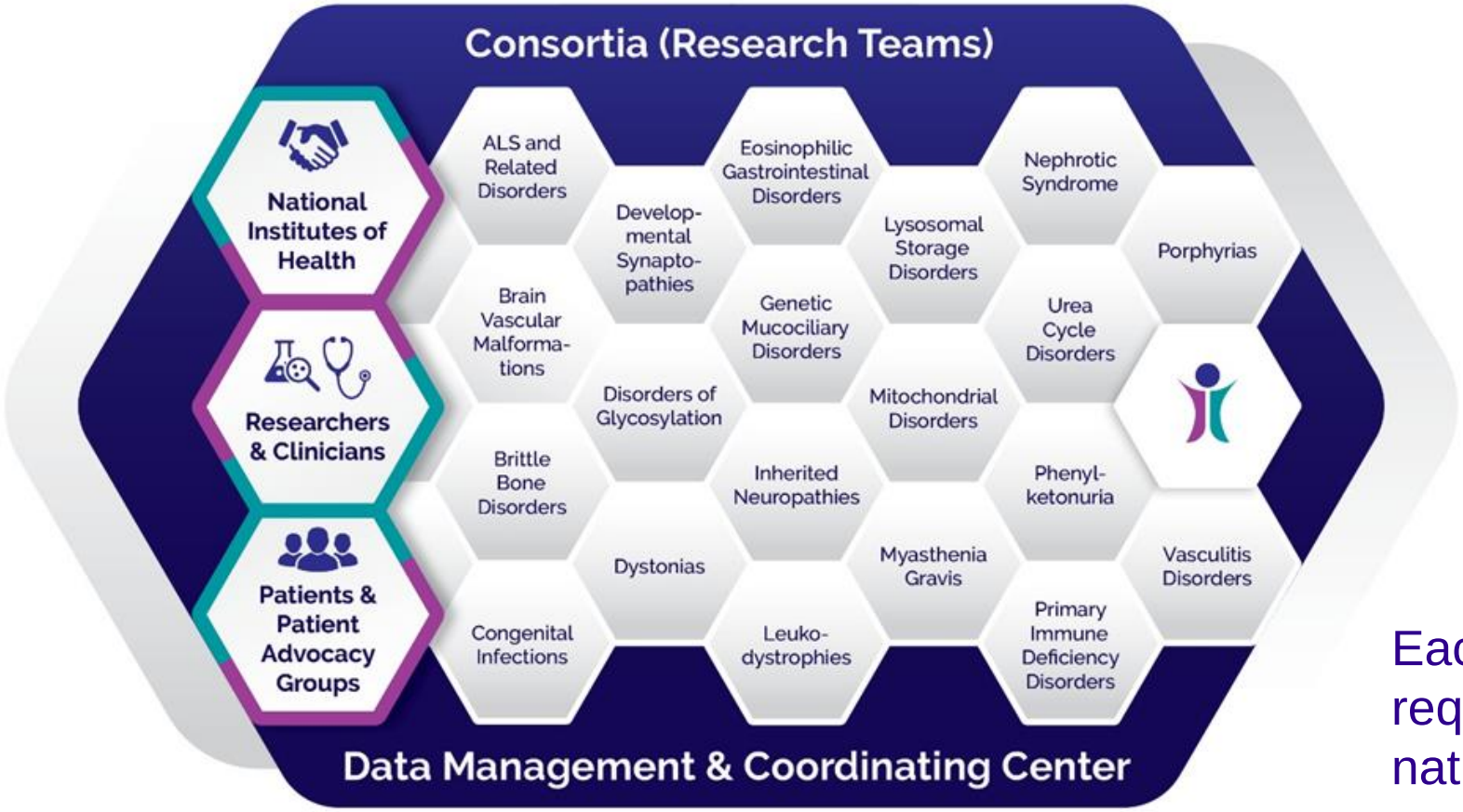
Agenda

- Overview of Rare Diseases Clinical Research Network (RDCRN)
- Data Collection, Formatting and Quality Assurance
- Data Storage, Maintenance and Sharing

RARE DISEASES
CLINICAL RESEARCH NETWORK

RARE DISEASES
CLINICAL RESEARCH NETWORK

A network of 20 research teams collaborating to achieve faster diagnosis and better treatments for patients with rare diseases



Each consortium is required to have a natural history study.

National Center for Advancing Translational Sciences | National Institute of Neurological Disorders and Stroke | National Institute of Allergy and Infectious Diseases | National Institute of Diabetes and Digestive and Kidney Diseases | *Eunice Kennedy Shriver* National Institute of Child Health and Human Development | National Institute of Arthritis and Musculoskeletal and Skin Diseases | National Heart, Lung, and Blood Institute | National Institute of Dental and Craniofacial Research | National Institute of Mental Health | Office of Dietary Supplements

Funded by the National Institutes of Health

- Now in its fourth 5-year funding cycle
- Led by the National Center for Advancing Translational Sciences (NCATS) through its Division of Rare Diseases Research Innovation (DRDRI).
- Established by Congress under the **Rare Diseases Act of 2002**
- Findings from the RDCRN have contributed to the **approval of 8 treatments** by the FDA.

RARE DISEASES
CLINICAL RESEARCH NETWORK

Data Collection, Formatting, and Quality Assurance

RARE DISEASES
CLINICAL RESEARCH NETWORK

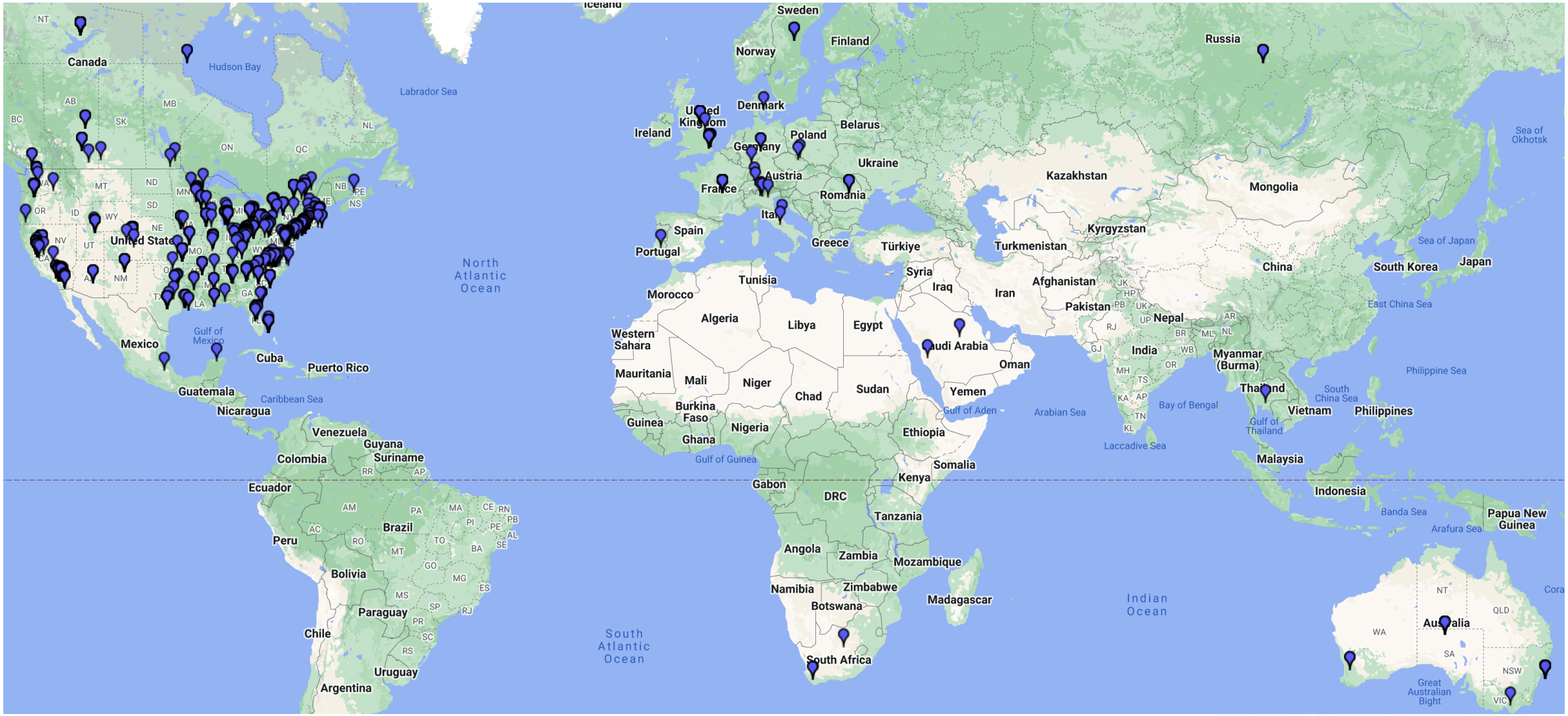
Data Collection Platform for RDCRN Natural History Studies: REDCap (Research Electronic Data Capture)

- A secure, web-based EDC system designed and supported by Vanderbilt U. featuring
  - an intuitive interface for validated data capture
  - audit trails for tracking data manipulation and export procedures
  - automated export procedures for seamless data downloads to common statistical packages
  - procedures for data integration and interoperability with external sources via APIs.

- Widely available, well supported by most academic health centers (7178 institutions, 156 countries, 2M projects, 3.1M Users)
- Projects and data are very portable
- CCHMC was early adopter and has deep expertise
- Good support for data standards in REDCap, availability of form libraries, great community support

RARE DISEASES
CLINICAL RESEARCH NETWORK

RDCRN REDCap logins (9/2022-8/2023)



Data Quality, Integrity, Standards for RDCRN

DMCC has policies and procedures in place

Every study has these 4 documents

- Data Management Plan (DMP)
- Data Quality Plan (DQP)
- Data Transfer Specifications (DTS)
- Database Lock Checklist

RARE DISEASES CLINICAL RESEARCH NETWORK

Data Standards for RDCRN Studies

CDISC/CDASH Standards whenever applicable

When CDISC not available, reference REDCap Shared Library, NDA Repository, NLM Library

Downloads direct from instrument publishers

Looking forward, increased use of direct REDCap links to CDASH forms and CDEs

https://bit.ly/3UopqZj - RDCRN REDCap codebook

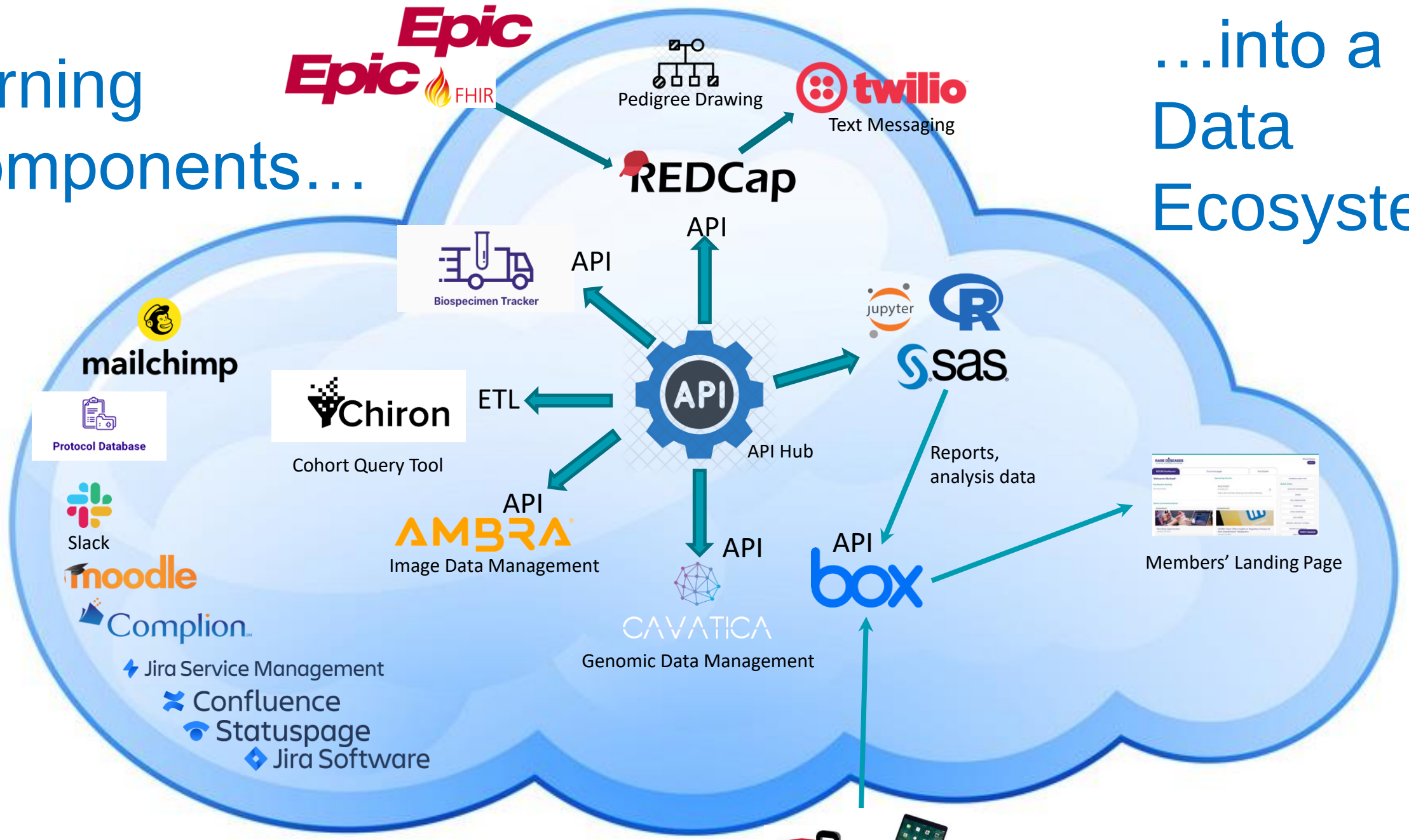
RARE DISEASES CLINICAL RESEARCH NETWORK

Data Storage, Maintenance and Sharing

RARE DISEASES
CLINICAL RESEARCH NETWORK

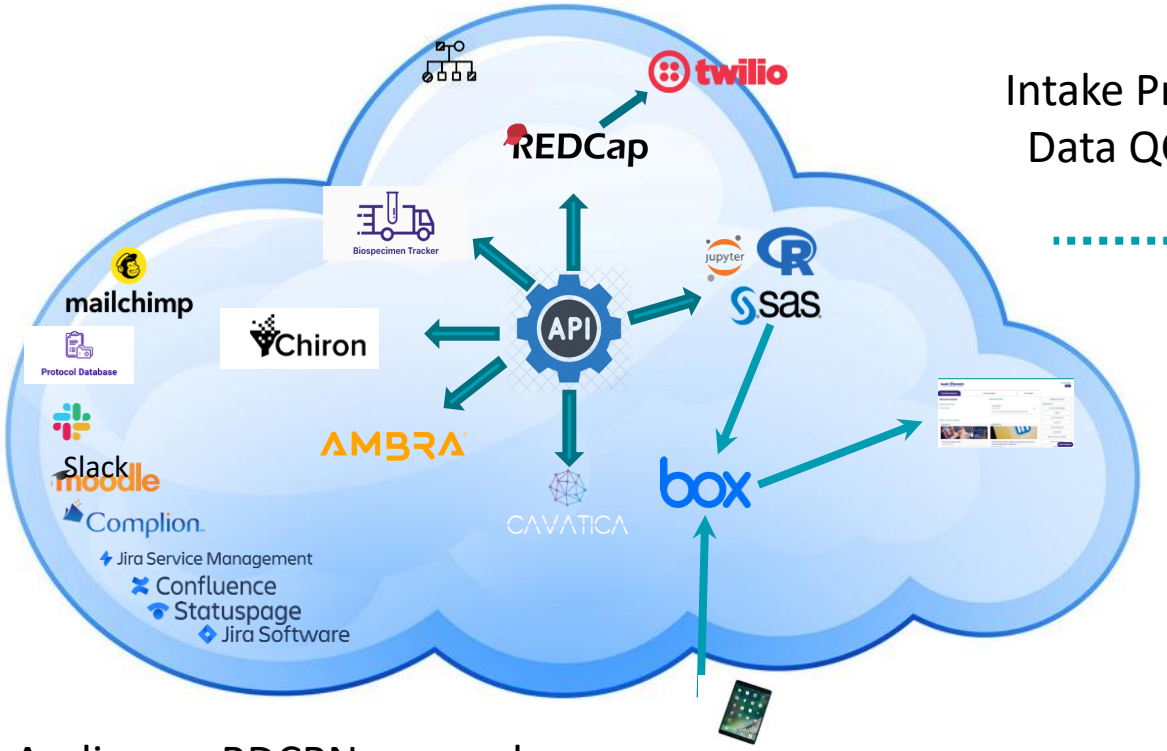
Turning Components…

…into a Data Ecosystem

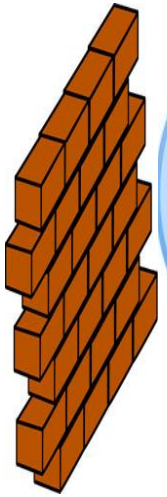


Operational Environment

RDCRN Data Repository



Intake Process: Metadata
Data QC, Data Use Limitations



Access Request Process

Intake Process

Palantir

Audience: RDCRN researchers
Authentication: RDCRN login page
Authorization: Consortia
Data governance: Consortia and DMCC
Internal data sharing

Audience: Public
Data Governance: NIH
NIH-regulated access and authorization
Official NIH repository

RARE DISEASES
CLINICAL RESEARCH NETWORK

RDCRN Data Sharing Framework

- NIH required Rare Disease Consortia to share data funded by RDCRN.
- DMCC developed framework: template language for DUAs and sharing agreements.
- DMCC helps consortia to document participant-level data use limitations in REDCap as metadata.
- NCATS Data Access Committee will adjudicate Data Repository access requests and ensure appropriate data use.

RARE DISEASES
CLINICAL RESEARCH NETWORK

Principles of Data Sharing – Informed Consent

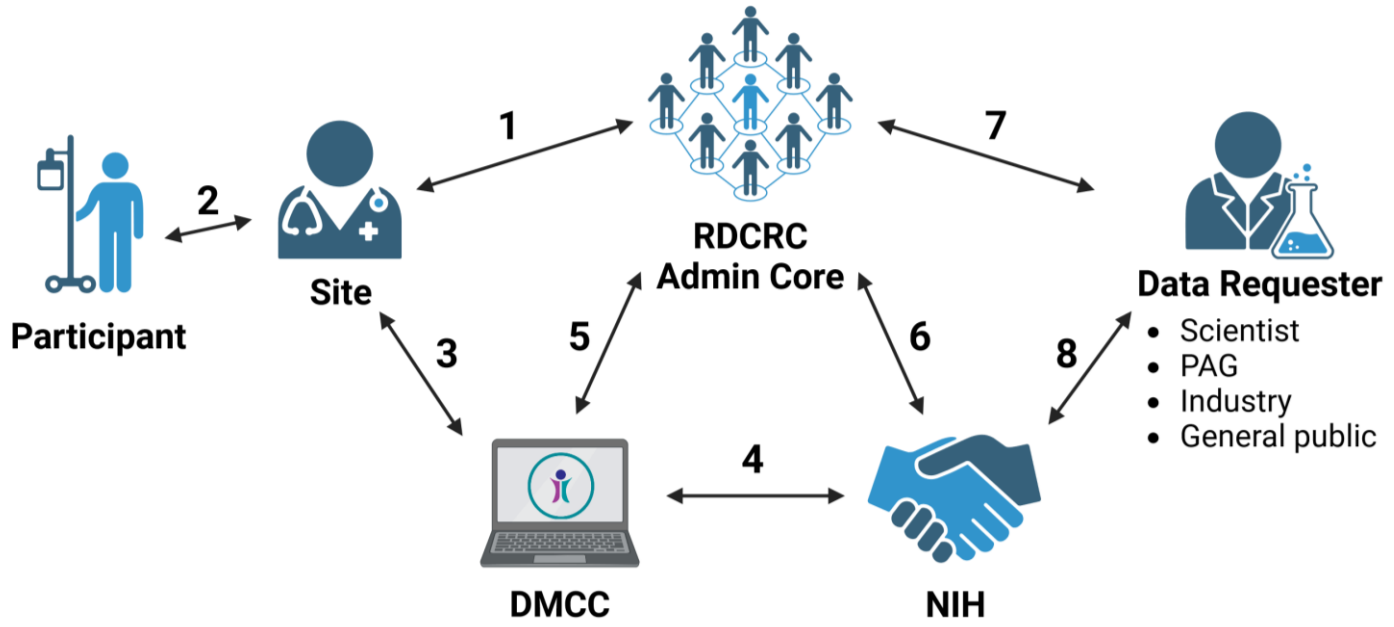
Informed Consent should include language that allows broad data sharing while protecting confidentiality of the participant:

- Sharing data with the Admin Core of the RDCRC as a limited data set.
- Sharing data with DMCC.
- Sharing data with other researchers for future studies.
- Allowing transfer of data, without identifiers, to a federal data repository.
- Options for restricting data sharing that investigators deem necessary to offer the participant (e.g., as mandated by the IRB).
- Incorporation of participant selections/consent category into the research database.

https://www.rarediseasesnetwork.org/research/data-sharing-and-standards/data-sharing-resources

RARE DISEASES
CLINICAL RESEARCH NETWORK

Relationships Among The Parties Involved In Data Sharing



1. Subcontract Award
2. Informed Consent
3. Data Use/Hosting Agreement
4. U2 Cooperative Agreement
5. Data Use/Transfer Agreement
6. U54 Cooperative Agreement
7. RDCRC Data Sharing Policy & Data Use Agreement
8. Federal DAC & Data Use Agreement

RARE DISEASES
CLINICAL RESEARCH NETWORK

RDCRN Data Repository - Required Metadata

Hard Requirements

- Schedule of Events
- Protocol Synopsis
- Data Dictionary
- Codebook
- Extramural Institutional Certification
- Consent Table

Soft Requirements

- IRB Approved Protocol
- Data Management Plan
- Data Quality Plan
- Annotated Blank CRFs

RARE DISEASES
CLINICAL RESEARCH NETWORK

RDCRN Data Repository – QC Framework

Hard Requirements

- Compare
  - Participant IDs in data tables to consent table
  - Variables from data dictionary to contents of data table
- Check for proper delimiters, carriage returns
- Convert dates to age at visit/event

Soft Requirements

- Compare
  - Schedule of Events (SoE) to visit/events in data
- Run Variable Code/Value Consistency report
- Check for version differences in submitted data sets

RARE DISEASES
CLINICAL RESEARCH NETWORK

RDCRN Data Repository – QC Framework

Hard Requirements

- Participant ID Anonymization
- Create Study ID for RDCRN Data Repository
- QC Checks for non-clinical data (i.e., imaging, EEGs, ECHO, etc.)
  - Convert dates to age at event/visit
  - Check for Participant ID; match to clinical data and consent table
- PII flagging process

RARE DISEASES CLINICAL RESEARCH NETWORK

Summary

- Natural history data for patients with rare diseases is critical for advancing rare disease research to speed diagnosis and identify new treatments
- Data must be collected and managed using state-of-the-art systems, processes and procedures to ensure high quality data
- NIH-funded studies are required to share data with the general research community which maximizes its value for clinical trial readiness and approval of treatments

RARE DISEASES
CLINICAL RESEARCH NETWORK

Thank you

5U2CTR002818

NIH National Center for Advancing Translational Sciences

COLLABORATE. INNOVATE. ACCELERATE.

Tiina Urv, Ph.D.
Joanne Lumsden, Ph.D.
Sam Michael, Ph.D.

CCHMC DMAC, IS4R & Research IT teams
RDCRN Project Managers
RDCRN Consortia and research participants, who entrust their data to us!

RARE DISEASES CLINICAL RESEARCH NETWORK

Learn More

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Rare Research Report

UNITED PORPHYRIAS ASSOCIATION

Advancing Awareness, Research and Therapies

Kristen Wheeden
President

UNITED PORPHYRIAS ASSOCIATION

porphyria.org

Our Patient Community

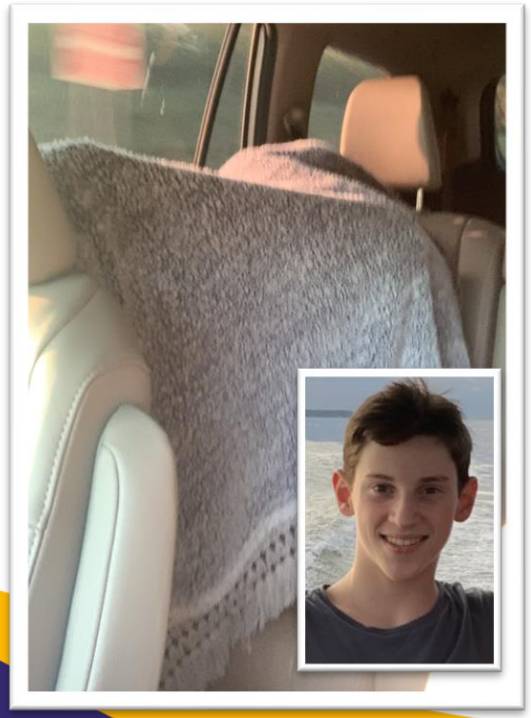
"Like putting my hand in a fire then cutting it with a knife"

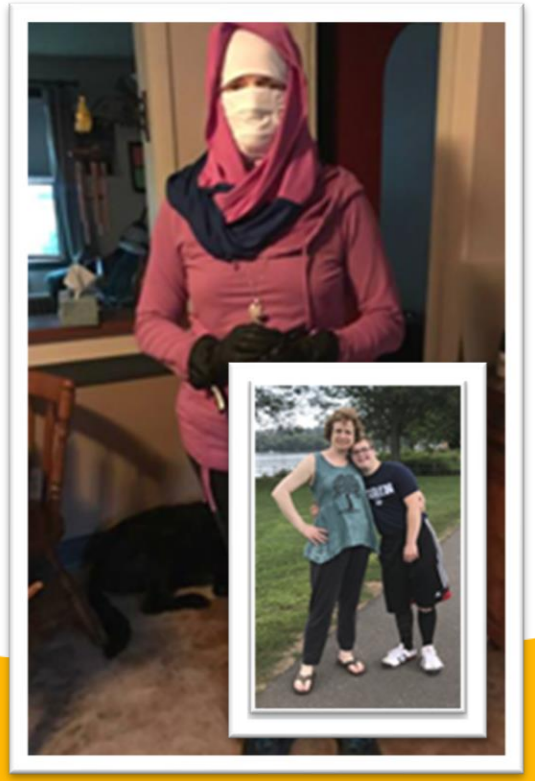
"There are no words in the English language to describe the pain"

"Like I'm trapped in a cage"

"Like being in boiling water"

"Like a chemical burn"





United Porphyrias Association

Research | Education | Awareness | Advocacy | Support

SCIENTIFIC ADVISORY BOARD
UNITED PORPHYRIAS ASSOCIATION

The PRESIDENT'S COUNCIL
UNITED PORPHYRIAS ASSOCIATION

UNITED PORPHYRIAS ASSOCIATION

PATIENT REGISTRIES

PATIENT REGISTRY IN PORPHYRIA

- ✓ Established in 2008
- ✓ 1000+ Participants
- ✓ 14 Academic Institutions/Study Sites
- ✓ Separate Contact Database (CRM)
- ✓ Results
  - ✓ Publications
  - ✓ Studies
  - ✓ Patient Reported Outcome measures

UNITED PORPHYRIAS ASSOCIATION

PATIENT REGISTRY CONSIDERATIONS

- ✓ **Objectives**
  - ✓ Research
  - ✓ Clinical Care
  - ✓ Advocacy and Funding
- ✓ **Stakeholder Engagement**
  - ✓ Engaging patients
  - ✓ Collaboration with researchers
  - ✓ Regulatory involvement
- ✓ **Ensure**
  - ✓ Inclusivity
  - ✓ Data Quality
  - ✓ Privacy and Ethics

UNITED PORPHYRIAS ASSOCIATION

PATIENT REGISTRY BEST PRACTICES

- ✓ Standardized Data Collection
- ✓ Technology Utilization
- ✓ Collaboration
- ✓ Considerations for rare diseases

UNITED PORPHYRIAS ASSOCIATION

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Addressing Challenges in Registry and Natural History Data Collection

Presenters

Benjamin Forred, MBA, ACRP-CP
Sanford Research

Zohreh Talebizadeh, PhD
Global Genes

Reactor Panel

Henry Kaminski, MD, George Washington University
Suzanne Pattee, Office of the Commissioner, FDA
Dominique Pichard, MD, MS, National Center for Advancing Translational Sciences, NIH

REAGAN-UDALL FOUNDATION FOR THE FDA

Addressing Challenges in Registry and Natural History Data Collection – Bioinformatics plans, Ethics, and Data Sharing & Privacy

Benjamin Forred
Director, Translational Research & the CoRDS Registry
Sanford Research

SANFORD RESEARCH

What is CoRDS?

- CoRDS is a patient registry for all rare diseases, unaffected carriers & the undiagnosed - it ties together patients, advocacy groups, and researchers.
- Unlike many other registries, as a Sanford Health sponsored initiative, CoRDS is made available at no cost to patients, advocacy groups, or researchers. It is free and it always will be.

Setting yourself up for effective bioinformatics approaches

- Standardize questions using established data elements
  - NIH common data elements & CoRDS
  - Interoperability with other formats (CDISC, OMOP, etc.)
- Discrete fields used contributes to clean data and decrease analysis time
  - Can lead to effective translation into other languages
- Systematic procedures for ingesting large datasets from external sources

Ethics Considerations

- Data needs to be collected the right way from the start
  - IRB approved protocol & consent documents
  - Privacy laws & regulations (21 cfr part 11, HIPAA, GDPR, etc.)
- Simply put: Participants must know what they're getting into when they sign on to participate. They have rights. It's your job to know them AND protect them.

Using and Sharing Data

- Put a governance and procedure around data sharing
  - CoRDS has an internal scientific advisory council that reviews requests for data
- Identifiable or deidentified data?
  - Be aware of the difference
  - You absolutely have to adhere to the language in the informed consent form
- Security measures around sharing data
  - HIPAA covered entity?
  - SFTP sites are commonly used
  - Get very clear answers before committing to a tool
  - Legal agreement with the recipient

Thanks to all of our participants – and thank you for your attention

Benjamin.Forred@sanfordhealth.org

Research.sanfordhealth.org

RARE-X Research Program:
Virtual Data Collection and Connection
Serving All Stakeholders in Rare Disease

Zohreh Talebizadeh, PhD

Senior Director, RARE-X Research Program

May 13, 2024

Global Genes® Allies in Rare Disease + RARE-X A Research Program of Global Genes

What Is RARE-X?

RARE-X, *a program of Global Genes*, launched in April 2021, to **accelerate** rare disease research & treatments by **removing barriers** for data collection & sharing

The speed and productivity of innovation in rare disease is limited by cost and lack of access to standardized, structured patient data

Data exists, but is captive within silos

Data is not in a structured, standardized format that is useful to research/patient communities

Data doesn't yet exist; many new diseases and most groups don't have resources to collect data properly

Global Genes RARE-X

RARE-X Data Collection Platform (DCP)

RARE-X Supports:

- Individuals (n=1, undiagnosed)
- Patient Communities (small or large)
- Disease Consortium (body system or symptom)

Patients / Individuals

Patient Communities

Disease Consortiums

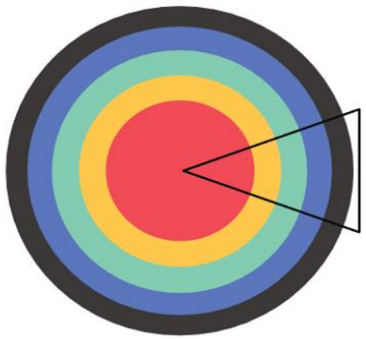
Branching Logic:

- Series of surveys - based on answers, additional prioritized & validated surveys open up

Consent & Data Sharing Preference

Demographics & Role

"Head to Toe" Survey
General Medical, Health & Development



1. **General core**
   - *"Head to Toe Survey"*
2. **Disease core (by domains)**
   - *HPO- mapped domain-specific data*
3. **Supplemental disease data**
   - *Detailed disease-specific data*
4. **Integrated &/or federated data**
   - *EMR/ EHR, clinical reports, custom curation*
5. **Exploratory study data**
   - *Research study-based, raw WGS data*

Level 2 Survey (ex: Neuro)

Level 2 Survey (ex: Cardiac)

Level 2 Survey (ex: Renal)

Survey Layer 3

Survey Layer 3

Survey Layer 3

Survey Layer 3

Validated Instrument

Validated Instrument

Validated Instrument

Validated Instrument

Layer 5 + - Continued buildout of Layered Patient Report Data layered and accessed based on preferences – Branch Chain Logic

Global Genes RARE-X

Patient-Reported Outcomes (PROs)

Domains Implemented:

- Neurodevelopmental
- Neurodegenerative
- Neuromuscular
- Central Disorders of Hypersomnolence

In Process:

- Primary Immune Deficiency (90% completion)
- Cognitive Decline & Associated Depression (adult onset neurodegenerative) (20% completion)

Expert Working Groups for Domain Development

Data Surveys Built to Generate Research-Grade, Comparable Data

Clinicians and scientists from industry and academia serve side-by-side with patients on expert working groups to identify robust data collection surveys, usually from standard measures.

Expert Working Group Formed

Prioritize Domains, Deep Review

Landscape to Identify Measures

Evaluate and Select Measures

License & Implement Measures

Global Genes RARE X

The RARE-X Partner Ecosystem

RARE-X has built a fully integrated platform to support patients as partners in research and has also developed a service model to support biopharma & researchers.
A turn-key comprehensive solution for patients.

Patient Advocates & Orgs

- Patient owned & stewarded data
- Technology & platform for data collection & sharing
- GDPR compliance, data privacy, and governance & consents
- No cost to patients or their orgs
- Education & communications support
- Sponsored studies & consortia

Researchers

- In-depth engagement with patient orgs and development of registries
- Natural history studies including clinician-reported data
- Analysis platform powered by Broad, facilitated by ontology architecture
- Federated learning & data connection for deeper analysis
- Sponsored studies & consortia

BioPharm

- Data sharing post study completion
- Clinical trial readiness surveys
- Patient identification for recruitment into clinical trials
- Federated learning & data connection for deeper analysis
- Sponsored studies & consortia

Global Genes RARE-X

RARE-X Data Overview

RARE-X

by the numbers

**As of May 7, 2024*

67
Disease Communities

106
Patient Advocacy Groups

7,704
Participants Enrolled

90
Countries
~39% ex-US

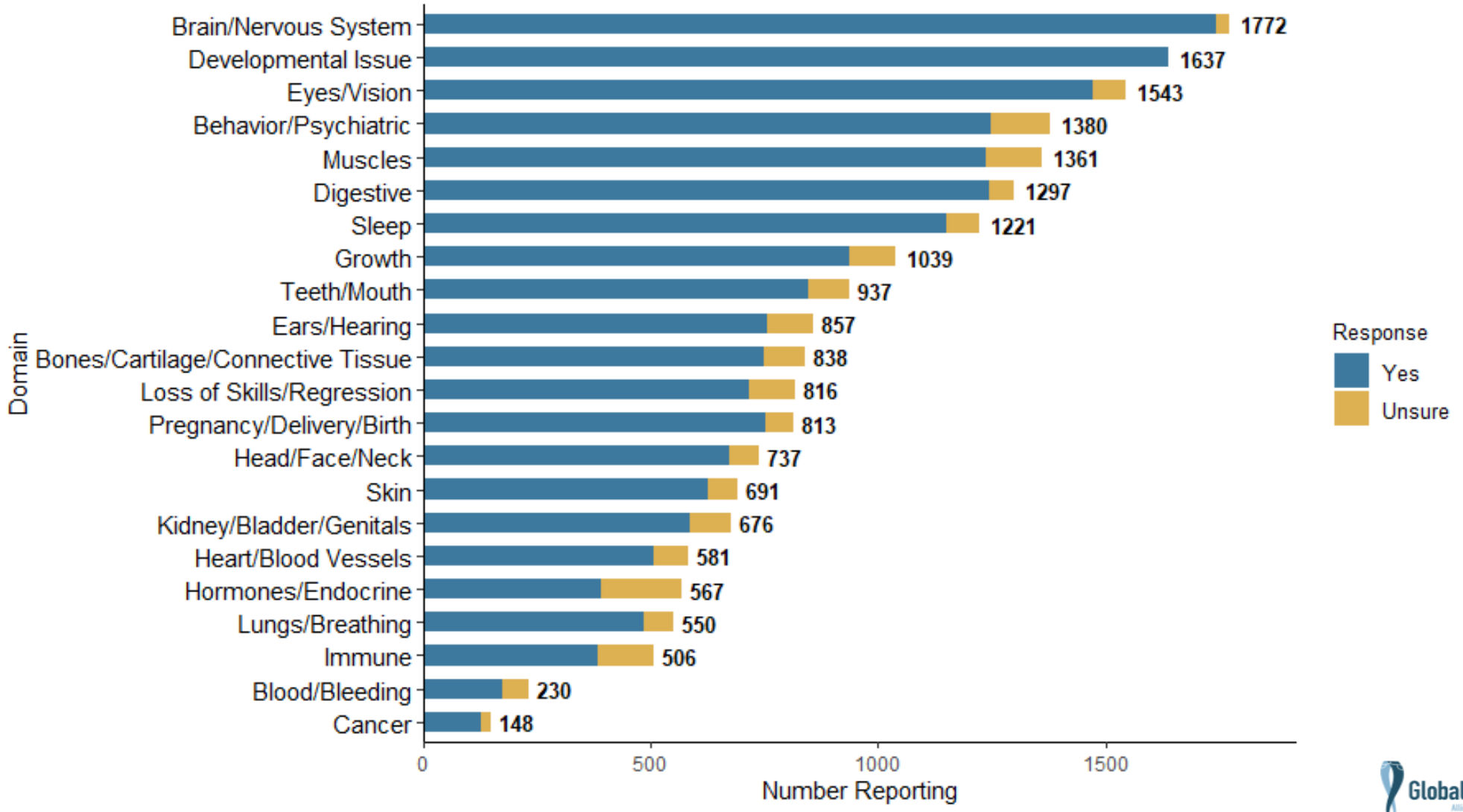
51%
Overall % of Surveys Completed

615
Reports uploaded with genetic testing information

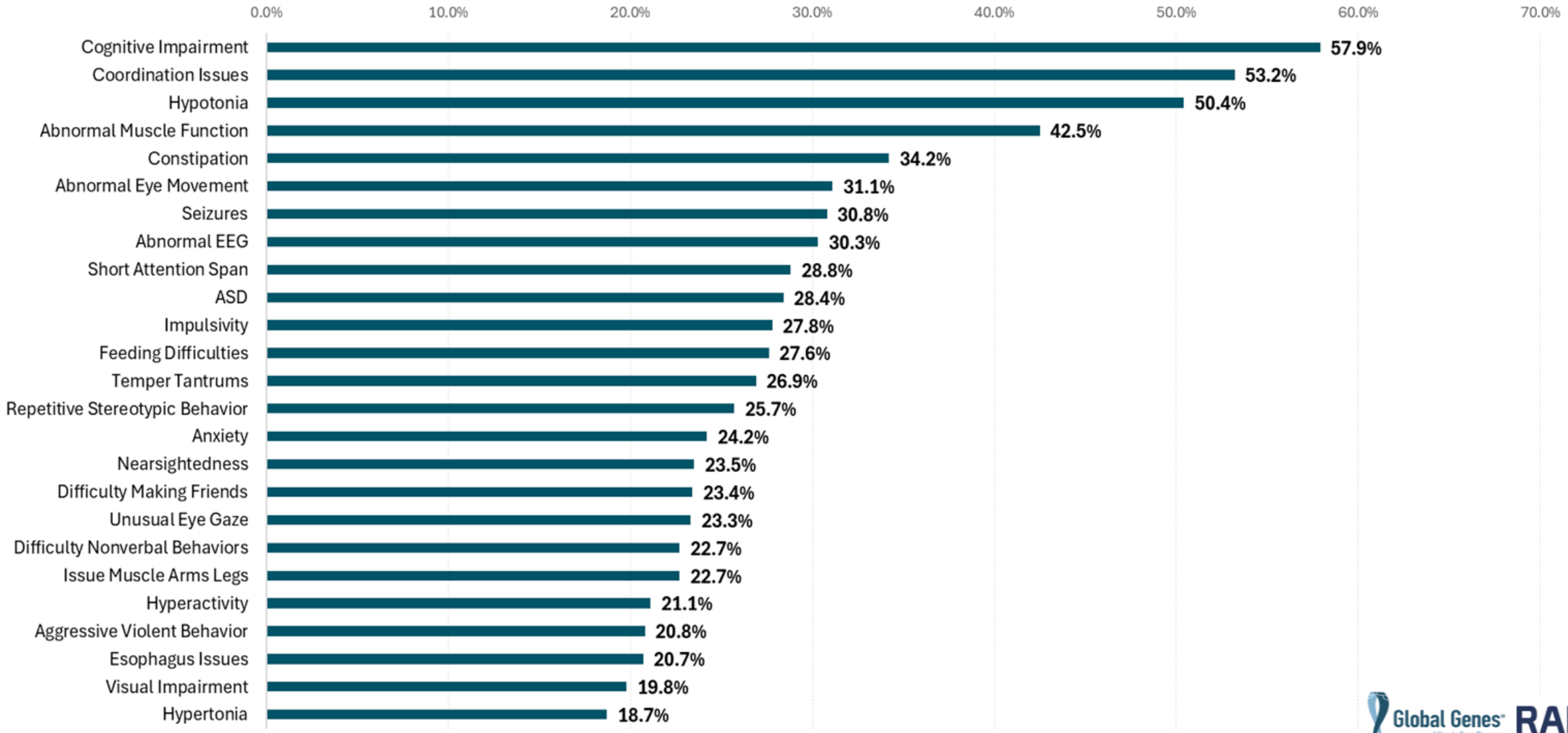
62%
Brain & Nervous System is top domain for patients symptoms

78%
Respondents reported having concern about development

Domains Patients Experience Symptoms in

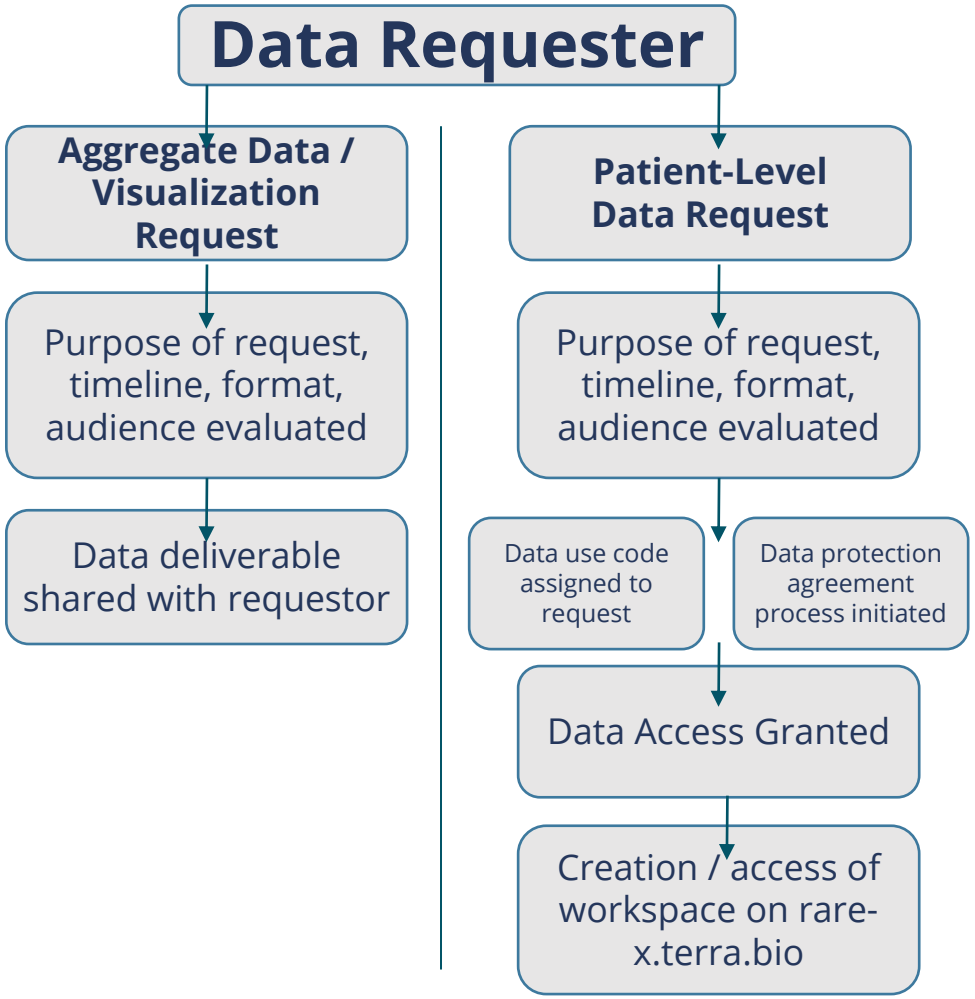


Top Symptoms Reported across the DCP



Data Access

Data Access



The RARE-X consent process enable the RARE-X program to assign data use ontologies and allows different levels of data access to requesters. Enrollees always have access to and control of, all their own data.

There are 2 types of external data access requests

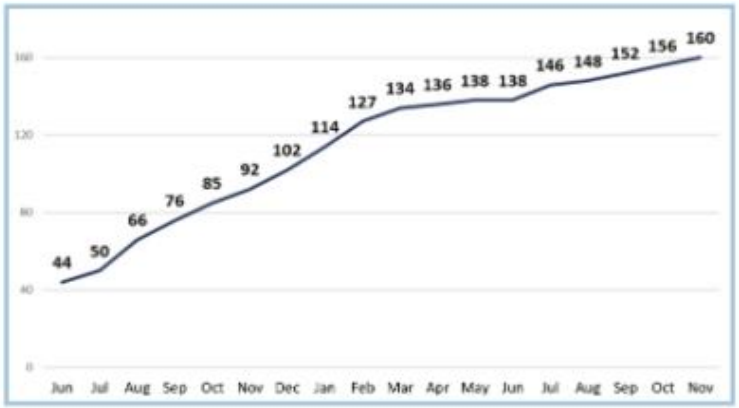
- Aggregate data (survey level counts, graphs, etc) via a project share.
- Participant level de-identified data (Via https://rare-x.terra.bio/)

All requesters are required to complete a **Data Access Request** form that outlines the requested data usage as well as data protection procedures.

- This allows Global Genes to track data use and analysis projects and timelines.
- All data requests are reviewed by **Global Genes RARE-X Data Access Committee**. This is to ensure the requestor's needs are being fulfilled as well as data protection requirements are met.

Global Genes RARE-X

Data Visualization Request Examples



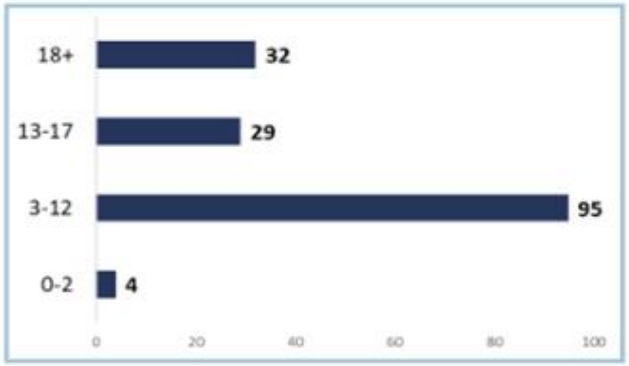
RARE X
A Research Program of Global Genes

PARTICIPATION OVER TIME

The number of **participants currently enrolled** in the PAG data collection program is **160**.

DISTRIBUTION BY AGE GROUP

Over half of participants fall in the age range of **3 to 12 years old** with the second most common age category being **participants aged 18 and above.**



84

Total enrollees that identify as **Male**. This makes up **52.5% of all participants**.

70

Total enrollees that identify as **Female**. This makes up **44% of all participants**.

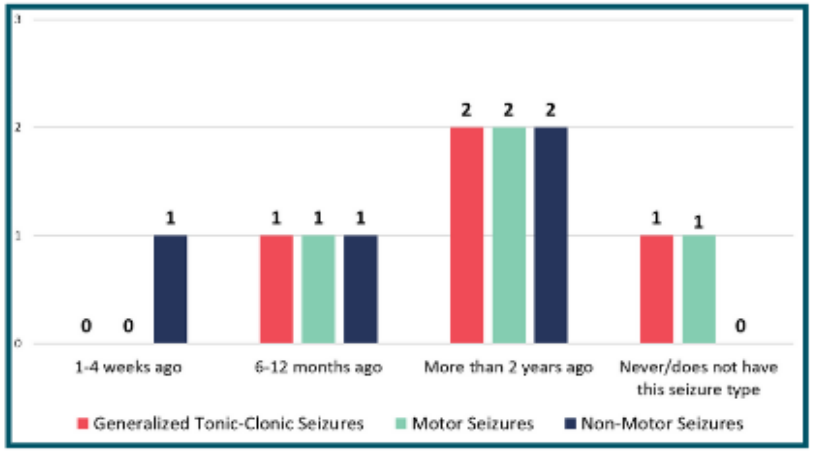
6

Total enrollees that identify as **Non-binary** or selected that they **Prefer Not To Answer.**

Data Visualization Request Examples

OF 4 PAG RESPONDENTS, 100% REPORTED THAT THE CHILD HAS EPILEPSY OR THE CHILD HAS HAD A SEIZURE.

When did the last Generalized Tonic-Clonic Seizure, Motor Seizure, and Non-Motor Seizure occur?



CURRENT EPILEPSY SYNDROMES REPORTED BY RESPONDENTS

Childhood. Benign epilepsy with centrotemporal spikes (BECTS)	1
DeSanto Shinawi Syndrome	1
Not a syndrome (nonsyndromic, uncertain, too early to tell)	1
Does not have epilepsy	1

50%

Reported that the patient's epilepsy type is **both focal & generalized**

50%

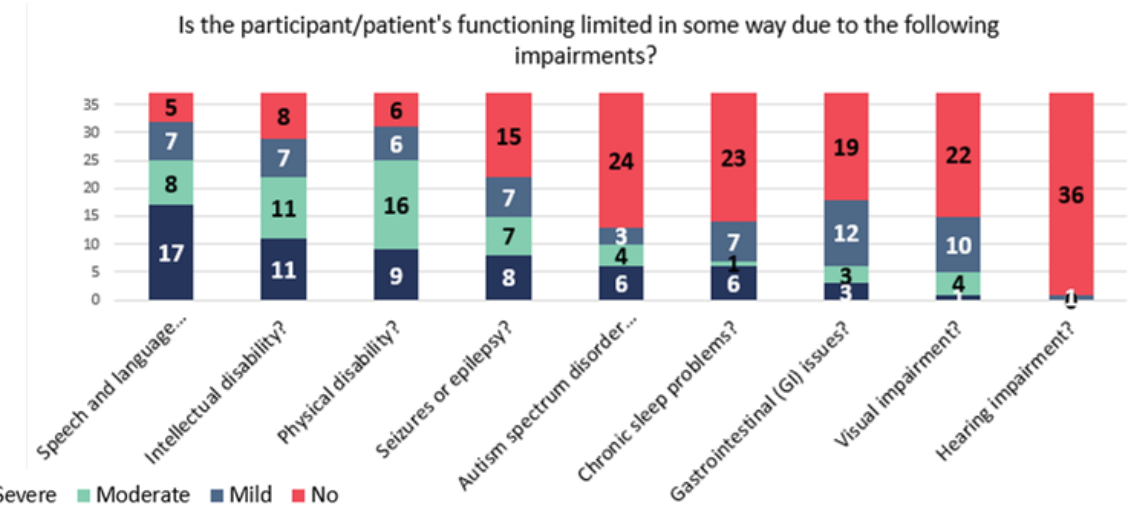
Reported that the patient's epilepsy type is **unknown**

100%

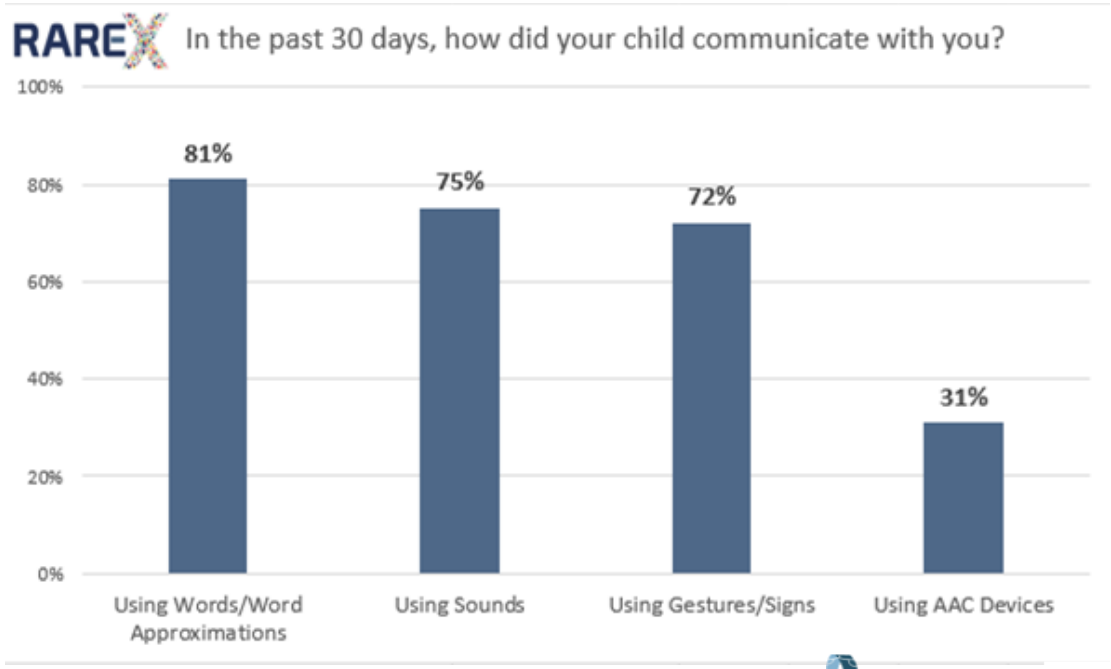
Of patients who have epilepsy reported that it is **NOT treatment resistant**

Data Visualization Request Examples

Is the participant/patient's functioning limited in some way due to the following impairments?	Severe	Moderate	Mild	No
Speech & language impairment	17	8	7	5
Intellectual disability	11	11	7	8
Physical activity	9	16	6	6
Seizures or epilepsy	8	7	7	15
Autism spectrum disorder (ASD)	6	4	3	24
Chronic sleep problems	6	1	7	23
Gastrointestinal (GI) issues	3	3	12	19
Visual impairment	1	4	10	22
Hearing impairment	0	0	1	36

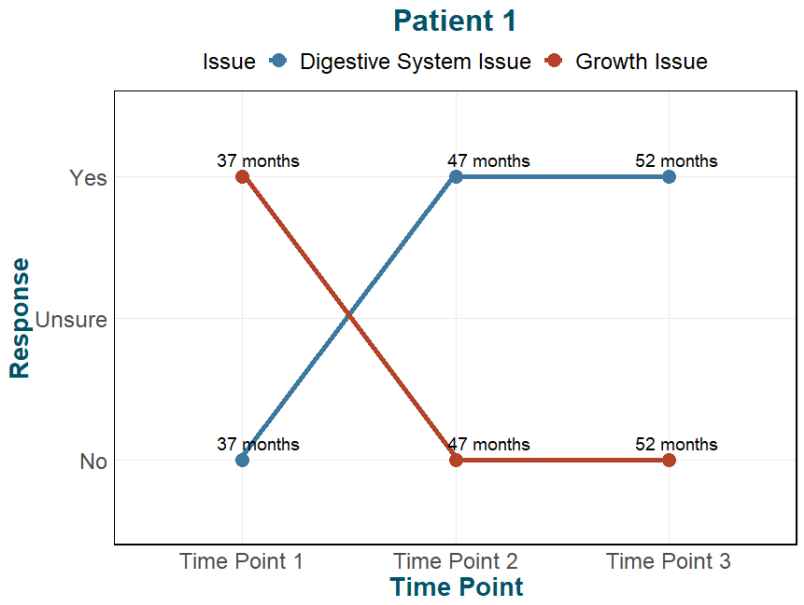


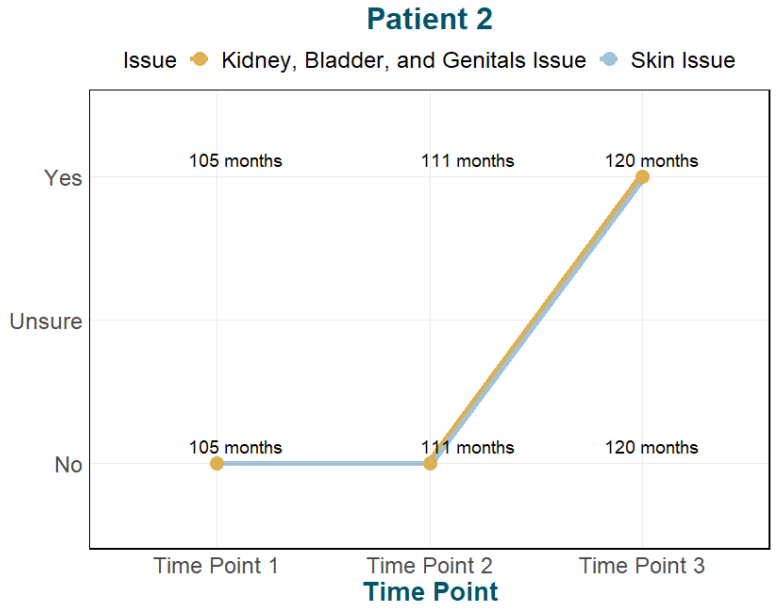
How patient communicated in past 30 days	% of all respondents	Number respondents
Using words/word approximations	81%	26
Using sounds	75%	24
Using gestures/signs	72%	23
Using AAC devices	31%	10

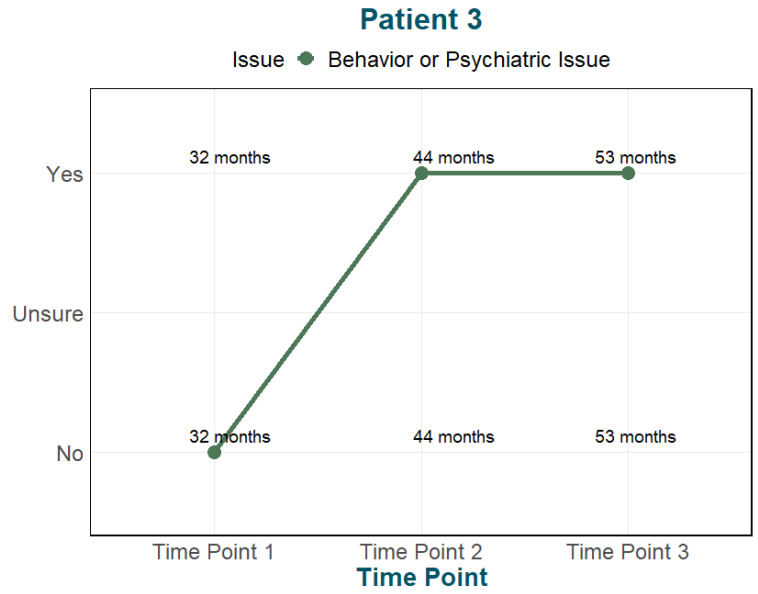


Longitudinal Data Collection Example

Three different patients with the same rare disease







Applications

Global Genes® Allies in Rare Disease + RARE X A Research Program of Global Genes

Applications

- **PRO Survey Validation**
  - Implement established surveys for validation in larger population
  - Development of new surveys addressing unmet needs, validated against established measures on RARE-X platform
- **Contribute to Natural History Studies**
  - Partner with IRB approved natural history study to administer & transfer PRO data to data collection site, enabling participants to update symptomes
  - Participants participating in RARE-X & natural history study to complete relevant PRO data one time for both studies, accelerating real word data collection on disease progression
- **Research Consortia**
  - Bring together diverse stakeholders to create collaborative data collection program with a specific aim
- **Partnership & Data Integration**
  - Rich repository of genetic data mapped to phenotypic data collected in platform
  - Robust data collection available to researchers

Partnership & Data Integration

With the Commission for Novel Technologies for Neurodevelopmental CNVs ("Commission")

Background: RARE-X previously completed biosample collections as a part of a sub-study that was developed in partnership with the Commission for Novel Technologies for Neurodevelopmental CNVs ("Commission").

RARE-X and the Commission partnered with the biotechnology company Illumina, and **sent blood samples to the Illumina team for long-read whole genome sequencing, short-read whole genome sequencing, and methylation testing**.

This partnership has led to a **rich repository of genetic data that is being mapped to phenotypic data that has been collected on the RARE-X** platform.

Many participants were also given clinical assessments at family conferences by partnering clinicians, or had clinical data collected at a Collaborative Clinic that enabled data sharing.

This effort has ultimately **allowed for large and robust data collection in a consortium of three ultra-rare disorders**. **The data collected is available to researchers upon request, encouraging research** into these rare and under-researched diseases.

Contribute to Natural History Studies

To get real world data on disease progression Patient-Reported Outcomes (PROs) are utilized to collect data based on signs/symptoms observed by the participant or a caregiver.

PROs are often given in a clinician office for the patient to take home and return at the next appointment. **RARE-X can partner with an IRB approved natural history study to administer and transfer the PRO data to the data collection site.** This partnership will **allow participants who are participating in both RARE-X, and a natural history study to complete the relevant PRO data a single time for both studies**.

Participants can go in an **update their symptoms on both a scheduled and as needed basis**. The ability to update their symptoms will help **capture the common symptoms/patterns but also patterns that were previously not visible**.

Conclusion

PAST:
Accomplishments

Stakeholder Partnership for PRO Data Collection
Established diverse partnerships for bi-directional input

Symptom-Based Data Collection
Enhanced understanding of disease manifestations by collecting patient-reported symptom data

Cross-Disease Database
Facilitated studying commonalities and differences across diseases

Genetic Data Curation
Developed workflow for curating genetic data from reports

Patient-Preferred Data Sharing
Implemented patient-preferred data sharing

Aggregate Data Reports
Developed templates for aggregate data reports

Individual-Level Data Access
Enabled secure access to individual-level data

Longitudinal Data Collection
Collected data from multiple timepoints

Research Interest Growth
Garnered increased researcher interest despite limited dissemination

PRESENT:
Promises

PRO Surveys
Piloted implementation of select PRO surveys, facilitating prioritization for large-scale natural history studies.

Open Science Data Challenge (OSDC)
Initiated an OSDC to promote broader access to our registry and encourage innovative analysis in rare disease.

Data Mapping
Piloted data mapping to external clinical datasets, expanding the scope and utility of our database.

Natural History Studies
Facilitated linkage with natural history study datasets, enhancing the richness and depth of available data.

Translation
Initiated a translation workflow to broaden the accessibility and reach of our platform, promoting inclusivity and diversity.

FUTURE: Challenges & Opportunities

Protocol Standardization
Help to facilitate **coordinated** efforts to address the lack of standard protocols for PRO data collection efforts.

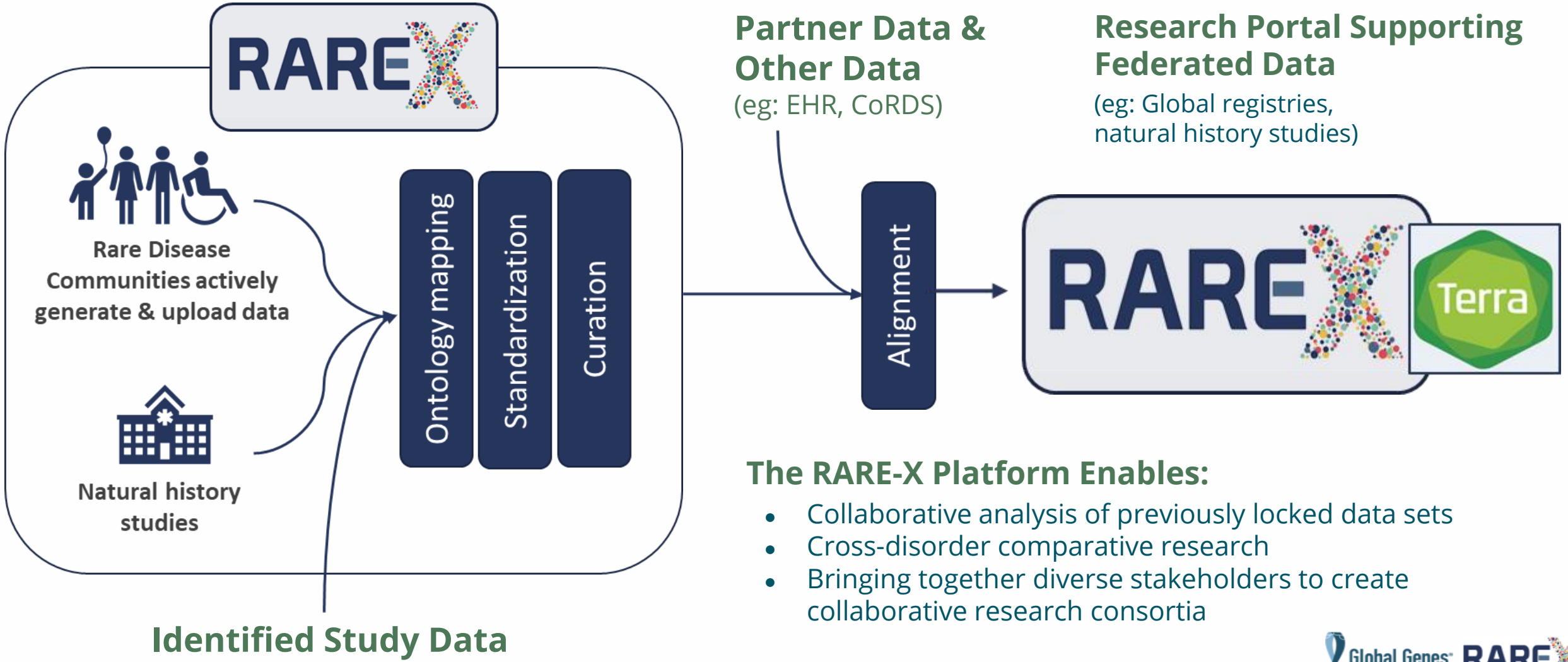
Evaluation Frameworks
Identify standardized **metrics** for evaluating the impact of PRO data collection efforts.

Analytical Feature Expansion
Identification and expansion of **analytical features** to streamline dynamic and real-time data mapping, enhancing usability and effectiveness of PRO data.

Longitudinal Data Workflow
Create a standard analytical **workflow** to leverage longitudinal data points while taking into consideration their inherent variation, to enhance the utility and accuracy of analyses derived from longitudinal PRO data.

National Taskforce Establishment
Landscape/Scope/Advocate the need for new dedicated funding pipelines to support the future direction of PRO data collection harmonization efforts and **sustainability** of these unique resources.

Visual Summary: Data Generation, Alignment, Federation



The RARE-X Platform Enables:

- Collaborative analysis of previously locked data sets
- Cross-disorder comparative research
- Bringing together diverse stakeholders to create collaborative research consortia

RARE-X

A Research Program of Global Genes

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National Center for Advancing Translational Sciences, NIH

Katherine Needleman, PhD, RAC
Office of Orphan Products Development, FDA

REAGAN-UDALL
FOUNDATION
FOR THE FDA

RARE DISEASES
CLINICAL RESEARCH NETWORK

Established by Rare Diseases Act of 2002
(Public Law 107-280)

"planning, establishing, or strengthening, and providing basic operating support for ***regional centers of excellence*** *for clinical research into, training in, and demonstration of diagnostic, prevention, control, and treatment methods for rare diseases"*

Established 2003
Recompeted every 5 years

Division of Rare Diseases Research Innovation

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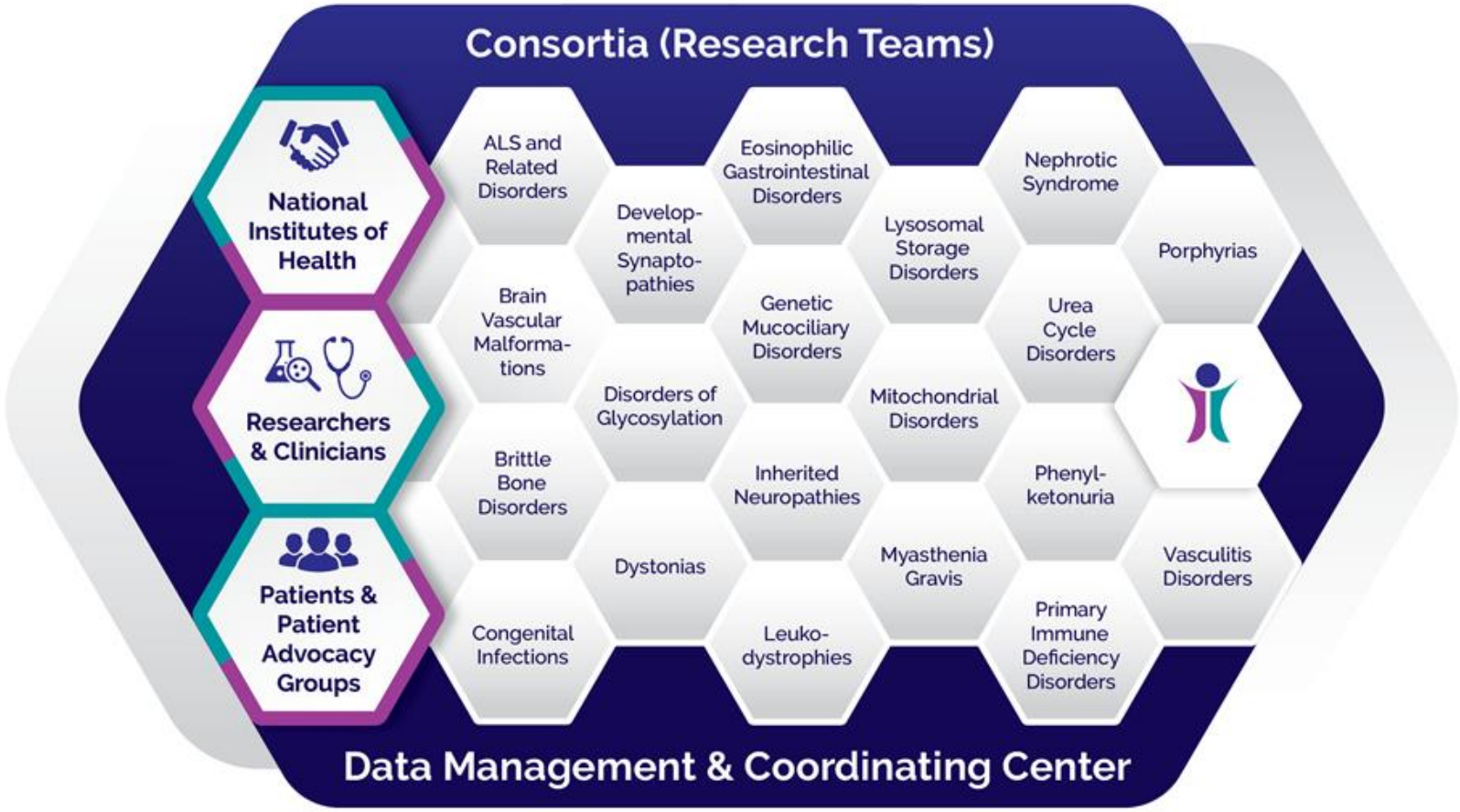
National Center for Advancing Translational Sciences

RARE DISEASES CLINICAL RESEARCH NETWORK

A network of 20 research teams collaborating to achieve faster diagnosis and better treatments for patients with rare diseases



Current 2024

National Center for Advancing Translational Sciences

National Center for Advancing Translational Sciences

National Institute of Dental and Craniofacial Research

National Institute of Diabetes and Digestive and Kidney Diseases

National Institute of Allergy and Infectious Diseases

National Institute of Arthritis and Musculoskeletal and Skin Diseases

National Institute of Neurological Disorders and Stroke

Eunice Kennedy Shriver National Institute of Child Health and Human Development

National Institute of Mental Health

National Heart, Lung, and Blood Institute

National Institutes of Health
Office of Dietary Supplements

Every RDCRN consortium:

Studies at least 3 related rare diseases

Career Enhancement Core
Works to develop the next generation of rare disease researchers

Admin Core
Is a partnership of researchers and clinicians, patients and patient advocates, and the NIH

Pilot/Feasibility Governance Core
Supports innovative pilot projects

Clinical Research Projects
Conducts 2-4 clinical research projects, including a natural history study

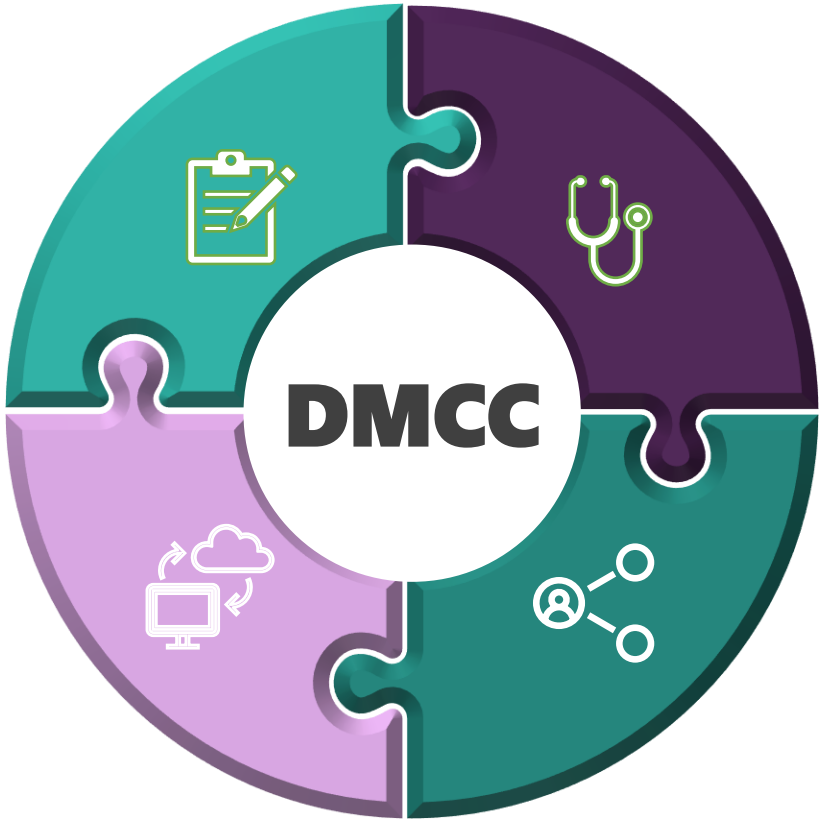
DMCC
Is supported by a central Data Management and Coordinating Center

RARE DISEASES
CLINICAL RESEARCH NETWORK

RDCRN Data Management and Coordinating Center

Administrative Support

Facilitates network operations, governance and communication



Clinical Research Support

Supports best practices in clinical research, protocol development and good data practices (FAIR)

Data Management

Builds and maintains a robust, secure data infrastructure for the RDCRN working closely with NCATS

Engagement and Dissemination

Promotes patient engagement and broad research dissemination

National Center for Advancing Translational Sciences

RARE DISEASES CLINICAL RESEARCH NETWORK

RDCRN Translational Impact

RARE DISEASES CLINICAL RESEARCH NETWORK

Clinical Trials directly funded by U54 grant

- Predominantly small **Phase 1/Phase 2**
- Currently 18 trials funded in RDCRN4
- Primarily repurposed drugs, diets, supplements, procedures, devices, some novel drugs

RDCRN-associated Clinical Trials

- Predominantly **Phase 2/Phase 3**
- Funded by industry, IC-specific grants, FDA, PAGs
- Leveraging disease phenotype, patient population, clinical sites, endpoints, biomarkers, early phase safety and efficacy data
- *No NCATS $$ involved*

12 FDA-approved treatments for 11 rare diseases

Consortium	Drug	Other Name	Indication	Company	Approval Date
UCDC	CARBAGLU®	carglumic acid	N-acetylglutamate synthetase (**NAGS**) deficiency	Orphan Europe	March 2010
VCRC	RITUXAN®	rituximab in combination with corticosteroids	Wegener's granulomatosis (**WG**) and microscopic polyangiitis (**MPA**)	Genentech and Biogen	April 2011
UCDC	RAVICTI®	glycerol phenylbutyrate	urea cycle disorders (**UCD**)	Hyperion Therapeutics	February 2013
RLDC	RAPAMUNE®	sirolimus	lymphangioleiomyomatosis (**LAM**)	Pfizer	May 2015
PC	SCENESSE®	afamelanotide	erythropoietic protoporphyria (**EPP**)	Clinuvel	October 2019
PC	GIVLAARI®	givosiran	acute hepatic porphyria (**AHP**)	Alnylam Pharmaceuticals	November 2019
RKSC	OXLUMO®	lumasiran	primary hyperoxaluria type 1 (**PH1**)	Alnylam Pharmaceuticals	November 2020
CEGIR	DUPIXENT®	dupilumab	eosinophilic esophagitis (**EoE**)	Regeneron	May 2022 Jan 2024 (pediatric)
RTT	DAYBUE™	trofinetide	**Rett** syndrome	Acadia Pharmaceuticals	March 2023
MGNet	RYSTIGGO®	rozanolixizumab-noli	generalized myasthenia gravis (**gMG**)	UCB	June 2023
RKSC	RIVFLOZA™	nedosiran	primary hyperoxaluria type 1 (**PH1**)	Novo Nordisk	October 2023
CEGIR	EOHILIA	budesonide oral suspension	eosinophilic esophagitis (**EoE**)	Takeda	February 2024

NIH National Center for Advancing Translational Sciences

PAR-24-206

Rare Diseases Clinical Research Consortia (RDCRC) for the Rare Diseases Clinical Research Network (RDCRN) (U54 Clinical Trial Optional)

The following types of studies are not responsive to this NOFO.

Applications proposing such studies will be considered non-responsive, will be withdrawn from review, and not considered for funding.

- Single site clinical studies
- Phase III Clinical Trials as part of Clinical Research Projects
- There are fewer than three rare diseases included
- There is not at least one longitudinal natural history study
- There are either less than two or more than four research projects submitted
- There is no patient advocacy group involved
- Basic sciences studies
- Applications that propose any type of animal studies within the RDCRC. The use of in vitro models must be relevant to clinical endpoints (i.e., testing drugs, validating biomarkers versus more basic research)

National Center for Advancing Translational Sciences

RARE DISEASES CLINICAL RESEARCH NETWORK

Rare Diseases Clinical Research Consortia (RDCRC) for the Rare Diseases Clinical Research Network (RDCRN) (U54 Clinical Trial Optional)

Key Dates

Posted Date	April 02, 2024
Open Date (Earliest Submission Date)	July 12, 2024
Letter of Intent Due Date(s)	30 days prior to the application due date

Application Due Dates			Review and Award Cycles		
New	Renewal / Resubmission / Revision (as allowed)	AIDS - New/Renewal/Resubmission/Revision, as allowed	Scientific Merit Review	Advisory Council Review	Earliest Start Date
August 13, 2024	August 13, 2024	Not Applicable	February 2025	May 2025	July 2025

All applications are due by 5:00 PM local time of applicant organization.

Applicants are encouraged to apply early to allow adequate time to make any corrections to errors found in the application during the submission process by the due date.

https://grants.nih.gov/grants/guide/pa-files/PAR-24-206.html

NIH National Center for Advancing Translational Sciences

NCATS

COLLABORATE. INNOVATE. ACCELERATE.

ncats.nih.gov @ncats_nih_gov @ncats.nih.gov NIH-NCATS

Tiina Urv, Ph.D.
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Scientific Program Manager
joanne.lumsden@mail.nih.gov

National Center for Advancing Translational Sciences

OOPD's Funding Opportunities for Rare Diseases

Katherine Needleman, MS, PhD, RAC
Director, Orphan Products Grants Program
FDA/OOPD
May 13, 2024

FDA/NIH/NCATS/Reagan Udall Foundation Public Workshop:
Natural History Studies and Patient Registries In the Development of Rare Disease Treatments

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

Rare Neurodegenerative Disease Grant Program

- **Established:** upon enactment of the ACT for ALS in December 2021.
- **FY2024 Budget:** $5M
- **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

Funding Opportunities Details

- **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 disease proposed to be studied meet the definition of a rare disease (prevalence of fewer than 200,000 persons in the US)
- **Budget:**
  - Yearly budget depends on the RFA. See RFA for limits.
- **How to Apply:**
  - Grants.gov
  - Instructions in the SF424 (R&R) Application Guide, except where noted otherwise
  - Helpful Hint documents for all FOA on OOPD's website
  - Registrations required to submit (e.g., SAM, eRA Commons, grants.gov)
  - Start Early!
- **Review and Awards:**
  - Reviewed by experts in the field
  - Number of awards is contingent upon FDA appropriations and submission of a sufficient number of meritorious applications
  - Funding dependent on **quality of application** and **availability of Federal funds**

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
- Efficient and Innovative Natural History Studies Addressing Unmet Needs in Rare Diseases (R01)
  - Receipt Dates: February 13, 2024
  - FOA Number: RFA-FD-22-001
- Natural History and Biomarker Studies of Rare Neurodegenerative Diseases (U01)
  - Receipt Dates: May 6, 2024
  - FOA Number: RFA-FD-24-024

Apply through Grants.gov – links in the RFA

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


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Lunch

The meeting will resume at 1:35 pm ET

REAGAN-UDALL FOUNDATION FOR THE FDA

Natural History Studies and Registries in the Development of Rare Disease Treatments

Hybrid Public Workshop

May 13, 2024 | 10am-4pm *(eastern)*

A workshop prepared in collaboration with the Food and Drug Administration and the NIH National Center for Advancing Translational Sciences

REAGAN-UDALL FOUNDATION FOR THE FDA

Collecting Fit for Purpose Data to Inform Regulatory Decision Making

Presenters

Jennifer Farmer, MS
Friedreich's Ataxia Research Alliance

Collin Hovinga, PharmD, MS, FCCP
Critical Path Institute

Reactor Panel

Benjamin Forred, MBA, ACRP-CP, Sanford Research
Donna Rivera, PharmD, MSc, Oncology Center of Excellence, FDA
Kimberly Smith, MD, MS, Center for Drug Evaluation and research, FDA
Tiina Urv, PhD, National Center for Advancing Translational Sciences, NIH

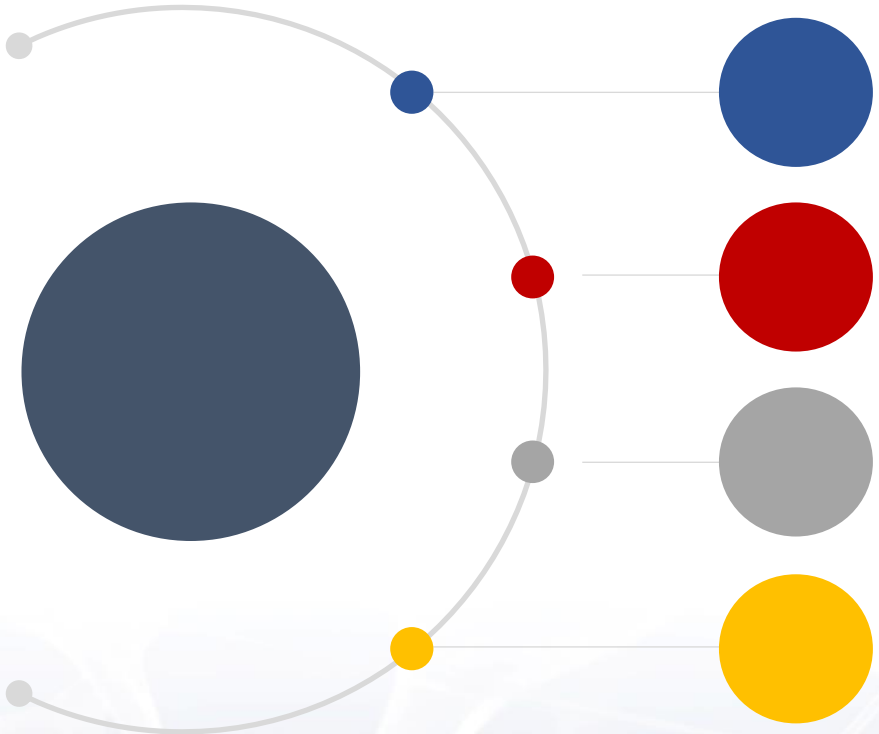
REAGAN-UDALL FOUNDATION FOR THE FDA

Collecting Fit-for-Purpose Data to support Regulatory Decision Making

Reagan Udall, May 2024

Jen Farmer, CEO, Friedreich's Ataxia Research Alliance (FARA)

Disclosures



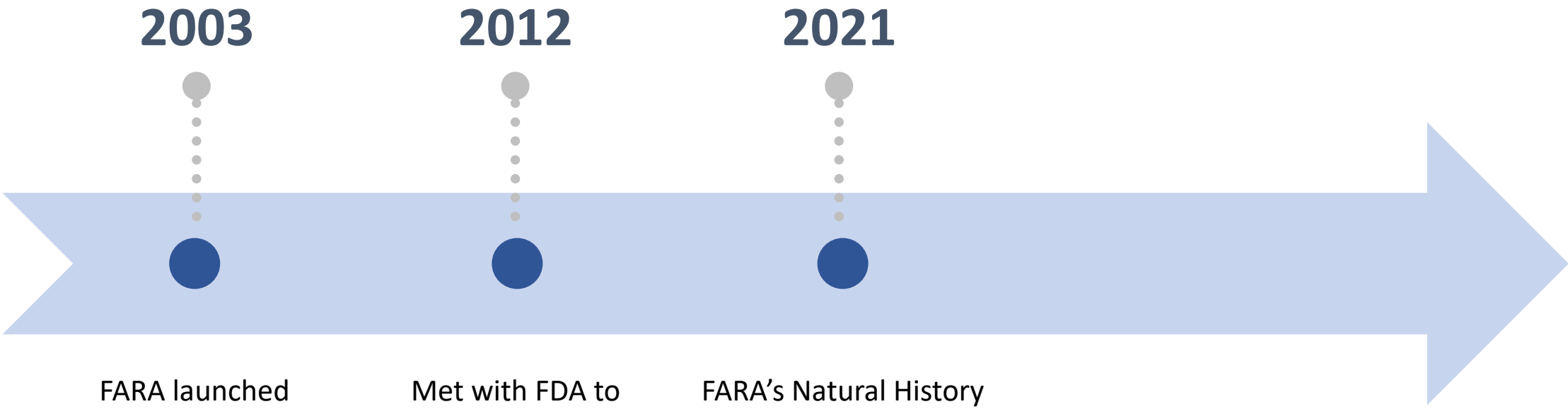
FA-COMS is primarily funded by community fundraising events

FDA funded a 3-year FA-CHILD pediatric study

Industry sponsorships do not directly fund the FA-COMS study

FARA has no additional disclosures to report

FARA's Natural History study began 20+ years ago



How FA-COMS began:

COAs for FA

MDA Muscular Dystrophy Association & FARA Friedreich's Ataxia Research Alliance

2003: Co-funded grant

- *Original to FA*
  FARS, ADL, staging scale
- *Borrowed measures from MS*
  9HPT, T25FW, PATA, Low Contrast Letter Acuity, MSQLI

Natural History Visits Begin

2006 : FARA commits to funding the natural history study and network

NOTE: Not designed to be a control arm for trials

Goal 1

Systemic Data Collection

Understand natural history of FA through systemic collection of clinical data

Goal 2

Disease Measures

Develop outcome measures and inform clinical trial design

Goal 3

Clinical Network

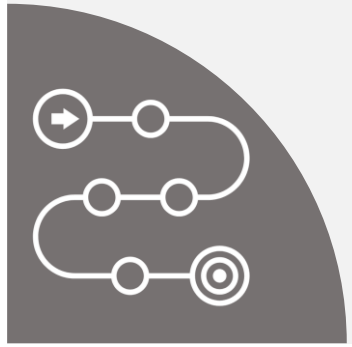
Create a network of clinical research centers in FA that will provide quantitative clinical data on patients.

FARA Friedreich's Ataxia Research Alliance

FA-COMS Study Design

Inclusion

Genetically confirmed FA
All ages and stages
Representative population



Prospective, Longitudinal

Intentionally forward-looking
Long-term commitment commensurate with the rate of disease progression

Annual Visits

Nearly all in-person visits (except some from 2020-2022 due to COVID)

Consistency

Treated it as a non-interventional trial – same protocol, visit schedules, sops/standardized procedures, data collection across all sites

Quality of the Data

NIH NINDS

Common data elements

Peer-reviewed publications share longitudinal data with the FA research community

Multicenter Study > Diabetes Res Clin Pract. 2022 Apr;186:109828.
doi: 10.1016/j.diabres.2022.109828. Epub 2022 Mar 14.

Friedreich's Ataxia related Diabetes: Epider and management practices

Jaclyn Tamaroff [1], Anna DeDi
Karla Leavens [4], Christian Ru

> J Neuroophthalmol. 2020 Jun;40(2):213-217. doi: 10.1097/WNO.0000000000000878.

Correlation of Visual Quality of Life With Clinical and Visual Status in Friedreich Ataxia

Parisa Afsharian [1], Rachel Nolan-Kenney, Abigail E Lynch, Laura J Balcer, David R Lynch

Observational Study > Ann Clin Transl Neurol. 2021 Ju
doi: 10.1002/acn3.51352. Epub 2021 May 5.

Scoliosis in Friedreich's ataxia: characterization in a large heter

Christian Rummey [1], John M Flynn [2],
George Wilmot [5], Sub H Subramony [6]

> Ann Clin Transl Neurol. 2020 Sep;7(9):1708-1712. doi: 10.1002/acn3.51118. Epub 2020 Aug 11.

Test–retest reliability of the F rating scale

> Neurol Genet. 2019 Oct 29;5(6):371. doi: 10.1212/NXG.0000000000000371.
eCollection 2019 Dec.

Psychometric properties of the Friedreich A Rating Scale

Christian Rummey [1], Louise A Corben [1], Martin B Delatycki [1], S H Subramony [1],
Khalaf Bushara [1], Christopher M Gomez [1], Joseph Chad Hoyle [1], Grace Yoon [1], Bernard R
Katherine D Mathews [1], George Wilmot [1], Theresa Zesiewicz [1], Susan Perlman [1],
Jennifer M Farmer [1], David R Lynch [1]

> EClinicalMedicine. 2020 Jan 8;18:100213. doi: 10.1016/j.eclinm.2019.1
eCollection 2020 Jan.

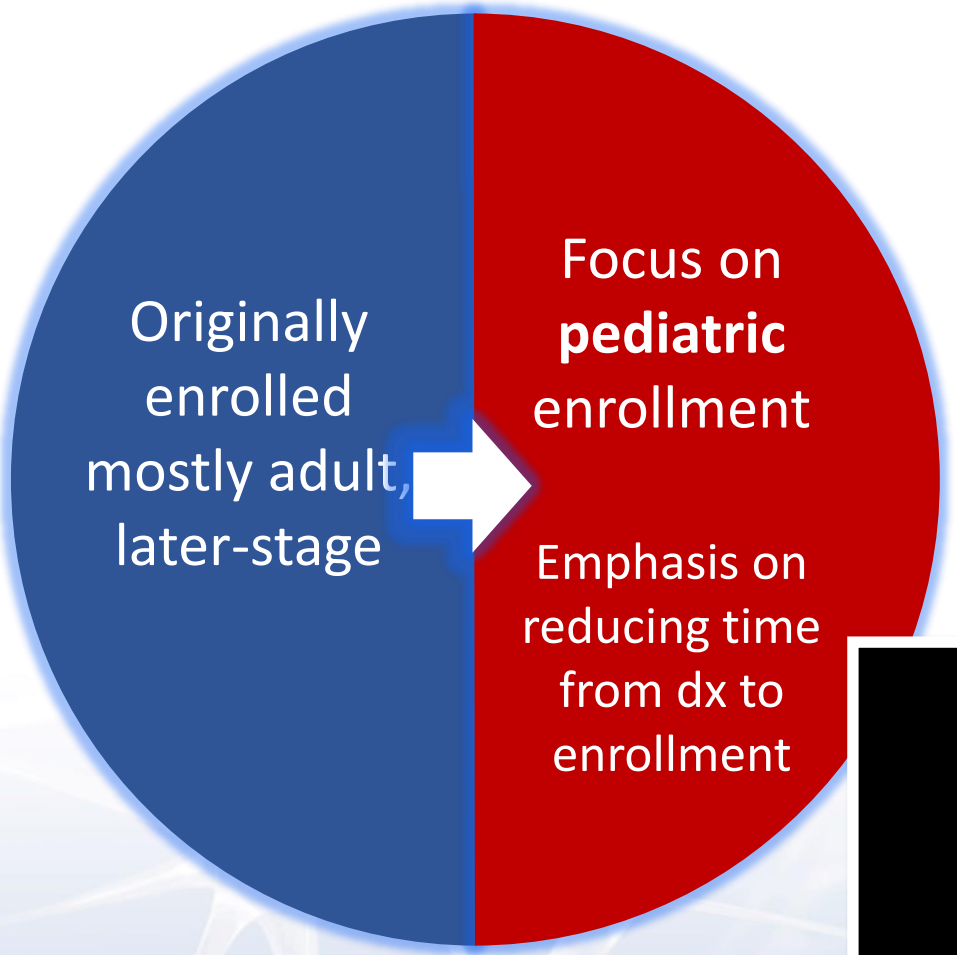
Predictors of loss of ambulation in Frie

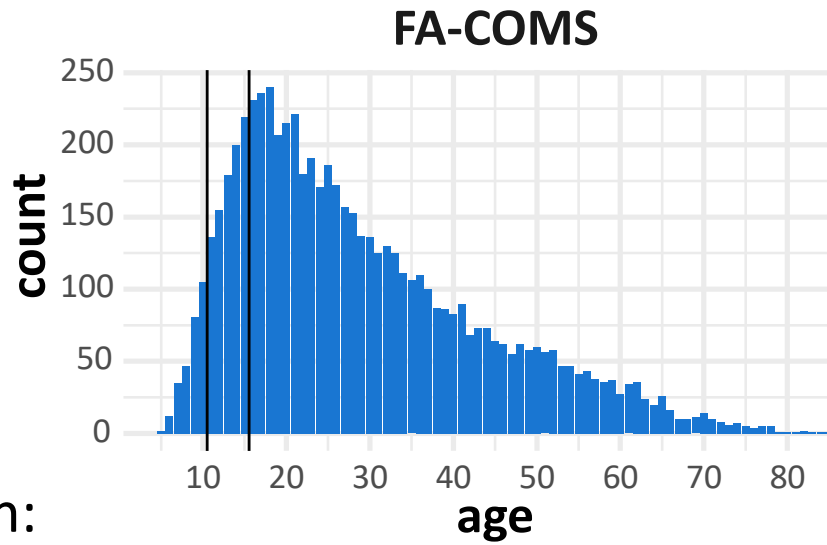
Christian Rummey [1], Jennifer M Farmer [2], David R Lynch [3]

>30 articles published based on the study's data

FARA Friedreich's Ataxia Research Alliance

Data Evolution : Population





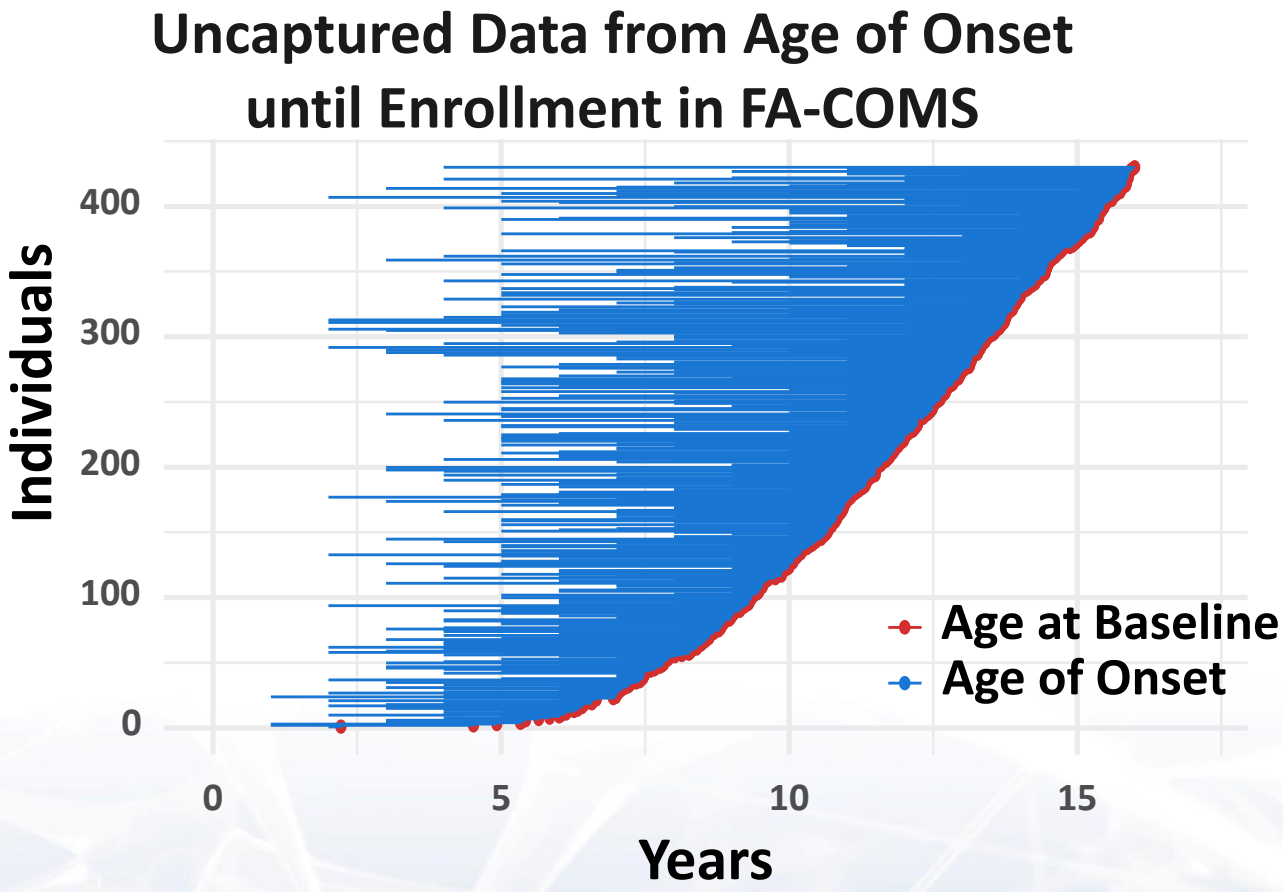
Achieved this shift through:

- Patient community outreach and education
- Added sites with pediatric neurologist PIs
- Additional funding – FDA/NIH grant

Goal:
An enrolled population representative of FA across all stages, genotypes and phenotypes

FARA Friedreich's Ataxia Research Alliance

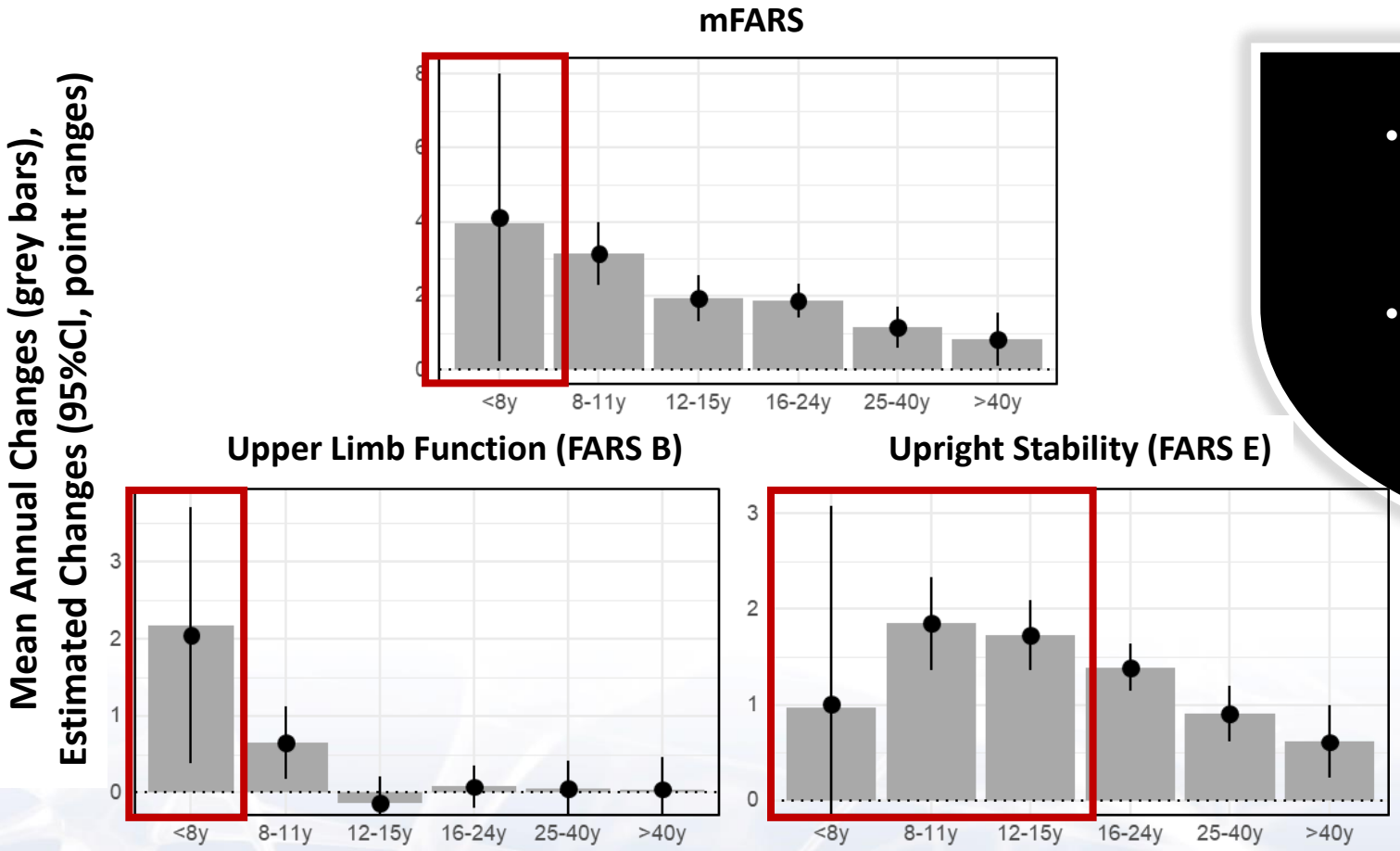
Data Evolution : Assessments



FA primarily begins in childhood

Goal: Capture data beginning at symptom onset

Data Evolution : Reducing variability and increasing consistency with our youngest children



- Variability in mFARS <8 yo
  - Working on more reliable measurements
- Change in Upright Stability reveals milestones gained from birth to 11yo and the tragedy of losing function after 11yo.

Rummey C, et al, Neurology 2022;99:e1499-e1510.

Consistency and Comparability

Duration

Study initiated in 2003 and still ongoing today with strong participant retention

Assessments

The natural history study uses the same assessments as clinical trials

Investigators

Same sites/investigators are conducting both the history study and clinical trials

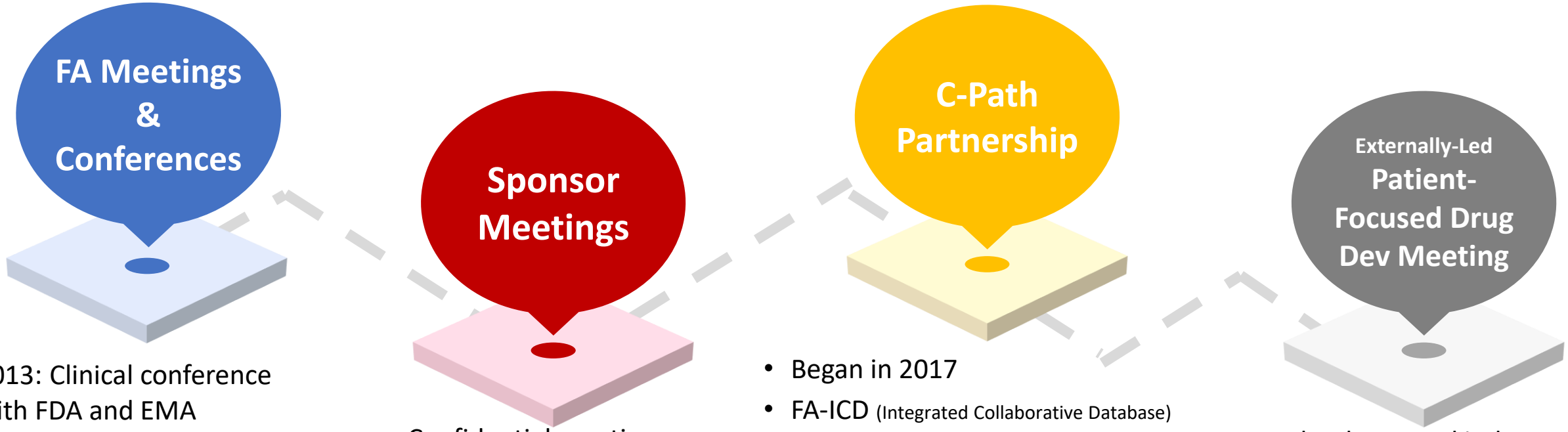
Contemporary Data

Collection of the natural history dataset is contemporary to clinical trials

Collecting Fit-for-Purpose Data **to support Regulatory Decision Making**

FARA Friedreich's Ataxia Research Alliance

Regulatory Engagement



2013: Clinical conference with FDA and EMA

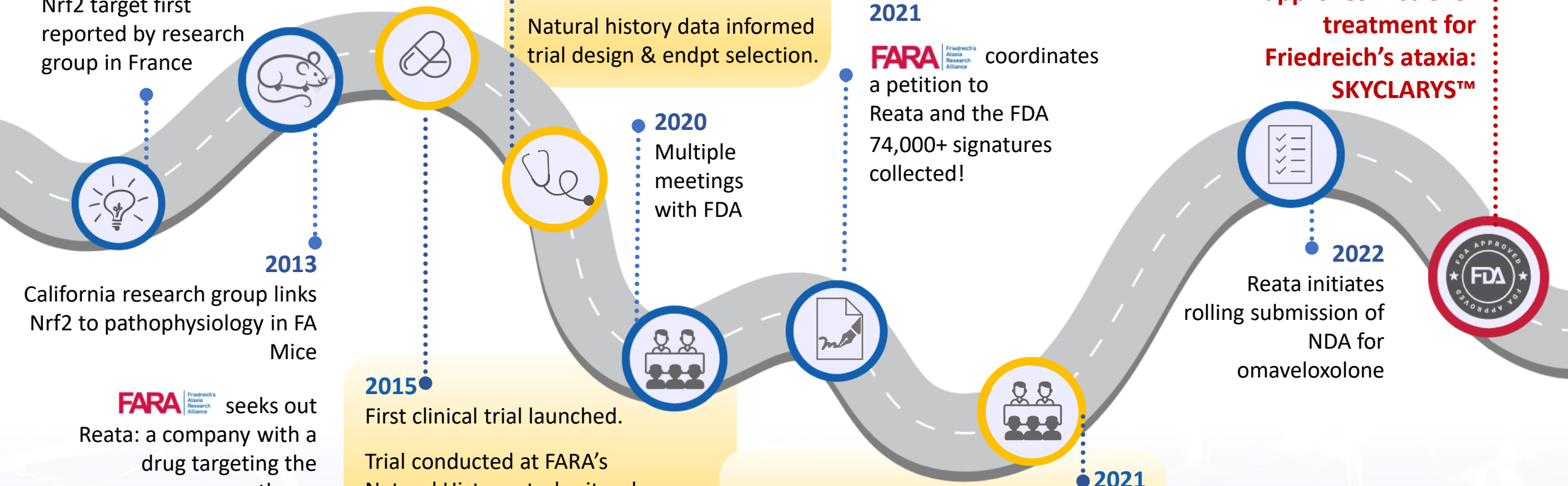
- Presented first 10 years of data
- Informal feedback
- Beginning of evolution from FARS to mFARS

- Confidential meetings
- FARA attends as a guest of our industry partner
- Opportunity to discuss how natural history data informs trial design and endpoints

- Began in 2017
- FA-ICD (Integrated Collaborative Database)
  - Includes FA-COMS & trial data
  - Available to industry sponsors, FDA, and RDCA-DAP
  - Data in CDISC STDM standard

- Helped FDA and industry partners understand the lived experience of FA
- Communicated outcomes that are valued by the community

The Path to the First Approval for Friedreich's Ataxia



2009
Nrf2 target first reported by research group in France

2013
California research group links Nrf2 to pathophysiology in FA Mice

FARA seeks out Reata: a company with a drug targeting the pathway

2015
First clinical trial launched.

Trial conducted at FARA's Natural History study sites, by Natural History study investigators.

2017
Second clinical trial launched.

Natural history data informed trial design & endpt selection.

2020
Multiple meetings with FDA

2021
FARA coordinates a petition to Reata and the FDA
74,000+ signatures collected!

2021
FARA Natural History study provides confirmatory evidence through a propensity-matched study.

2022
Reata initiates rolling submission of NDA for omaveloxolone

2023
FDA approves first-ever treatment for Friedreich's ataxia: SKYCLARYS™

FARA Friedreich's Ataxia Research Alliance

Use of Natural History in Skyclarys Approval

Propensity-Matched Analysis
Comparable Baseline Characteristics

Demographics and baseline characteristics balanced between the two groups

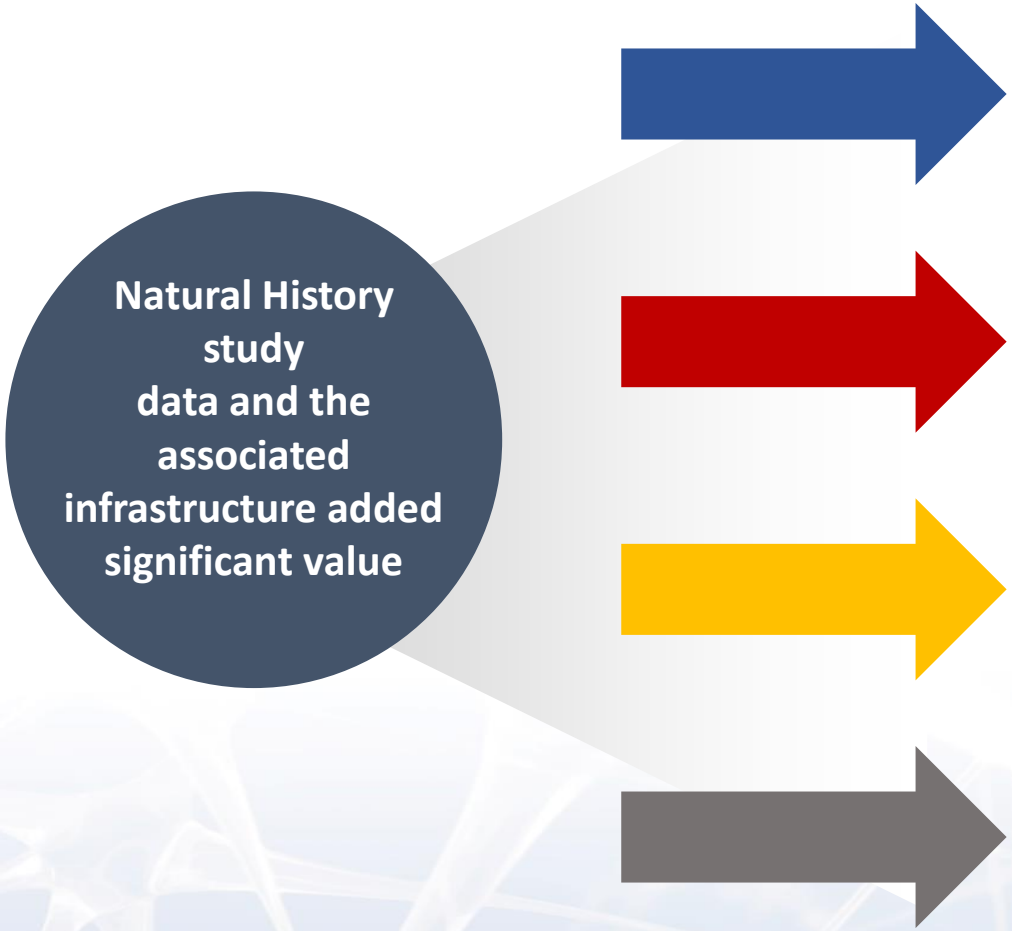
Median treatment/follow-up duration of approximately 3 years

Demographics and Baseline Characteristics for Primary Pooled Population

Characteristic	Statistic	Matched FA-COMS (n=136)	MOXIe Extension (n=136)
Age (years)	Mean (SD)	26.2 (13.72)	26.6 (7.26)
Age at FA Onset	Mean (SD)	15.2 (10.48)	15.5 (5.30)
Sex, Female	N (%)	70 (51.5%)	70 (51.5%)
mFARS	Mean (SD)	41.0 (16.10)	42.2 (12.60)
Gait	Mean (SD)	2.7 (1.69)	2.8 (1.36)

This analysis served as one piece of confirmatory evidence for the NDA submission

FARA's Natural History Study played a pivotal role in the path to the first approval



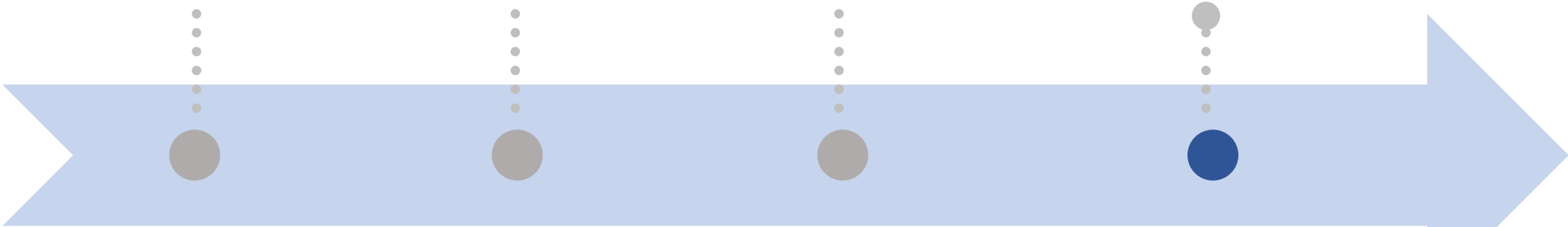
Trial Design: Data from natural history study informed power analysis

Primary Outcome Measure: Regulatory alignment

Data Quality and Consistency: Clinical trial sites were also Natural History Study sites. Study PIs were familiar with the endpoint measurement. Resulted in reduced variability, better confidence in the quality of the data.

Confirmatory evidence: Propensity-matched study was possible because there was a representative cohort enrolled in the natural history study

FARA's Natural History study began 20+ years ago



FARA launches Clinical Outcome Assessments study.

Meeting with FDA to validate endpoints.

FARA's Natural History study provides confirmatory evidence through a propensity-matched study.

Leads to first approval for Friedreich's ataxia.

Continued investment.

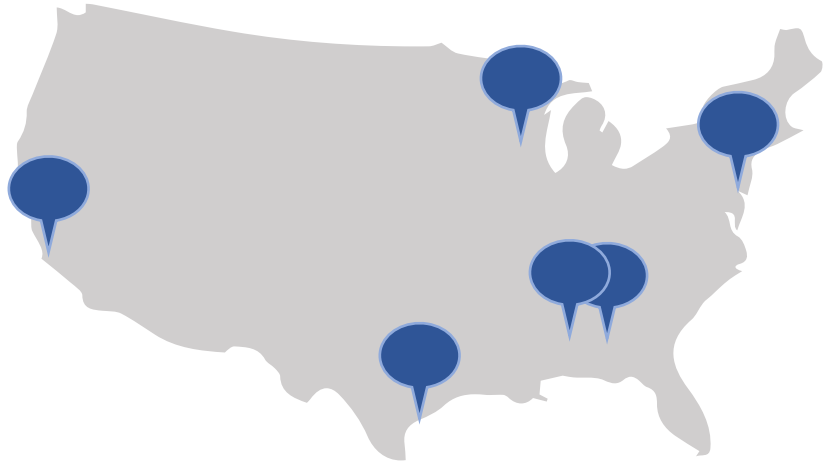
Positioning to support tomorrow's clinical trials.

Keeping the data contemporary.

Developing and validating the next generation of clinical trial endpoints.

Global reach.

Expanding Global Reach



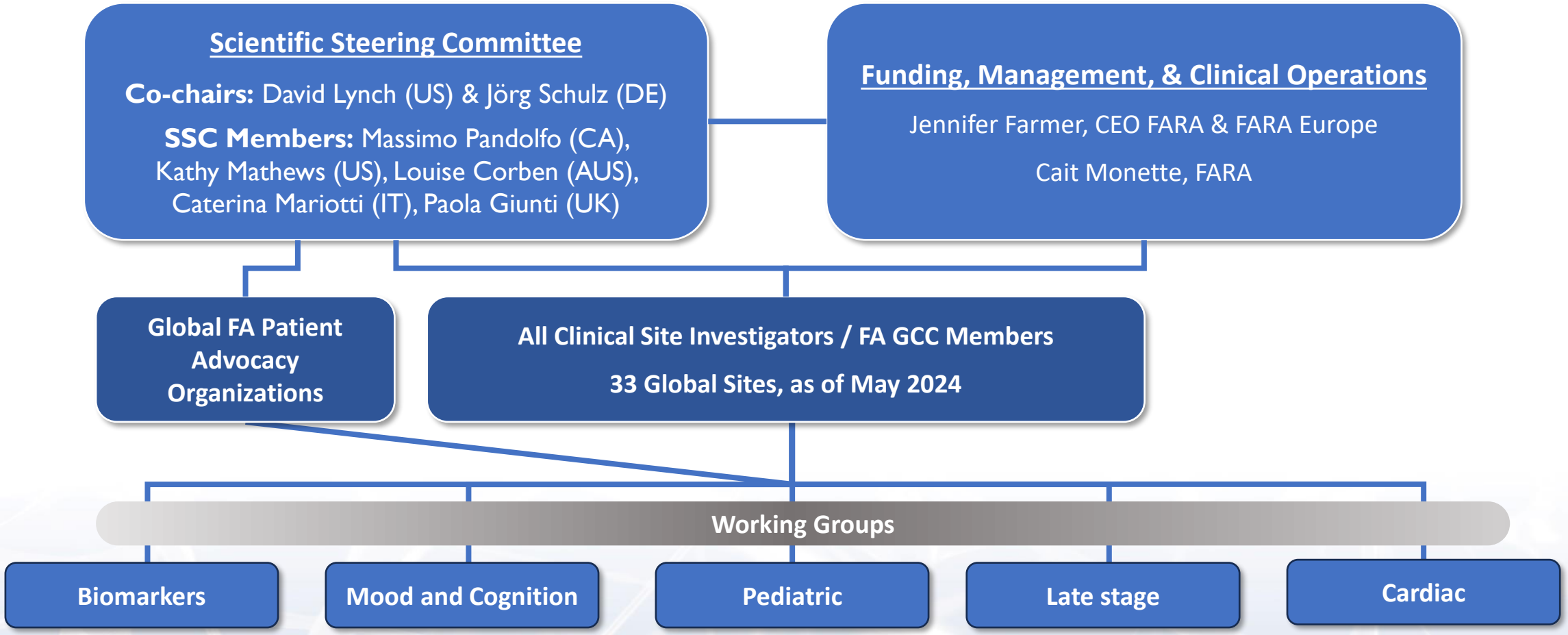
Started with 6 sites across the USA

Grown to 33 sites across 5 continents

Focused on:

- **Adding sites**
- **Funding for travel**
- **Enrolling subjects in multiple studies at the same visits**

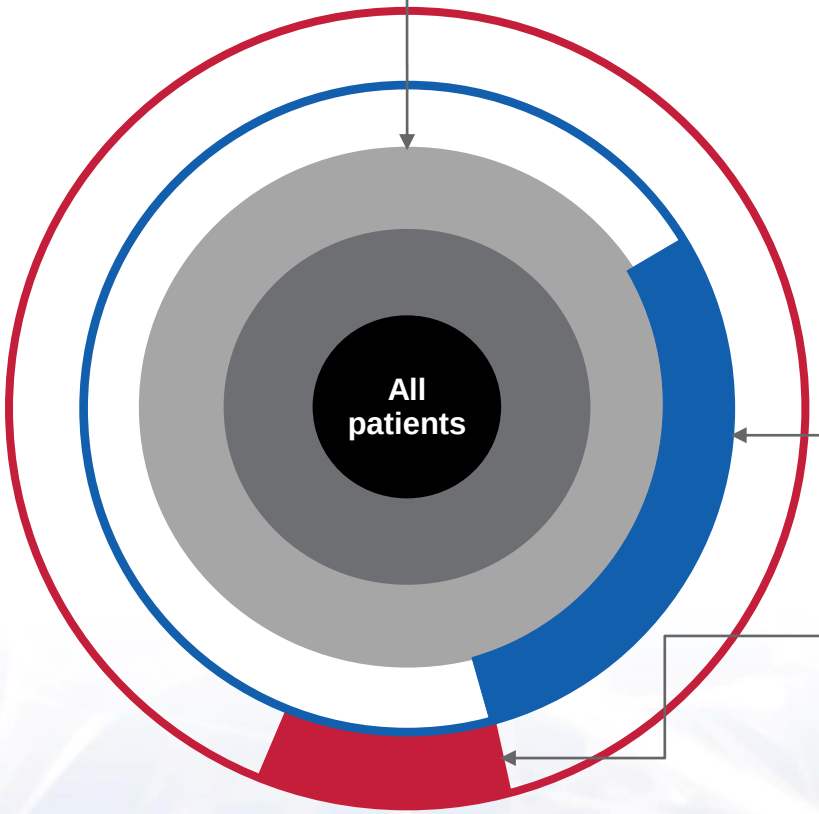
THE FA GCC GLOBAL CLINICAL CONSORTIUM



UNIFAI Study
Natural History Enrollments

Core data elements

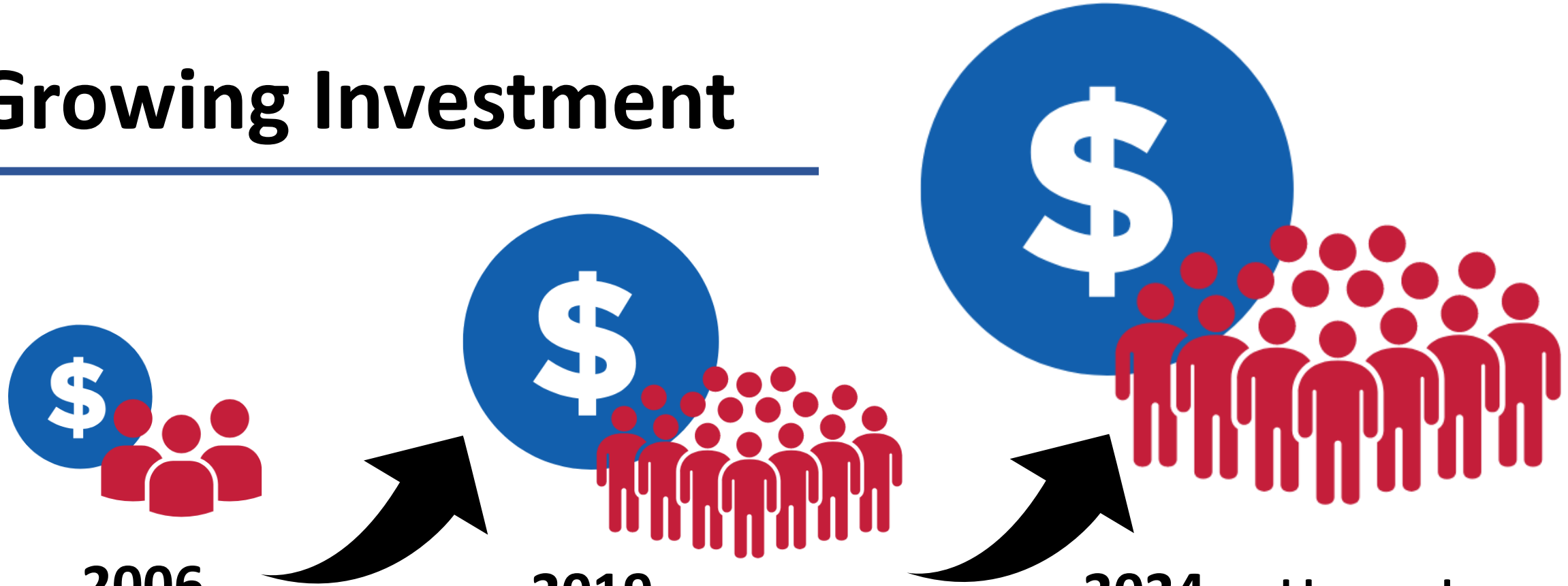
Supplemental tests and surveys



Other FA trials
(Industry and Academic Partnerships)

Other non-interventional studies
(e.g. Biomarker or Pediatric substudies)

Growing Investment



2006

$175,000

150 subjects

6 sites

2019

$1,000,000

>1,000 subjects

14 sites

2024 and beyond

$2,000,000

>3,000 subjects

33 sites

Looking ahead: Expanding and Improving

Capture data that describes the earliest onset of disease

Refine outcome measures for young children

Data collection in late stages of disease, despite the challenges of travel

Study population should be contemporary with the population

Longitudinal data answers basic questions and prompts a new round of deeper inquiries

Thank You!

Acknowledgements:

FA-COMS Site Investigators

Friedreich's Ataxia community

for participating in our natural history study, clinical trials, and for raising funds to enable these efforts

FARA Friedreich's Ataxia Research Alliance

CRITICAL PATH INSTITUTE

RARE AND ORPHAN DISEASE PROGRAMS

Collecting Fit for Purpose Data to Inform Regulatory Decision Making

Collin Hovinga, PharmD, MS, FCCP

VP Rare and Orphan Diseases

Building a rare disease community that works. Together.

c-path.org

5-13-2024

Practical Considerations

- Non-interventional/observational studies or registries to understand the clinical course of a rare disease
- Capture of real world data longitudinally with an intended regulatory use
- Data sharing considerations
- Examples (trial simulation, disease staging)

Fit for Use Data Considerations

Reliable

Represents the intended underlying medical concepts and thus are considered trustworthy and credible

Relevant

Represents the population of interest and can answer the research question in the clinical context of interest

First Step-Preparation Work

- Begin with the end in mind
- Gather input and landscape what has been done
  - Get input from persons with lived experience, clinicians
  - Literature review
  - Define the unmet need, avoid duplication
- How are you going to collect the data and from whom?
- Refine data collection strategy to sufficiently address your questions but not overly burdensome
- Use global unique identifiers to account for participation in multiple research efforts

Protocol Elements

Population*	• Inclusion/exclusion criteria • Demographics • Concurrent treatments	• Consider all comers vs subpopulations • Presymptomatic vs symptomatic
Disease-related*	• Signs and symptoms and severity • Age at onset/diagnosis • Family history • Genotype • Biomarkers	• Identify areas of interest in multiorgan impacted disease (brain vs liver?)
Outcome assessments	• Clinician/observer reported outcomes • Patient reported outcomes • Measurement scales • Assessments/tests (MRI, FVC, labs) • Interviews/free text diaries	• Exploratory, clinical vs regulatory grade • Qualitative • Describe measurement methods and how the test was performed

* Variables that could be covariates or be used to enrich the study population or usefully for matching criteria (external controls)

Protocol Elements

General methods	• Who/where/how/data collected? • Duration of study overall and for the subject • Schedule of events • Number of sites • Total N	• Clear, standards, definitions and measurement methods • Consider forms with structured data elements
Analysis Plan	• Statistical methods will be based upon your questions • Inter/intra-rater reliability for assessments • Plan for analyzing with missing data or subjects lost to follow up	• Consider sources of bias • Interim analysis plans may help identify high sources of variability • Are raw measurements being collected vs algorithm derived data?
Quality	• Audit plan and documentation/trail • Quality checks and correction • Data access and reproducibility • Amendments-continued relevance and updates	• Documentation of amendments and justification • Can the data be readily reproduced? • Includes security • Protections

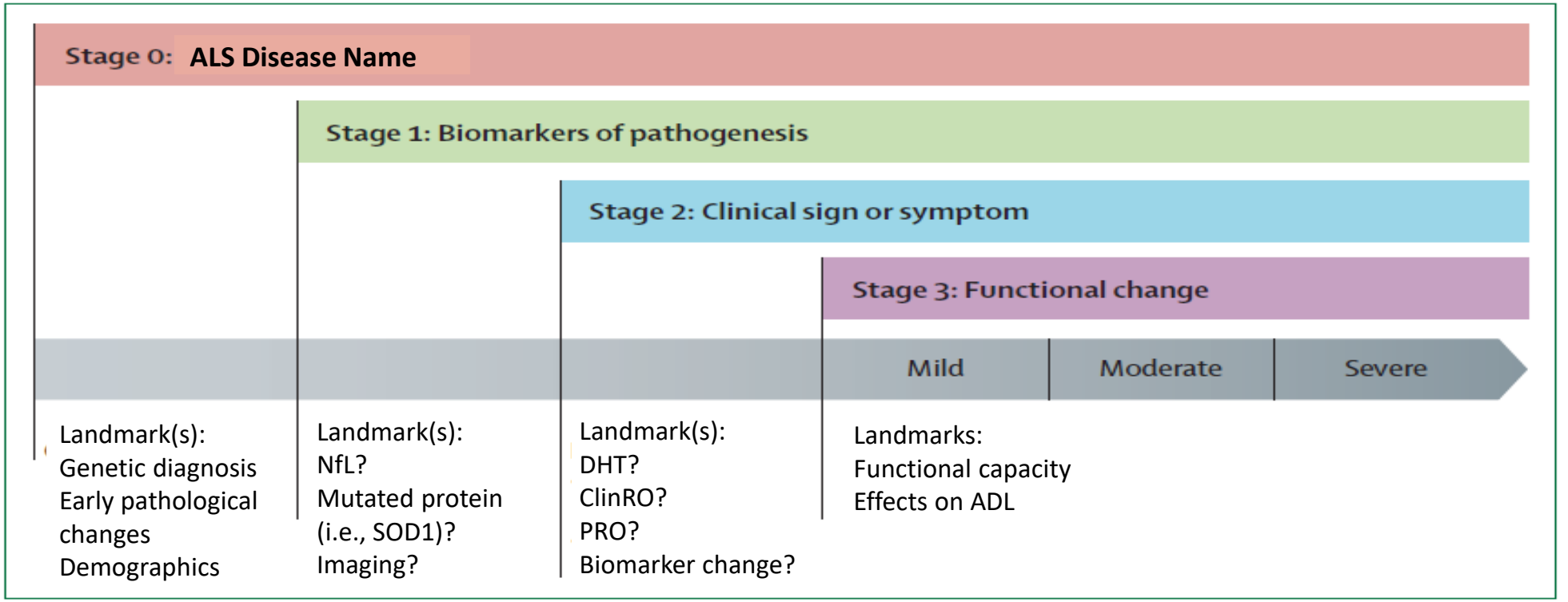
Clinical Outcome Assessments

- Priorities in natural history studies should consider those that have been associated with measuring clinical benefit (improvement in how a patient feels, functions or survives)
- Should be meaningful to the patient
- Example: May not provide a clinically meaningful information
  - Clinician reporting exam changes of decreased vibratory sense
  - Changes may suggest a change in the disease status but do not reflect any impact on patient symptoms or daily functioning

- Example: Does provide clinically meaningful information
  - Numbness in hands that interferes with the ability to button clothes
  - Weakness in hands that interferes with ability to hold spoon and eat

- Make sure that the COA has support for its use in your rare disease population (unless that's planned)
- Methods to collect and assure reproducibility should be described

Framework for Biology-Driven Disease Staging



Each data field should have descriptions and information (meta data) about how and when it is collected.

Abbreviations:
NfL = neurofilament light chain
DHT = digital health technology
ClinRO = clinician reported outcome
PRO = patient reported outcome
ADL = activities of daily living

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

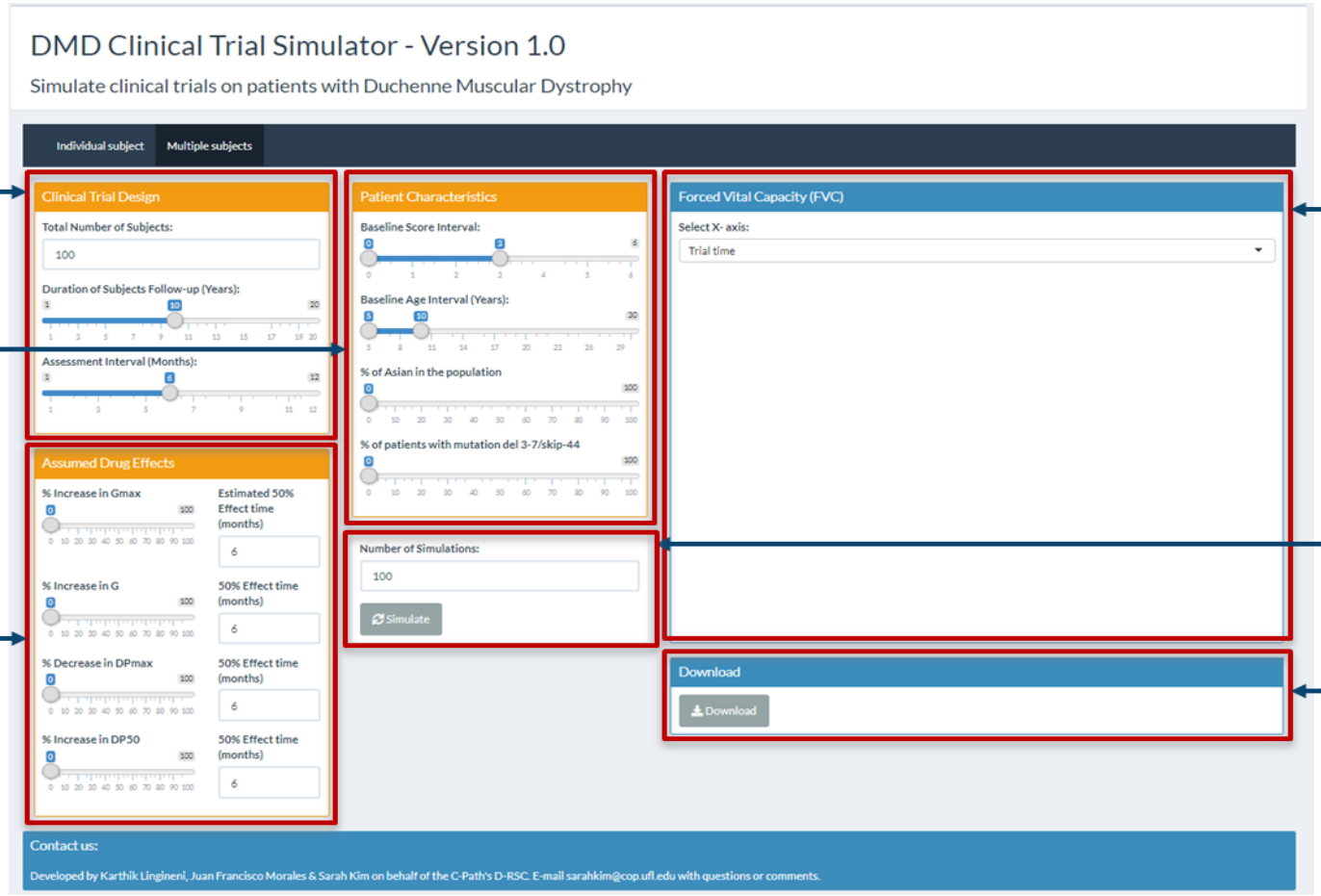
Clinical Trial Simulation Tool

CRITICAL PATH INSTITUTE

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

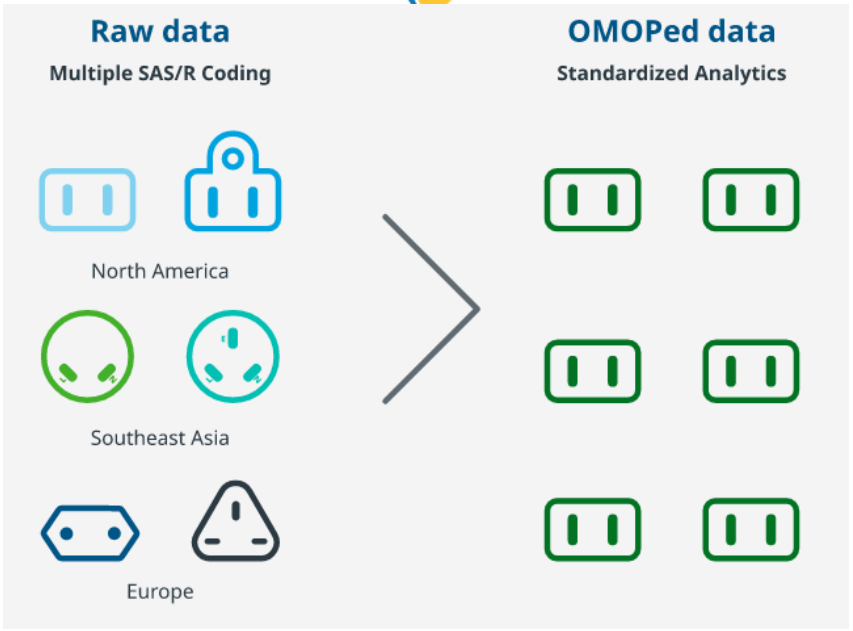
A Model-based Clinical Trial Simulation Tool to Optimize Clinical Trial Design of Studies to Investigate Efficacy of Potential Therapies for Duchenne Muscular Dystrophy Briefing Document submitted to the FDA's Fit-for-Purpose Initiative Consultation and Advice pathway. Revisions submitted to FDA/EMA

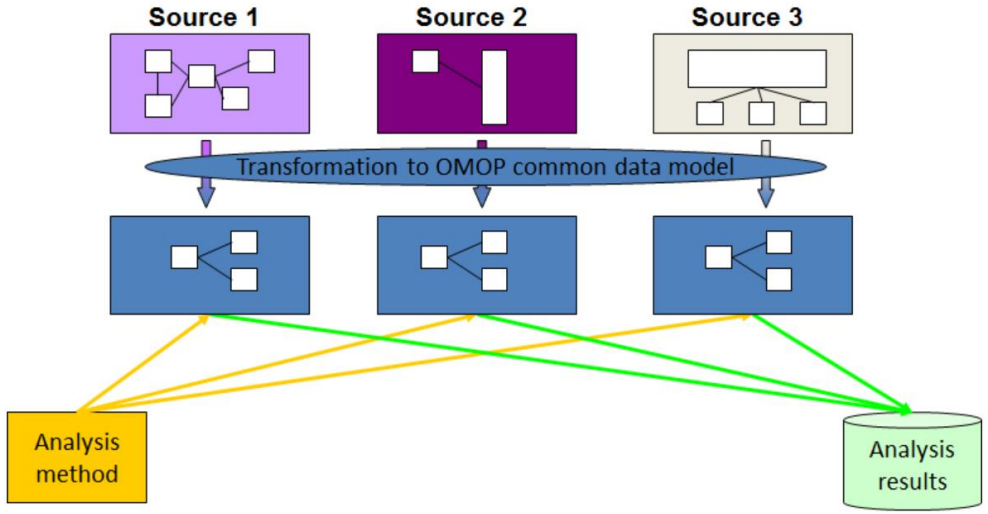
Data Standard Considerations

- Data dictionary (meta data) describing database/tables, variable definitions and standards should be outlined prior to collection of data is essential

- Data can be further standardized to a common data model to depending on the intended audience and use case

- Common data models (including terms, format and vocabularies) allow for data from different sources to be combined more reproducibly
  - SDTM-CDISC
  - OMOP





Sharing of Data IRB-Considerations “Anonymized” vs. “De-identified” Data

- **Anonymized**: Identifiers are removed from patient data, and ***no code exists*** to link patient identifiers to patient data
- **De-identified**: Direct identifiers are removed from patient data, but ***a link exists*** between coded data and identifiers
  - ***Coded link not shared***: *Individuals associated with the creation of the data maintain a link, but the link is not shared with investigators using the data for research.*
  - **Coded link shared**: The link is shared with investigators using the Study/Registry data for research.

Example Consent Form Language for Data Sharing

- *"To ensure that your information collected for this Natural History/Registry will be kept private, your name or other information that could be used to identify you will not be used whenever possible. A code will be used to identify your information, and the key linking the code to information that could be used to identify you will not be shared, except with others as needed to manage the Registry."*

- *"Identifiers will be removed from your identifiable private information or identifiable biospecimens collected for this Study/Registry and then your information/biospecimens will be used for future research studies or distributed to other investigators for future research studies without additional informed consent."*

THANK YOU!

Questions?

Building a rare disease community that works. Together.

c-path.org

Case Example:
Nulibry for molybdenum cofactor deficiency

Presenters

Ronen Spiegel, MD
Emek Medical Center

Liza Squires, MD
Sentynl Therapeutics

REAGAN-UDALL FOUNDATION FOR THE FDA

Leveraging Natural History Data for Rare Disease Drug Development and Approval:

Demonstrated Increased Survival in MoCD Type A Patients Treated With Fosdenopterin

Ronen Spiegel, MD

Clinical Associate Professor, Director of Pediatric B Department,
and Head of Center for Rare Diseases, Emek Medical Center, Afula, Israel

Liza Squires, MD

Former Chief Medical Officer, Origin Biosciences
Sentynl Therapeutics, Inc.

SENTYNL THERAPEUTICS, INC.

Molybdenum Cofactor Deficiency (MoCD) Type A

- Rare, autosomal-recessive in-born error of metabolism caused by pathogenic variants in the *MOCS1* gene[1,2]
- Rapidly progressive, irreversible neurologic damage due to loss of the MoCo-dependent enzyme sulfite oxidase, resulting in neurotoxic sulfite accumulation[1,3]
- Patients rarely survive beyond the first few years of life[1]
- Early diagnosis is crucial[4]
- Biomarkers[1,4]
  - Decreasing, low, or undetectable plasma or urinary uric acid
  - Increased plasma and urine xanthine/hypoxanthine
  - Increased urinary sulfites
  - Increased SSC in the plasma and urine

Signs and symptoms often present in the first hours to weeks of life[1]

Intractable Seizures

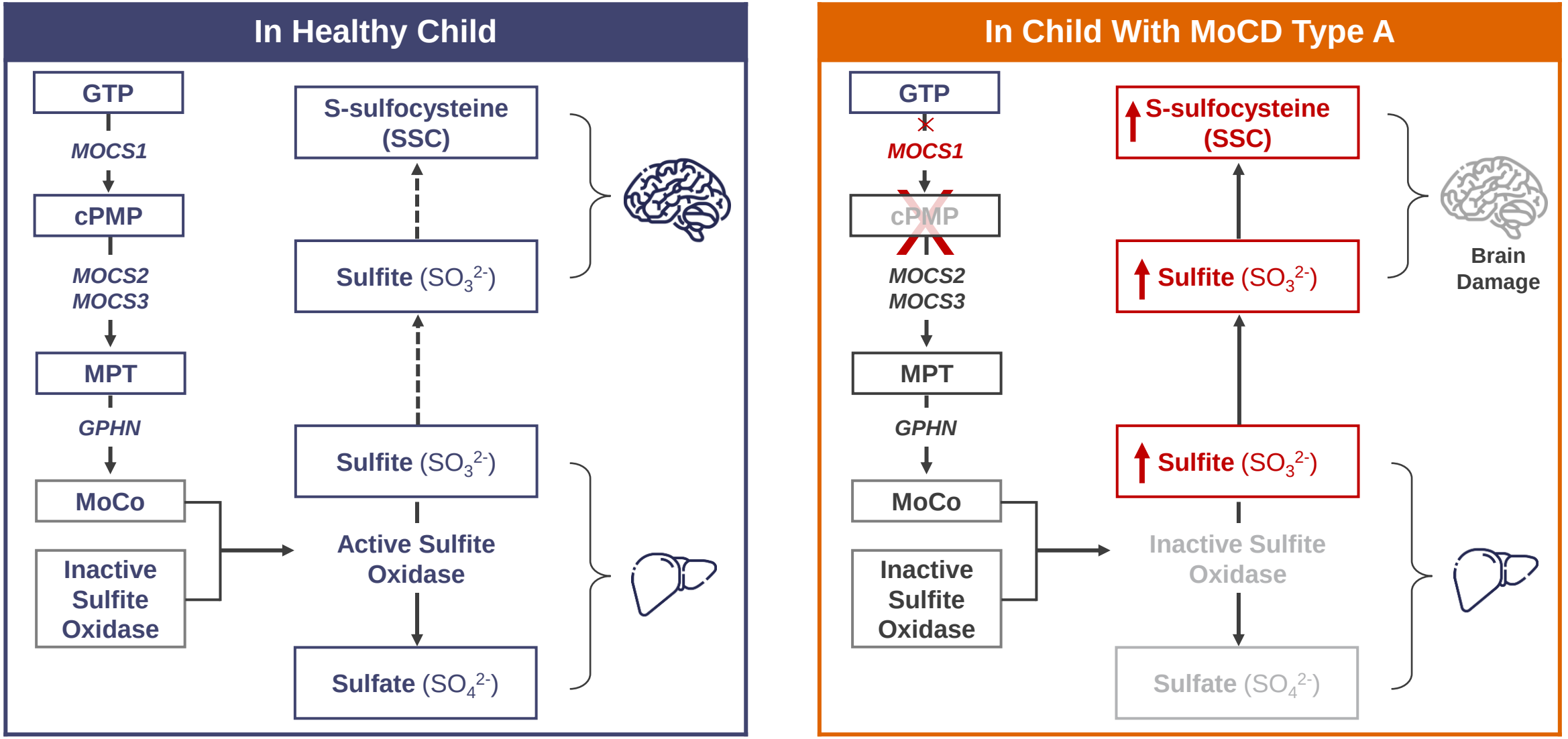
Feeding Difficulties

Abnormal Neuro Examination

MoCD, molybdenum cofactor deficiency; MoCo, molybdenum cofactor; *MOCS1*, molybdenum cofactor synthesis 1; SSC, S-sulfocysteine.

1. Atwal PS, et al. *Mol Genet Metab*. 2016;117:1-4; 2. Reiss J, et al. *Hum Mutat*. 2011;32:10-18; 3. Mechler K, et al. *Genet Med*. 2015;17:965-970; 4. Kumar A, et al. *J Clin Invest*. 2017;127:4365-4378

Biochemical Pathology of MoCD[1-3]



cPMP, cyclic pyranopterin monophosphate; *GPHN*, gephyrin; GTP, guanosine triphosphate; MoCD, molybdenum cofactor deficiency; MoCo, molybdenum cofactor; *MOCS1/2/3*, molybdenum cofactor synthesis 1/2/3; MPT, molybdopterin.

1. Reiss J, et al. *Hum Mutat*. 2011;32:10-18; 2. Atwal PS, et al. *Mol Genet Metab*. 2016;117:1-4; 3. Kumar A, et al. *J Clin Invest*. 2017;127:4365-4378.

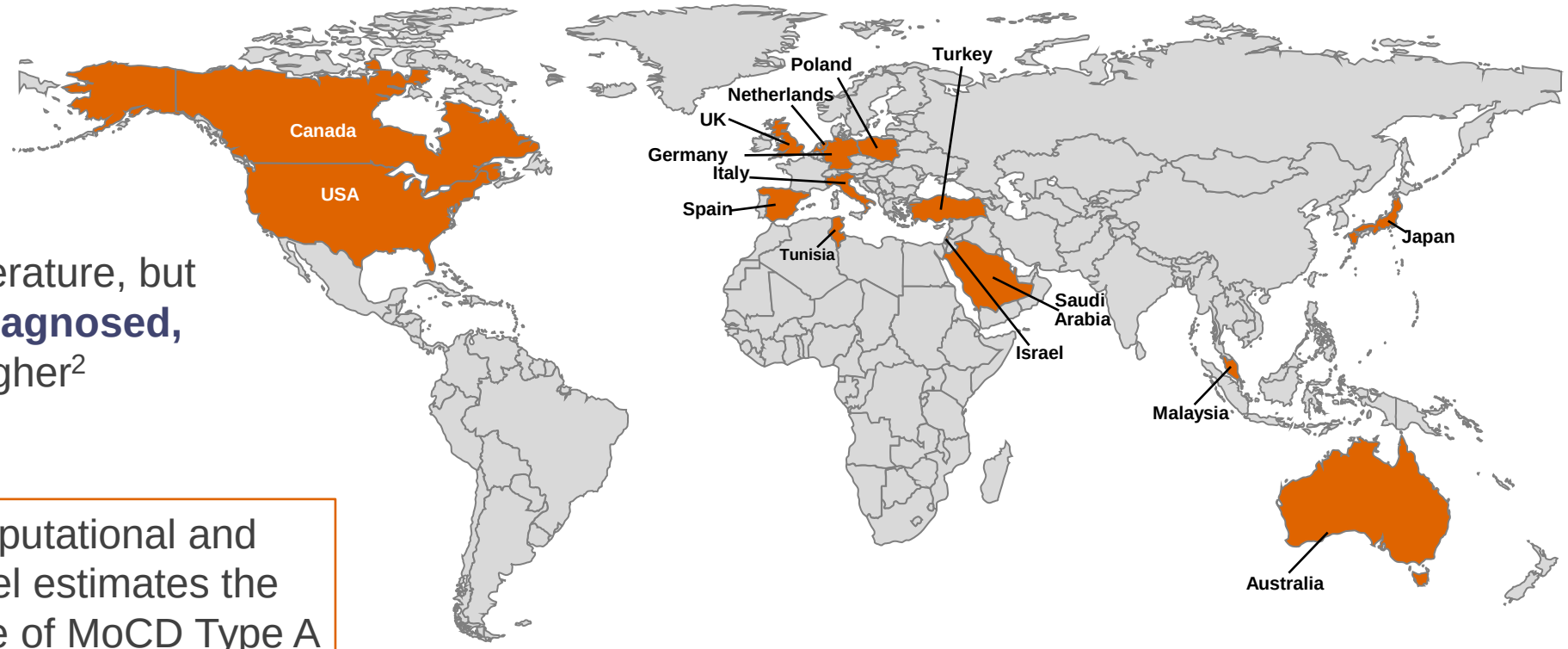
Epidemiology of MoCD: An Ultra-Rare Disease

MoCD Occurs Worldwide, With "Hot Spots" in Multiple Countries[1]

MoCD is an **ultra-rare, pan-ethnic** disease

>100

cases reported in the literature, but **MoCD is likely underdiagnosed,** and numbers may be higher[2]



An iterative computational and biochemical model estimates the worldwide incidence of MoCD Type A is **1:342,000 to 411,000** births[3]

MoCD, molybdenum cofactor deficiency.

1. Spiegel R, et al. A natural history study of molybdenum cofactor and isolated sulfite oxidase deficiencies. Presented at the 2019 SSIEM meeting; September 3-6, 2019; Rotterdam, The Netherlands; 2. NIH. https://ghr.nlm.nih.gov/condition/molybdenum-cofactor-deficiency. Accessed April 25, 2024; 3. Mayr SJ, et al. Forecasting the incidence of rare diseases: an iterative computational and biochemical approach in molybdenum cofactor deficiency type A. Presented at the 2019 SSIEM meeting; September 3-6, 2019; Rotterdam, The Netherlands.

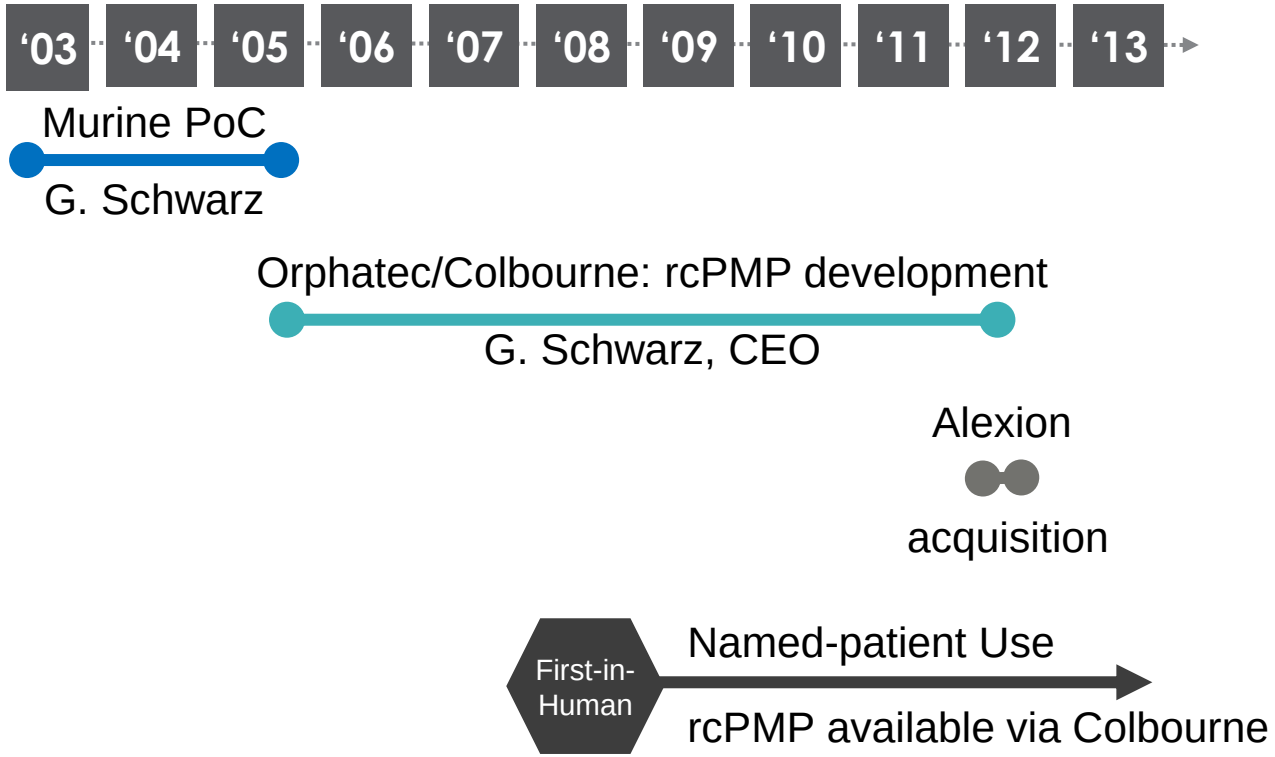
cPMP Replacement Therapy | First-in-Human Experience

- Prof Guenter Schwarz in Cologne, Germany, discovers that **cPMP is produced as a natural chemical byproduct** by *Escherichia coli*
- Selects for **strains of *Escherichia coli*** to manufacture **recombinant form of cPMP**
- Dr Schwarz's lab **tests cPMP in *MOCS1*-knockout mouse model**, showing its potential as replacement therapy
- **First baby is treated** with recombinant cPMP and **shows rapid biochemical response in 2008**
- Colbourne Pharmaceuticals **begins named-patient program** with recombinant cPMP

Dr Guenter Schwarz

cPMP, cyclic pyranopterin monophosphate; MoCD, molybdenum cofactor deficiency; *MOCS1*, molybdenum cofactor synthesis 1.

First 10 Years of Recombinant cPMP Therapy



- **No approved treatments**; supportive care only
- **No patient advocacy group**
- 10 patients with MoCD Type A **treated with recombinant cPMP** gave consent for retrospective data
- Named-patient use, with **each dose prepared by fermentation** in the lab
- **Unethical to initiate a randomized, placebo-controlled trial** in patients with an ultra-rare and fatal disease

cPMP, cyclic pyranopterin monophosphate; MoCD, molybdenum cofactor deficiency; rcPMP, recombinant cyclic pyranopterin monophosphate.

Natural History Study Design (MCD-502)

Multinational, multicenter, retrospective, and prospective study in patients with MoCD or isolated SOX deficiency

Primary Objective

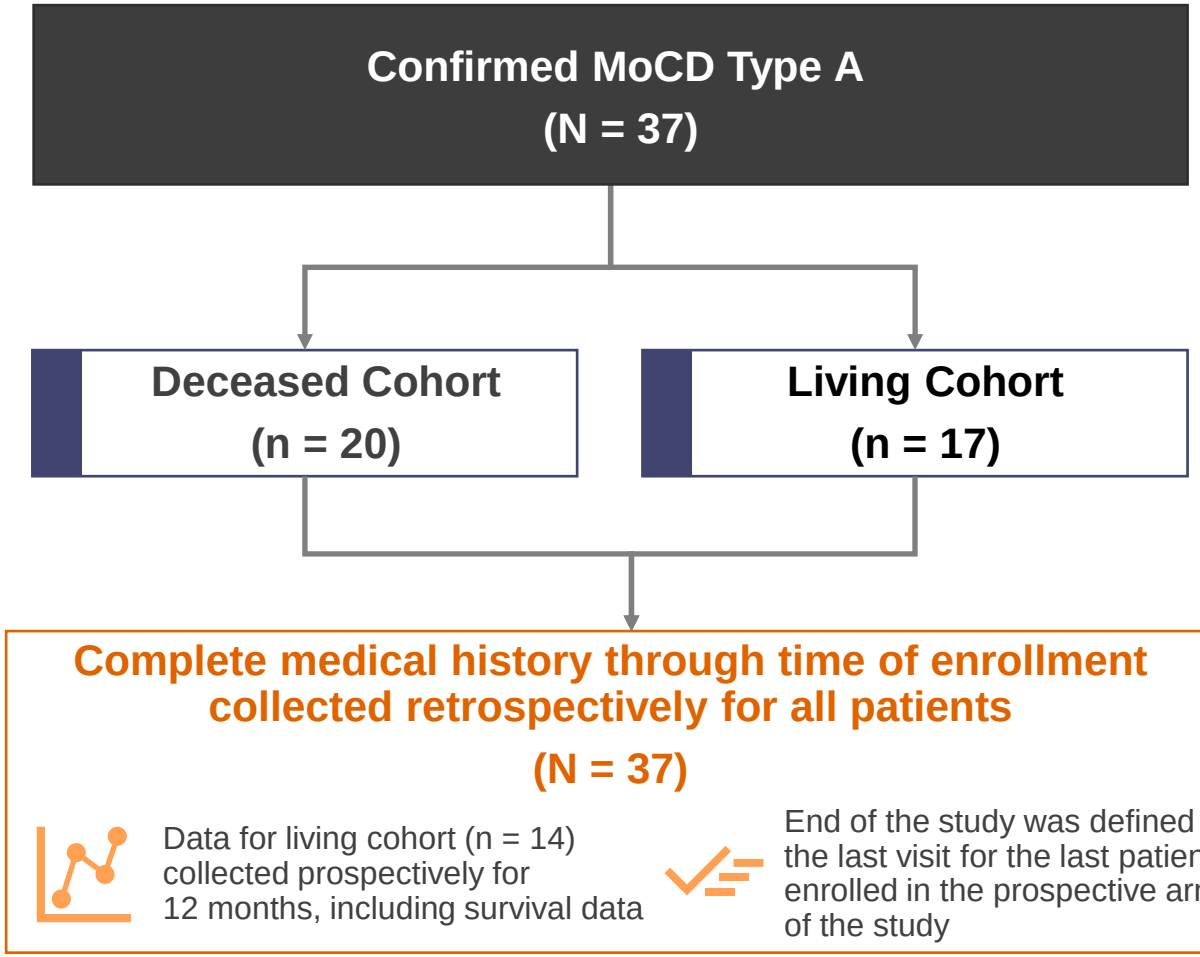
- ✓ To characterize the natural history of patients with MoCD by
  - Documenting the natural progression of the disease
  - Developing a more complete understanding of the phenotype
  - Describing the clinical and biochemical variability of the condition

Inclusion Criteria

- ✓ MoCD or isolated SOX deficiency
  - Clinical and biochemical diagnosis
    - Elevated SSC levels in urine, serum, or plasma
    - Positive urine sulfite dipstick

OR

- ✓ Genetic diagnosis



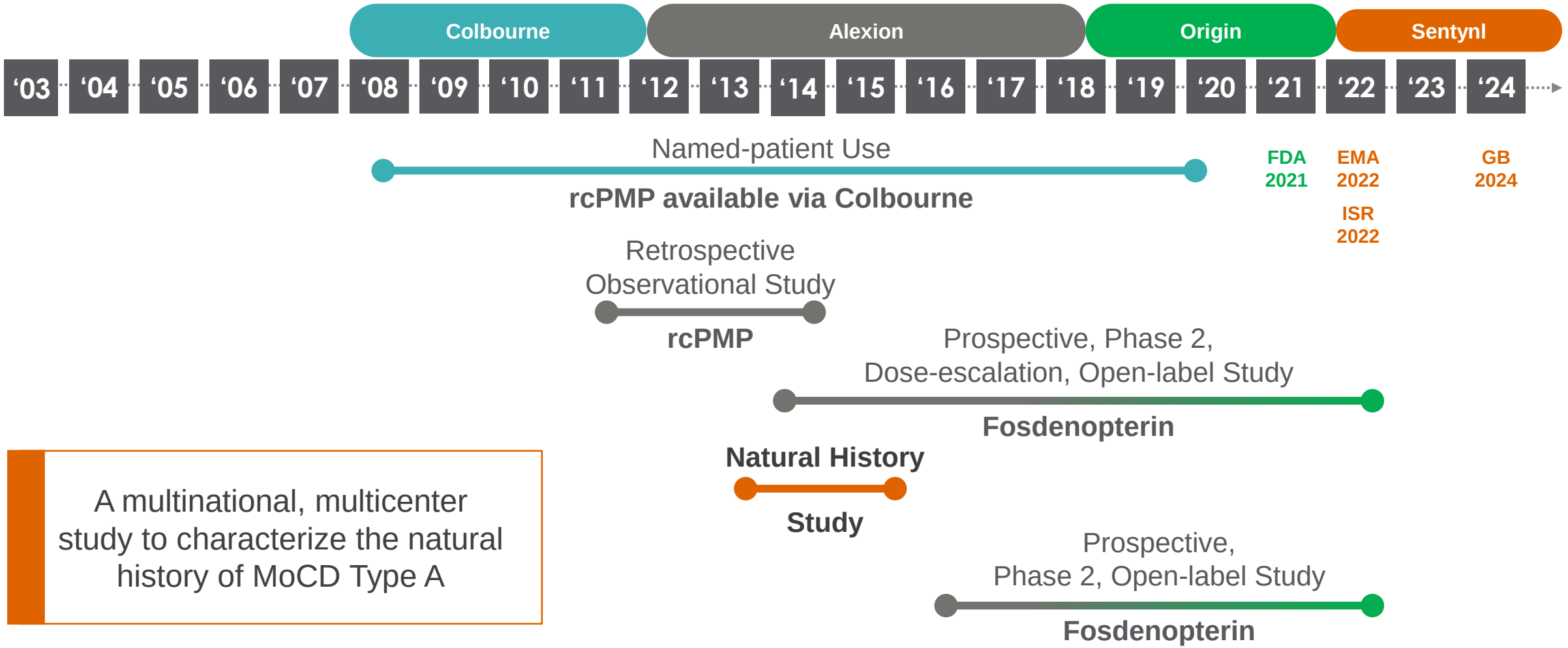
MoCD, molybdenum cofactor deficiency; SOX, sulfite oxidase.

Natural History Data as a Surrogate Placebo Group

SENTYNL THERAPEUTICS, INC.

Developed and approved for use in the US only.

Clinical Development of Fosdenopterin (cPMP)



A multinational, multicenter study to characterize the natural history of MoCD Type A

cPMP, cyclic pyranopterin monophosphate; MoCD, molybdenum cofactor deficiency; rcPMP, recombinant cyclic pyranopterin monophosphate.

cPMP Clinical Development Program: Using Natural History Data

Objectives

- Summarize clinical efficacy of cPMP (inclusive of both recombinant cPMP and fosdenopterin)
  - Retrospective, observational study (MCD-501)
  - Phase 2, open-label, dose-escalation study (MCD-201)
  - Phase 2/3 open-label study (MCD-202)
- Interpret the response to cPMP in patients with MoCD Type A
- Compare the survival rate of children with MoCD Type A treated with cPMP replacement therapy with the survival rate of untreated patients with MoCD Type A from a natural history study

Key Variables Assessed in the Clinical Studies

- Baseline characteristics
- Growth parameters
- Overall survival
- GMFCS-ER
- Biomarkers
- Seizures
- Feeding patterns
- Neurologic examinations
- Developmental assessments

cPMP, cyclic pyranopterin monophosphate; GMFCS, Gross Motor Function Classification System-Expanded and Revised; MoCD, molybdenum cofactor deficiency.

Full Analysis Set

Patients with MoCD Type A treated with cPMP replacement therapy (recombinant cPMP and/or fosdenopterin) from 1 retrospective, observational study and 2 prospective, open-label, single-arm studies (N = 13)

VS

Patients with MoCD Type A who were enrolled in a multinational, multicenter, retrospective/prospective natural history study (N = 37)

cPMP, cyclic pyranopterin monophosphate; MoCD, molybdenum cofactor deficiency.

Patient Demographics

Characteristics, n (%)	cPMP-Treated Patients (N = 13)	Untreated Controls (N = 37)
Male	7 (53.8)	28 (75.7)
Female	6 (46.2)	9 (24.3)
Region of birth		
North America	2 (15.4)	3 (8.1)
Europe	6 (46.2)	14 (37.8)
Rest of world	5 (38.5)	20 (54.1)
Age of first MoCD symptom category		
≤ 28 days	13 (100)	33 (89.2)
> 28 days	0	4 (10.8)

cPMP, cyclic pyranopterin monophosphate; MoCD, molybdenum cofactor deficiency.

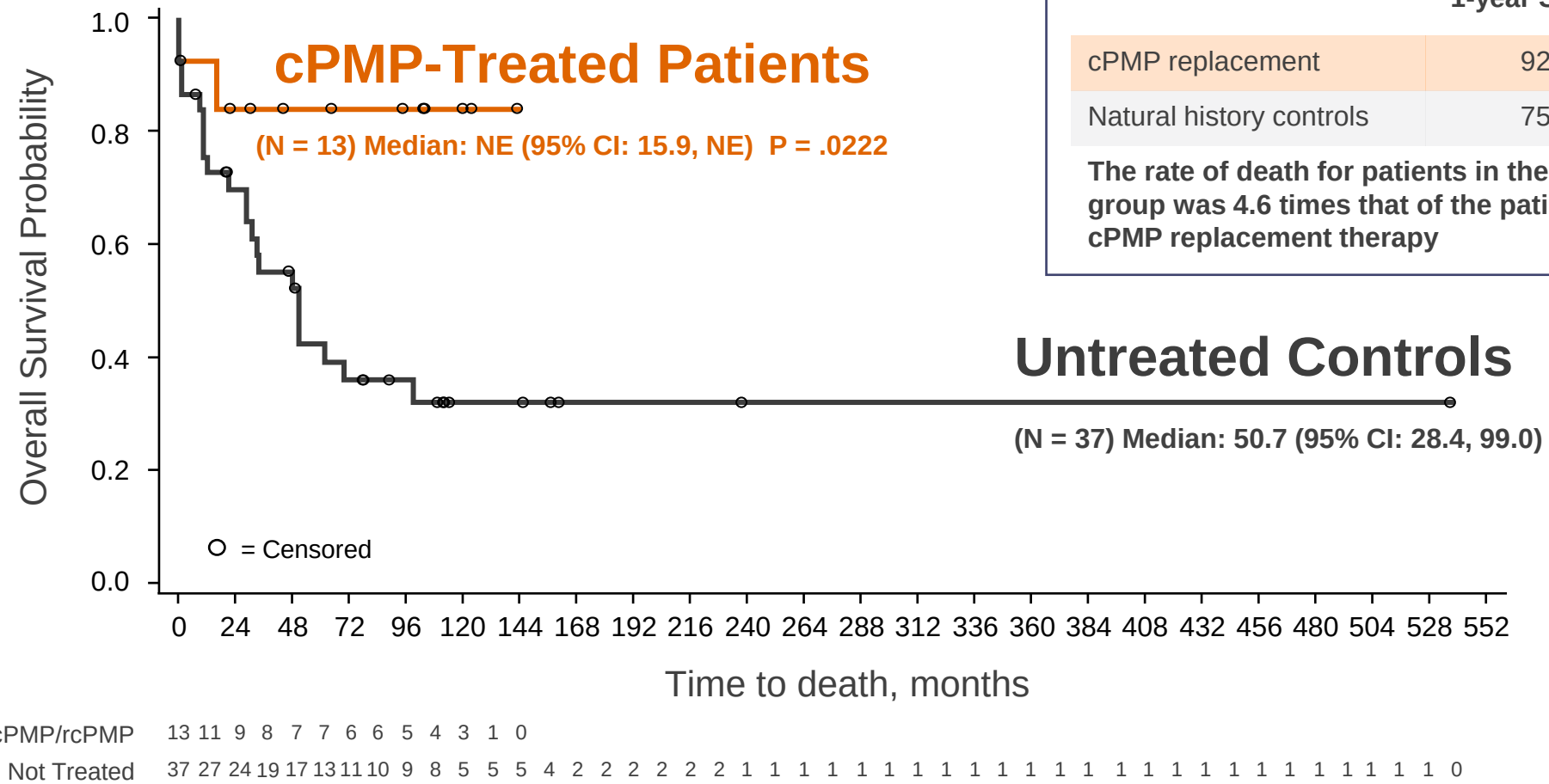
MoCD Presenting Signs and Symptoms

Parameters, n (%)	cPMP-Treated Patients (N = 13)	Untreated Controls (N = 37)
Seizures	9 (69.2)	34 (91.9)
Feeding difficulties	8 (61.5)	31 (83.8)
High-pitched cry	7 (53.8)	16 (43.2)
Exaggerated startle response	5 (38.5)	12 (32.4)
Number of reported other symptoms[a]	21	20

cPMP, cyclic pyranopterin monophosphate; MoCD, molybdenum cofactor deficiency.

[a]Other signs and symptoms included but were not limited to metabolic acidosis, hypertonia, hypotonia, encephalopathy, intracranial hemorrhage.

cPMP Replacement Therapy Improves Overall Survival

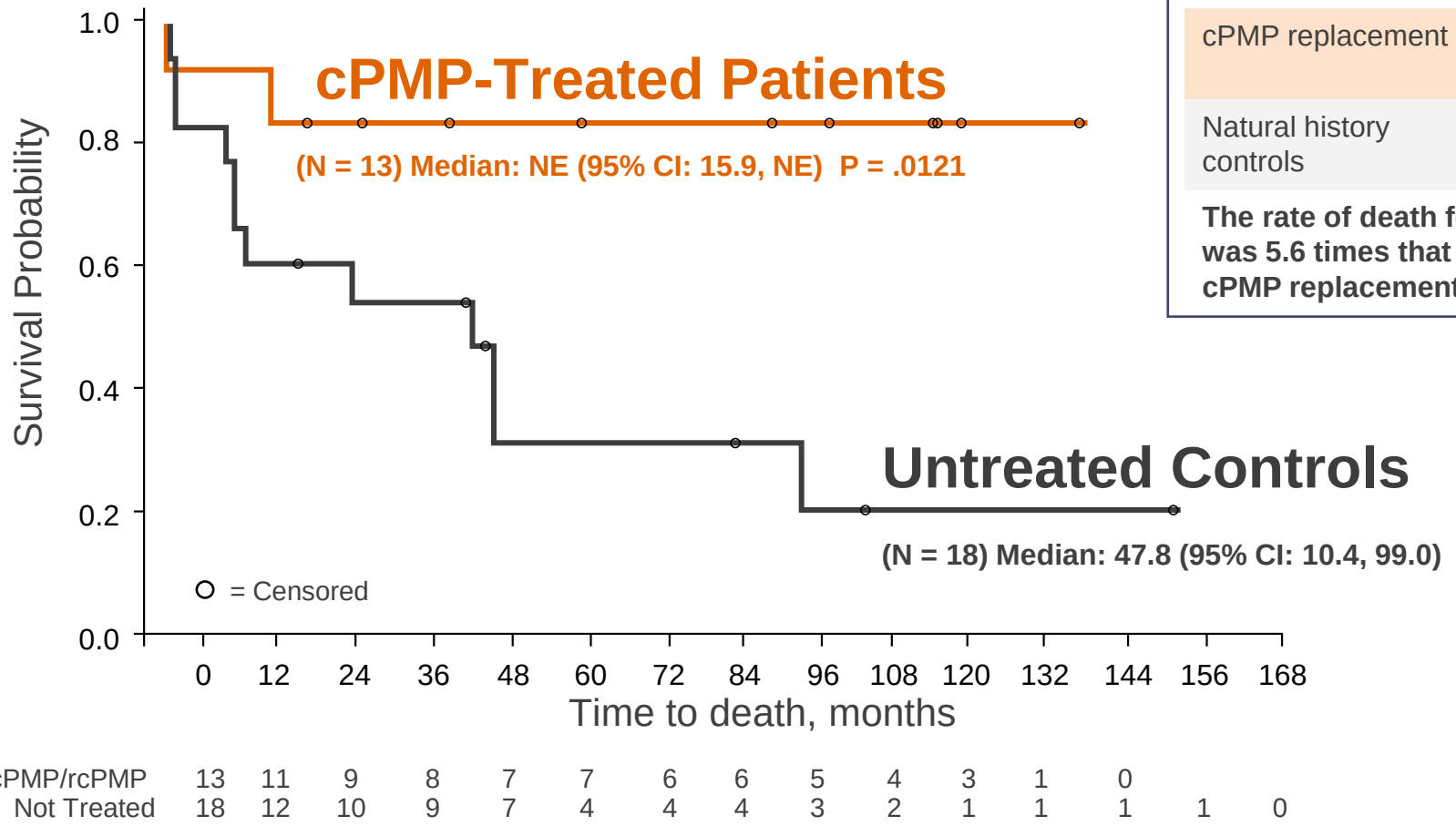


	1-year Survival	2-year Survival
cPMP replacement	92%	84%
Natural history controls	75%	70%

The rate of death for patients in the untreated control group was 4.6 times that of the patients who received cPMP replacement therapy

cPMP, cyclic pyranopterin monophosphate; NE, not evaluable; rcPMP, recombinant cyclic pyranopterin monophosphate.

cPMP Replacement Therapy Improved Overall Survival: Genotype-Matched Controls



	1-year Survival	2-year Survival	3-year Survival
cPMP replacement	92%	84%	84%
Natural history controls	67%	61%	55%

The rate of death for patients in the untreated control group was 5.6 times that of the patients who received cPMP replacement therapy

cPMP, cyclic pyranopterin monophosphate; NE, not evaluable; rcPMP, recombinant cyclic pyranopterin monophosphate.

Urine SSC Levels in cPMP-treated Patients vs Controls

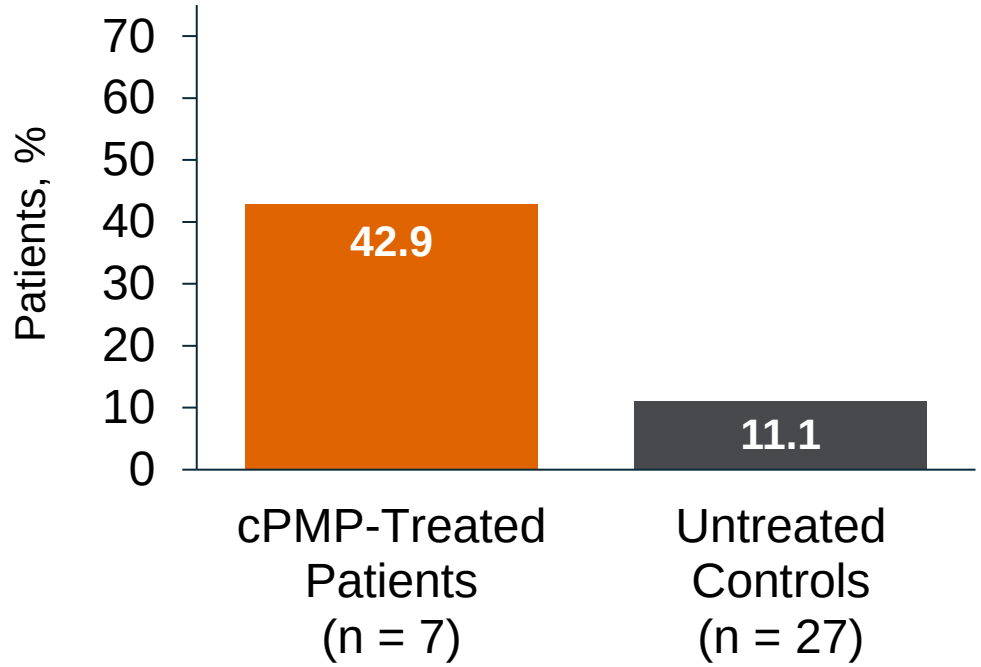
S-sulfocysteine/creatinine, µmol/mmol	cPMP-Treated Patients (N = 12)	Untreated Controls (N = 37)
Baseline, first value, n	12	22
Mean (SD)	181.1 (282.53)	136.3 (87.21)
Last visit, n	12	22
Mean (SD)	11.4 (6.87)	156.6 (100.70)
Change to last visit, n	12	18
Mean (SD)	−169.6 (282.44)	24.8 (104.61)

Pathological values of S-sulfocysteine are > 50 µmol/mmol creatinine

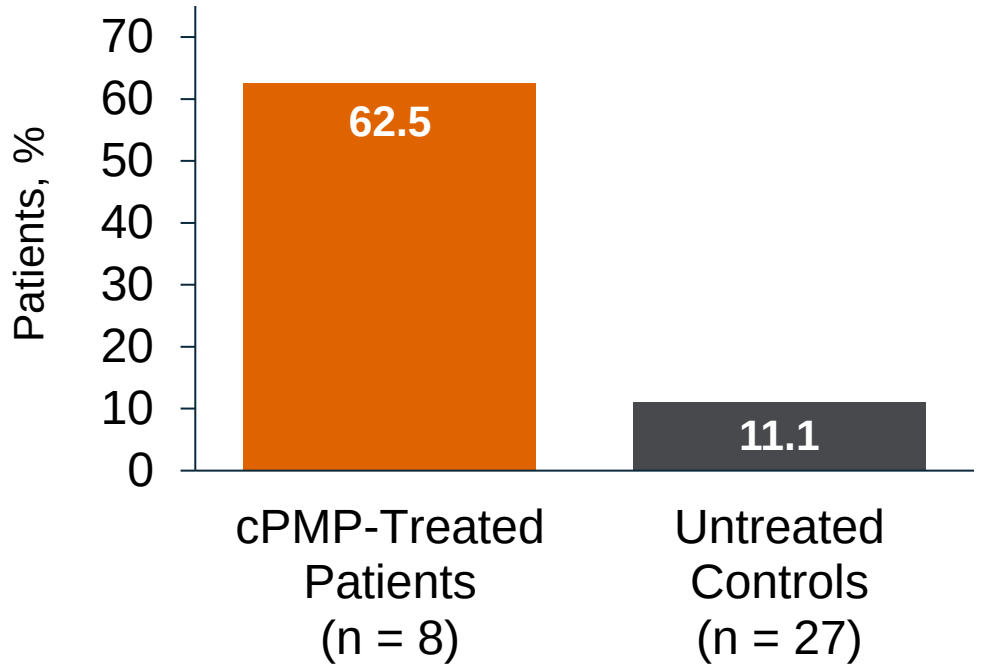
cPMP, cyclic pyranopterin monophosphate.

Sitting Unassisted in cPMP-Treated Patients vs Controls

Unassisted Sitting by 12 Months[a]



Unassisted Sitting at Any Time[a]

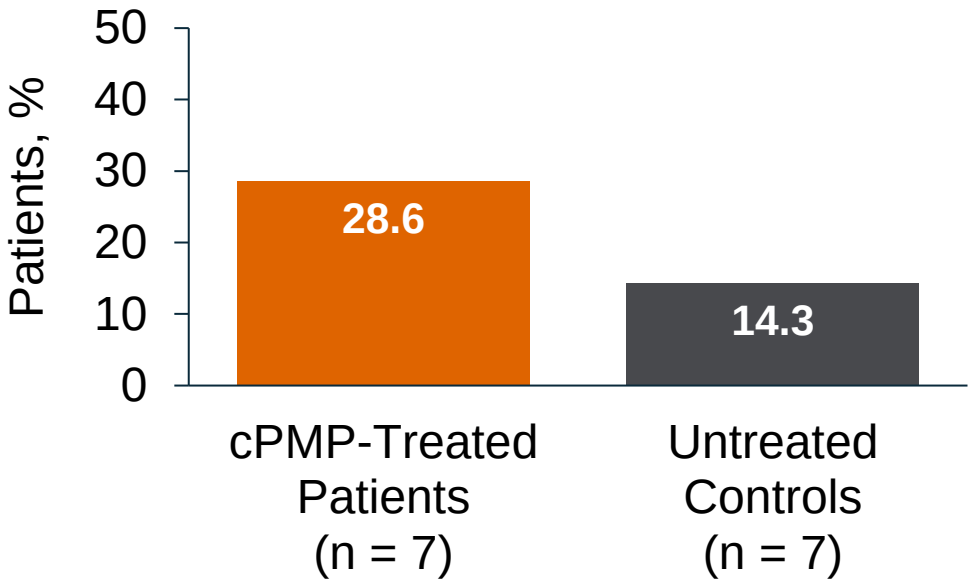


cPMP, cyclic pyranopterin monophosphate.

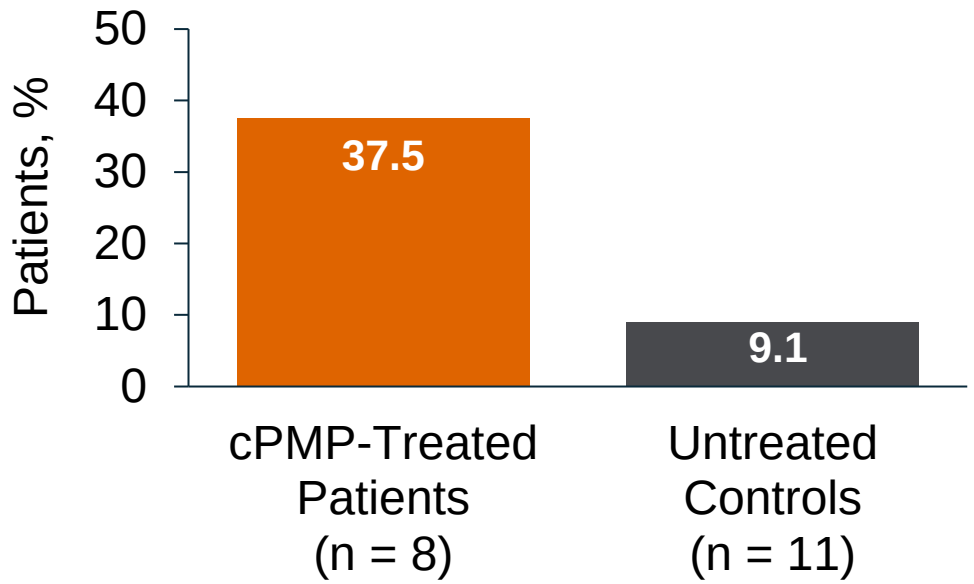
[a]Unassisted sitting was measured as ability to sit independently for 30 seconds.

Achievement of GMFCS Level 1 in cPMP-Treated Patients vs Controls

Achieving GMFCS-ER Level 1 at Month 12



Achieving GMFCS-ER Level 1 at Last Visit

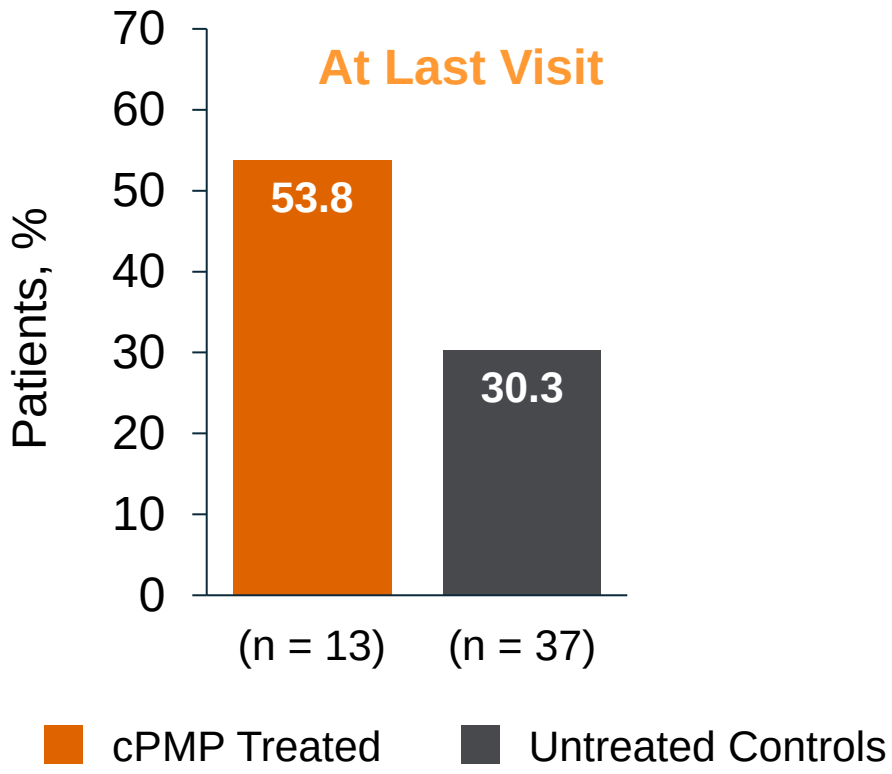


GMFCS-ER Level I represents the highest-rated functioning level on this scale. Children aged 2 and older who are rated as Level I are able to walk independently and, by age 6, can perform higher-level gross motor skills such as running, jumping, and stair climbing.

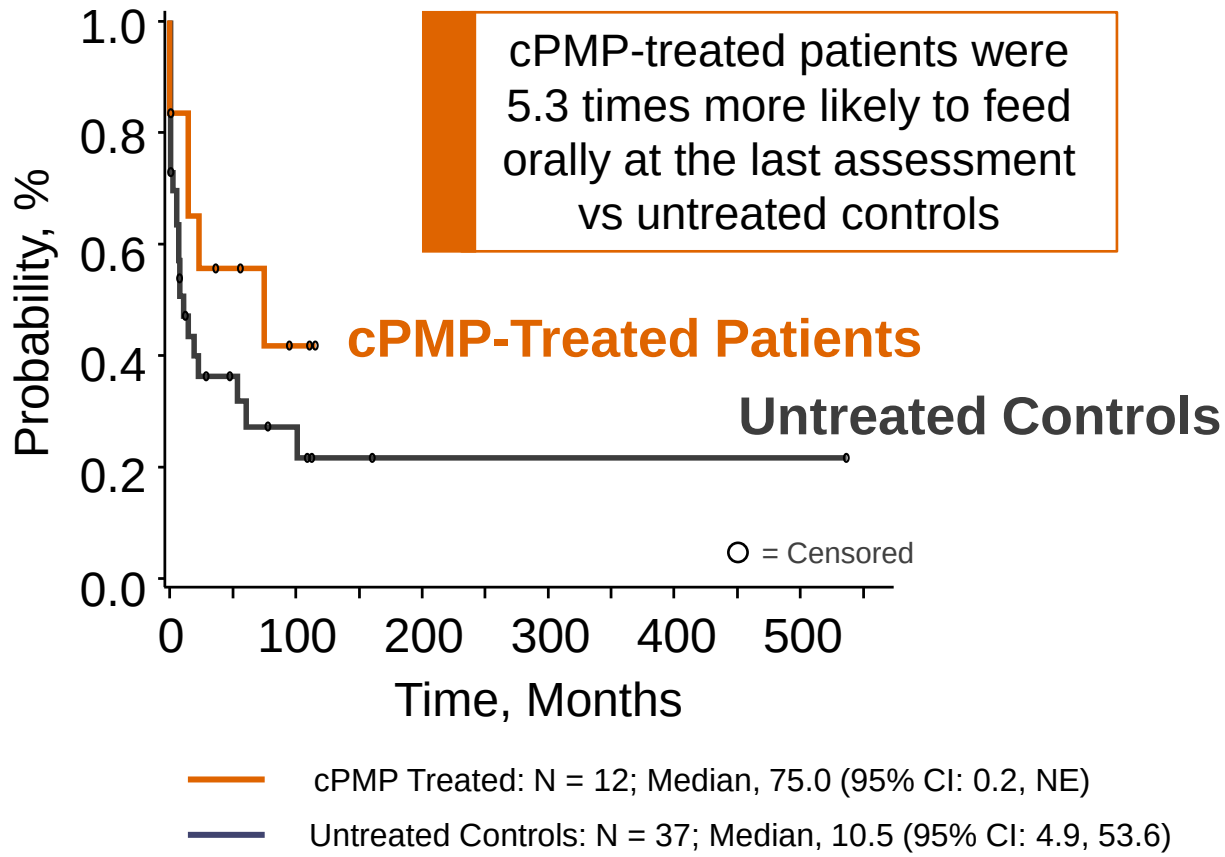
cPMP, cyclic pyranopterin monophosphate; GMFCS-ER, Gross Motor Function Classification System Expanded and Revised.

Oral Feeding in cPMP-Treated Patients vs Controls

Feeding Orally



Time to Sustained Nonoral Feeding[a]



cPMP, cyclic pyranopterin monophosphate; NE = not estimable.

[a]Sustained nonoral feeding was defined as the time at which the patient never subsequently returned to an oral method of feeding

Safety of cPMP

- Most treatment adverse events were mild to moderate, and not related to study drug
  - Most common side effects in fosdenopterin-treated patients were infusion catheter–related complications, pyrexia (fever), viral infection, pneumonia, otitis media (ear infection), vomiting, cough/sneezing, viral upper respiratory infection (common cold/flu-like infection), gastroenteritis (stomach flu-like symptoms), diarrhea, and bacteremia (bacteria in the blood)
  - Side effects for recombinant cPMP-treated patients were similar to the side effects among fosdenopterin-treated patients
- There were no discontinuations or dose modifications due to adverse events
- 2 deaths were noted in the retrospective data
  - 1 patient died due to necrotizing enterocolitis judged as possibly related to study drug
  - 1 patient died due to respiratory syncytial virus pneumonia unrelated to study treatment

Potential for Photosensitivity

- cPMP (fosdenopterin) can make the patient oversensitive to sunlight
- Patients or their caregivers are advised to avoid or minimize patient exposure to sunlight and artificial UV light and adopt precautionary measures when exposed to the sun, including wearing protective clothing and sunglasses, and using broad-spectrum sunscreen with high SPF in patients 6 months of age and older
- If photosensitivity occurs, caregivers/patients are advised to seek medical attention immediately and consider a dermatological evaluation

cPMP, cyclic pyranopterin monophosphate; SPF, sun protection factor; UV, ultraviolet.

Conclusions Leading to the Approval of Fosdenopterin for MoCD Type A

Patients treated with cPMP had **improved overall survival** when compared with untreated historical controls

Patients treated with cPMP **demonstrated decreased urine SSC levels** when compared with untreated historical controls

Additional confirmatory evidence was **provided by the animal model** of MoCD Type A

cPMP (fosdenopterin) was **safe and well-tolerated**

cPMP, cyclic pyranopterin monophosphate; MoCD, molybdenum cofactor deficiency.

Farrell S, et al. *J Inherit Metab Dis*. 2021;44:1085-1087.

Natural History Studies

Provide an opportunity to:

- Characterize ultra-rare and rare disorders
- Develop appropriate disease biomarkers
- Ethically study potentially life-saving treatments
- Facilitate the development of therapeutics in ultra-rare and rare disorders

Thank You

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Case Example: Lumasiran and Nedosiran for Primary Hyperoxaluria

Presenter

John Lieske MD
Mayo Clinic Hospital – Rochester

REAGAN-UDALL FOUNDATION FOR THE FDA

Case Study:
Use of registry data to define the natural history of primary hyperoxaluria

FDA Symposium
May 13, 2024

John C Lieske, MD, FASN

Mayo Clinic Division of Nephrology and Hypertension

Disclosures

Relevant Financial Relationship(s)

Grant funding* and consulting@:

Allena*@

Alnylam*@

BioMarin @

Chinook @

Dicerna/ Novo Nordisc*@

Federation Bio@

Novobiome@

Orfan Bridgebio@

Oxidien @

OxThera*@

Precision Biosciences @

Synlogic*@

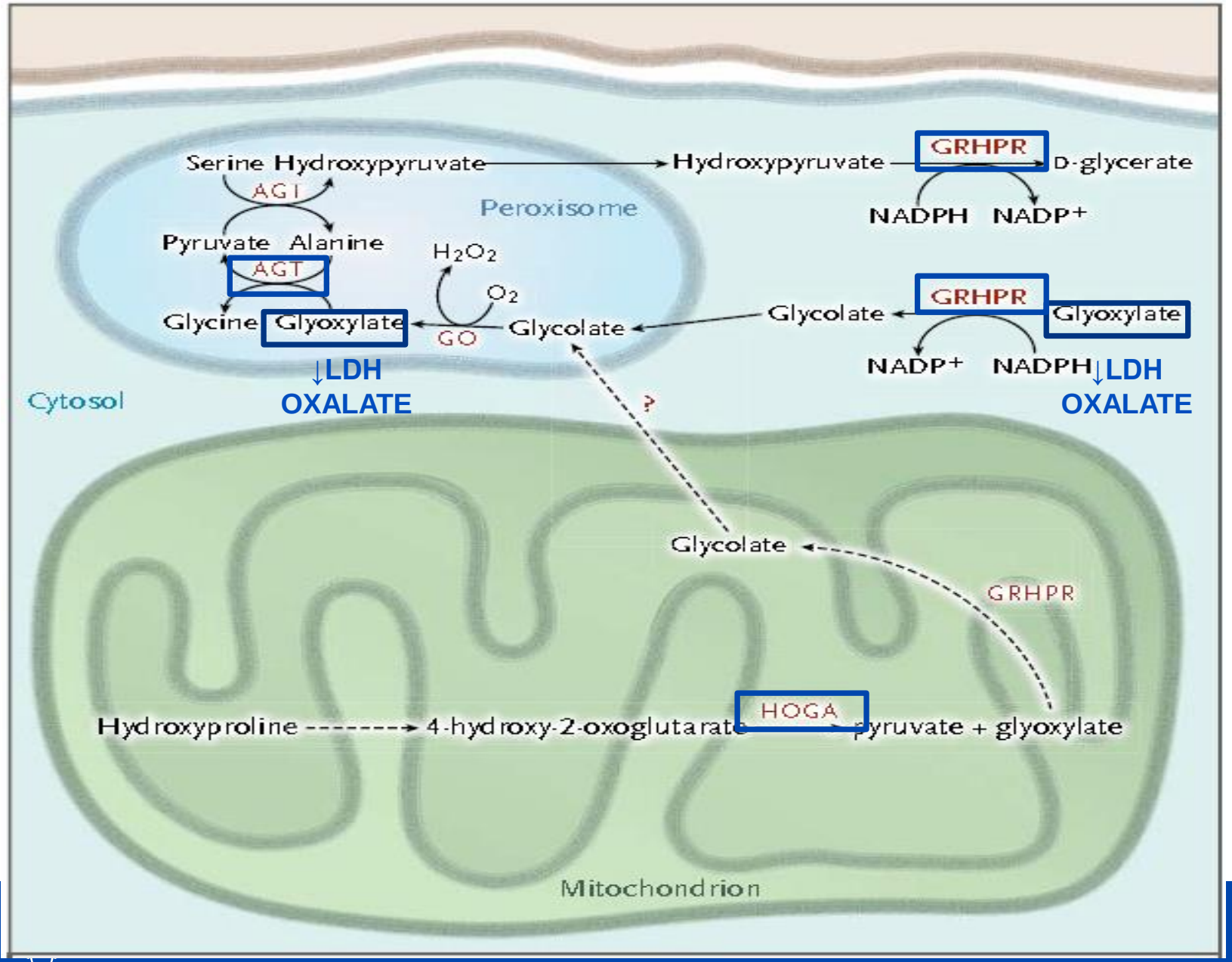
Off Label Usage

None

Outline

- Primary Hyperoxaluria
- Key Role of Patient Advocacy Group (PAG) and ASN to develop registry, disease background, and ultimately engage FDA under the auspices of the Kidney Health Initiative
- Key natural history features that informed treatment efficacy measures
- Ultimate outcome of efforts

Primary Hyperoxaluria: Hepatic oxalate overproduction



Gene mutation

PH type 1 (30%): *AGT*
PH type 2 (10%): *GRHPR*
PH type 3 (60%): *HOGA*

Enzymes implicated

PH 1 and PH2:
Cytosolic LDH
Glyoxalate → Oxalate

PH3: ??

Ancillary tests

PH1: ↑ glycolate
PH2: ↑ glycerate
PH3: ↑ 4-hydroxyglutarate

Hyperoxaluria

High concentrations of oxalate in urine lead to stones, nephrocalcinosis, CKD, and kidney failure, and can result in systemic oxalosis causing multiorgan damage.

Types of Hyperoxaluria

- Primary hyperoxaluria (PH) due to increased hepatic oxalate production caused by any of three known genetic defects in glyoxylate and hydroxyproline metabolism in the liver.

  Rare disease: 1-3 per million population

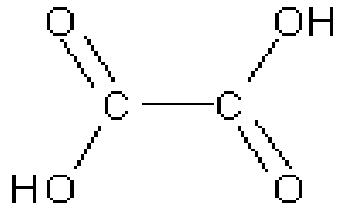
- Enteric hyperoxaluria (EH) caused by fat malabsorption which leads to high absorption of oxalate in small intestine.

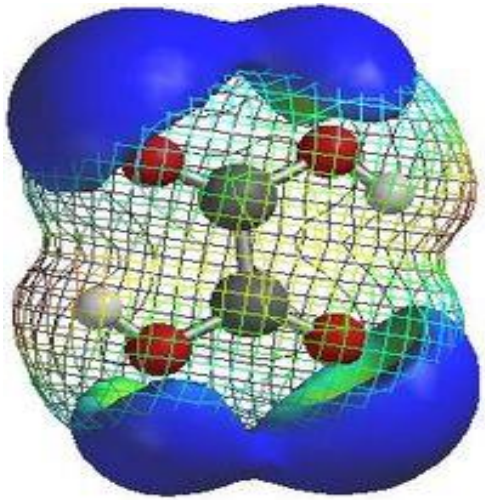
  Estimated to affect ~150,000 patients

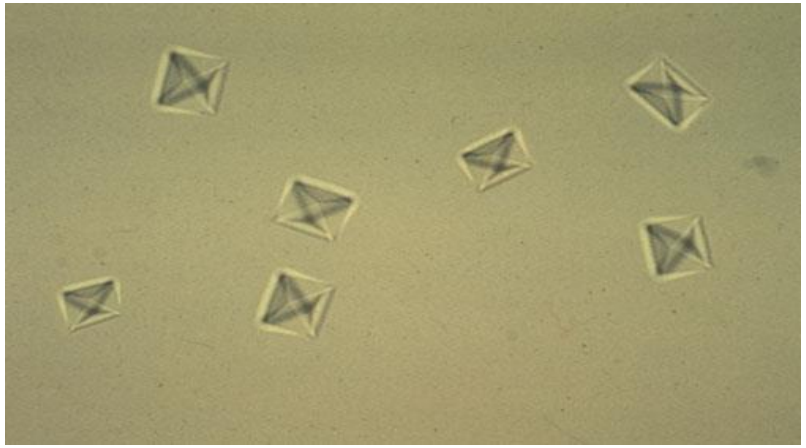
What is oxalate?

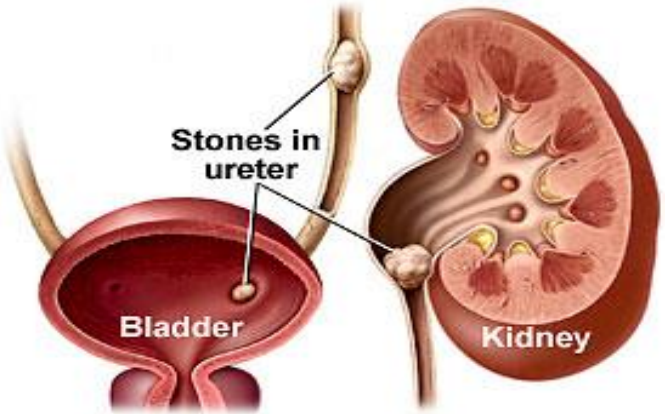
TABLE 3. *Foods with high oxalate content*

Food	Serving size	Oxalate (mg)
Rhubarb	½ cup	720–1032
Spinach	½ cup	570–675
Beetroot	½ cup	573
Swiss chard	½ cup	568
Pokeweed	½ cup	390
Cocoa powder	1 ounce	174
Okra	½ cup	117
Wheat germ	1 ounce	75
Tea (4 min infusion)	1 teaspoon	72
Green gooseberries	½ cup	66
Collards	½ cup	63
Crackers, soybean	1 ounce	58
Pecans	1 ounce	56
Peanuts	1 ounce	52
Grits, white corn	½ cup	50
Sweet potato	½ cup	34
Chocolate	1 ounce	33
Black raspberries	½ cup	32
Leek	½ cup	23
Celery	2 stalks (80 g)	16
Rutabaga	½ cup	16
Eggplant	1 cup	15
Summer squash	½ cup	14
Blackberries	½ cup	13
Green beans	½ cup	11
Blueberries	½ cup	11
Currants, red	½ cup	11
Dewberries	½ cup	10
Black pepper	1 tsp	8
Green pepper	½ cup	8









Time machine travel to 2016

Increasing possibility for clinical trials in oxalate-related diseases

- Alter gastrointestinal oxalate absorption and/or secretion
  - Manipulate the gastrointestinal microbiome
  - Oral oxalate degrading enzymes
- Inhibition or manipulation of hepatic enzyme pathways
  - siRNA
    - Small molecules
    - Chaperones

2016 OHF Annual Scientific Advisory Board meeting

- **Primary and enteric hyperoxaluria are rare diseases**
  - Clinical trials with renal function, CKD, kidney failure, or kidney stones are not feasible
  - The FDA is increasingly receptive to alternatives to these hard clinical endpoints, as long as well-justified
    - Duchenne muscular dystrophy is one example
- Idea of an FDA white paper on oxalate studies discussed with scientific, industry, and patient representatives at a half day meeting.
  - Concept enthusiastically endorsed by all present
  - Despite being an “unfunded mandate” efforts moved forward…

OHF team to DC in Spring 2016

D Milliner

J Lieske

T Lowther

K Hollander

J Bertarelli

Stop 1: ASN

- The mission of KHI is to advance scientific understanding of the kidney health and patient safety implications of new and existing medical products and to foster development of therapies for diseases that affect the kidney by creating a collaborative environment in which the FDA and the greater nephrology community can interact to optimize the evaluation of drugs, devices, biologics, and food products.

https://www.asn-online.org/khi/

Who can join KHI?

- KHI is a collaborative environment for all stakeholders in the kidney community to help foster development of optimum therapies for diseases that affect the kidney. KHI members may include:
  - Patient organizations
  - Health professional organizations
  - Research Institutions
  - Foundations
  - Pharmaceutical and biotechnology companies
  - Device manufacturers
  - Dialysis providers
  - US and international government agencies

Current KHI projects (2016)

- Advancing Technologies to Facilitate Remote Management of Patient Self-Care in Renal Replacement Therapy (RRT)
- Clinical Trial Endpoints for Dialysis Vascular Access
- Data Harmonization in Kidney Transplant
- Data Standards in Diabetic Kidney Disease
- Development of a Roadmap for Innovations in Renal Replacement Therapy (RRT)
- **Identifying Surrogate Endpoints for Clinical Trials in IgA Nephropathy**
- Overcoming Barriers to Drug Development in Children with CKD
- Pragmatic Trials in Dialysis: Challenges and Opportunities
- Prioritizing Symptoms of ESRD Patients for Developing Therapeutic Interventions
- Regulatory Policies and Positions Affecting Device Approval in the US: Tools to Assess the Process and Foster Device Development for Patients with Kidney Disease
- Workshop to Elucidate Role of Patient Preferences in Support of CDRH Regulatory Actions in Kidney Disease

Stop 2: FDA meeting

- Well attended “1 hr” meeting with ~20 FDA representatives
- In general seemed receptive to our message that large clinical trials with hard endpoints are not feasible
- There is a mechanism to submit paperwork to validate a surrogate endpoint (like oxalate), but was mentioned maybe not be the best approach
- No firm advice r/e next best steps

Kidney Health Initiative (KHI)

- OHF proposal submitted for mid 2016 cycle to help with developing guidance for appropriate endpoints in hyperoxaluria trials
- Well received but ultimately not approved
- Feedback: Not eager to take on “validation of a surrogate endpoint” with all the lab work, etc. that effort might entail
- Plan to reapply for Spring 2017 cycle, and attend stakeholders meeting in May 2017
  - OHF and several officers are now KHI members

OHF SAB meeting 2017

- While waiting to reapply to KHI, we have decided now is the time to seize our momentum and work on a summary document that will:
  - be used when we engage the FDA in further discussion, hopefully culminating in the request from them for us to develop a guidance document
  - form the basis (or starting point) for this comprehensive guidance document

Workgroups

1	Biology of oxalate, including biosynthetic pathways
2	Renal and gastrointestinal oxalate transport
3	Genetics of Primary Hyperoxaluria
4	Pathophysiology of enteric hyperoxaluria
5	Diagnosis of hyperoxaluria, including algorithms and laboratory issues
6	Pathophysiology of calcium oxalate kidney stones and nephrocalcinosis in hyperoxaluric states
7	Treatment strategies for hyperoxaluria- current and future
8	The clinical needs for hyperoxaluria trials from the patients' perspective

Group Leader	Group Members					
T Lowther	B Cellini	J Knight	C Danpure	T McGregor	A Quinn	
M Hatch	Rholmes	D Goldfarb	D Sas	E Lindner		
D Milliner	E Salido	Y Frishberg	M Baum			
J Lieske	A Kausz	J Asplin	D Assimos			
J Asplin	D Milliner	Y Frishberg	M Hatch	J Knight	A Kauz	
D Goldfarb	D Sas	R Holmes	J Lieske	A Kausz	E Lindner	
M Baum	D Assimos	T Lowther	T McGregor	E Salido	B Cellini	A Quinn
J Lawrence	B Kissinger	K Hollander	J Subramanyam	I Aquino		

MAYO CLINIC

Subsequent Timeline

- February 25, 2017
  - Working meeting
- March-April 2017
  - Small group follow-up
- May-June 2017
  - Roll into one document
- July 2017
  - Discussions at OHF workshop

KHI Project

- **May-Sept 2017** Application submitted to KHI and approved
- Initial stakeholders meeting **Feb 22, 2018.**
  - Good representation from industry, academia, patients and families.

Specific Objectives

1. Consensus recommendations for potential surrogate endpoints

- Identify candidate surrogate markers for clinical trials in hyperoxaluria
- Critically assess candidate measures for appropriateness
- Identify gaps in the data and future research needs to fully establish acceptable biochemical marker(s) for clinical trials in hyperoxaluria

2. Develop recommendations for industry guidelines for expedited clinical trials and approvals

- Identify characteristics of patients with differing risks of progression
- Develop a consensus statement of risk tolerance of hyperoxaluric patients/families for clinical trial participation and medication use

Surrogate End Points for Clinical Trials

***Endpoint markers for clinical trials are expected meet the following criteria*:**

- **Biologic plausibility** that the biochemical marker is on the biologic pathway to a hard endpoint such as kidney failure or death
- Epidemiologic or other **data showing consistent association between the biochemical marker and the clinical outcome** of interest
- Any available **data from clinical trials showing that the effects of treatment on the candidate marker largely account for their effects on clinical outcome**
- **An assessment of quantitative effect** on the endpoint marker that is **needed to be clinically significant**

PH Registry Enrollment March-2023

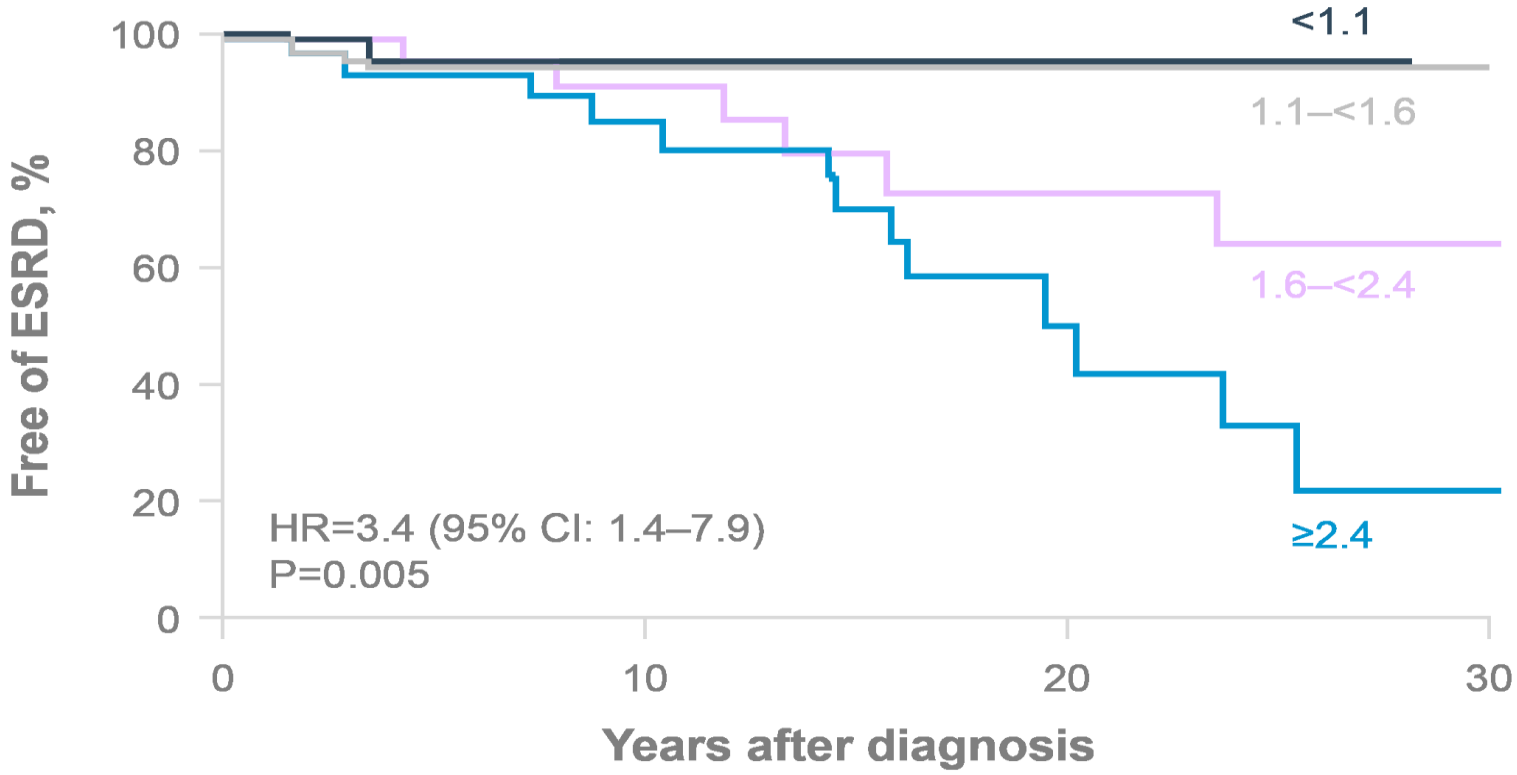
	Total (N=603)
Sex, n (%)	
M	**326 (54.4%)**
F	**273 (45.6%)**
Not Recorded	**4**
Race, n (%)	
Am. Indian	**3 (0.5%)**
Asian	**126 (20.9%)**
African American	**14 (2.3%)**
Hawaiian	**2 (0.3%)**
White	**357 (59.2%)**
Not Disclosed	**101 (16.7%)**
Ethnicity, n (%)	
Hispanic or Latino	**34 (5.6%)**
Non Hispanic or Latino	**339 (56.2%)**
Not Disclosed	**230 (38.1%)**
Deceased, n (%)	
No	**534 (88.6%)**
Yes	**69 (11.4%)**

PH Registry Enrollment March-2023

Renal Failure, n (%)	
No	**349 (57.9%)**
Yes	**254 (42.1%)**
Patients with Serum Labs	
N	**539**
Mean (SD)	**7.5 (7.70)**
Median	**5**
Range	**1.0, 46.0**
Patients with Urine Labs	
N	**490**
Mean (SD)	**6.6 (6.48)**
Median	**4**
Range	**1.0, 30.0**
Year LFU, n (%)	
<=2019	**417 (69.2%)**
2020	**62 (10.3%)**
2021	**45 (7.5%)**
2022	**67 (11.1%)**
2023	**12 (2.0%)**
FU Years	
N	**603**
Mean (SD)	**9.1 (11.59)**
Median	**4.9**
Range	**0.0, 64.1**

Urine oxalate is a key risk factor for kidney failure in PH

RARE KIDNEY STONE CONSORTIUM



UOx quartile mM/day

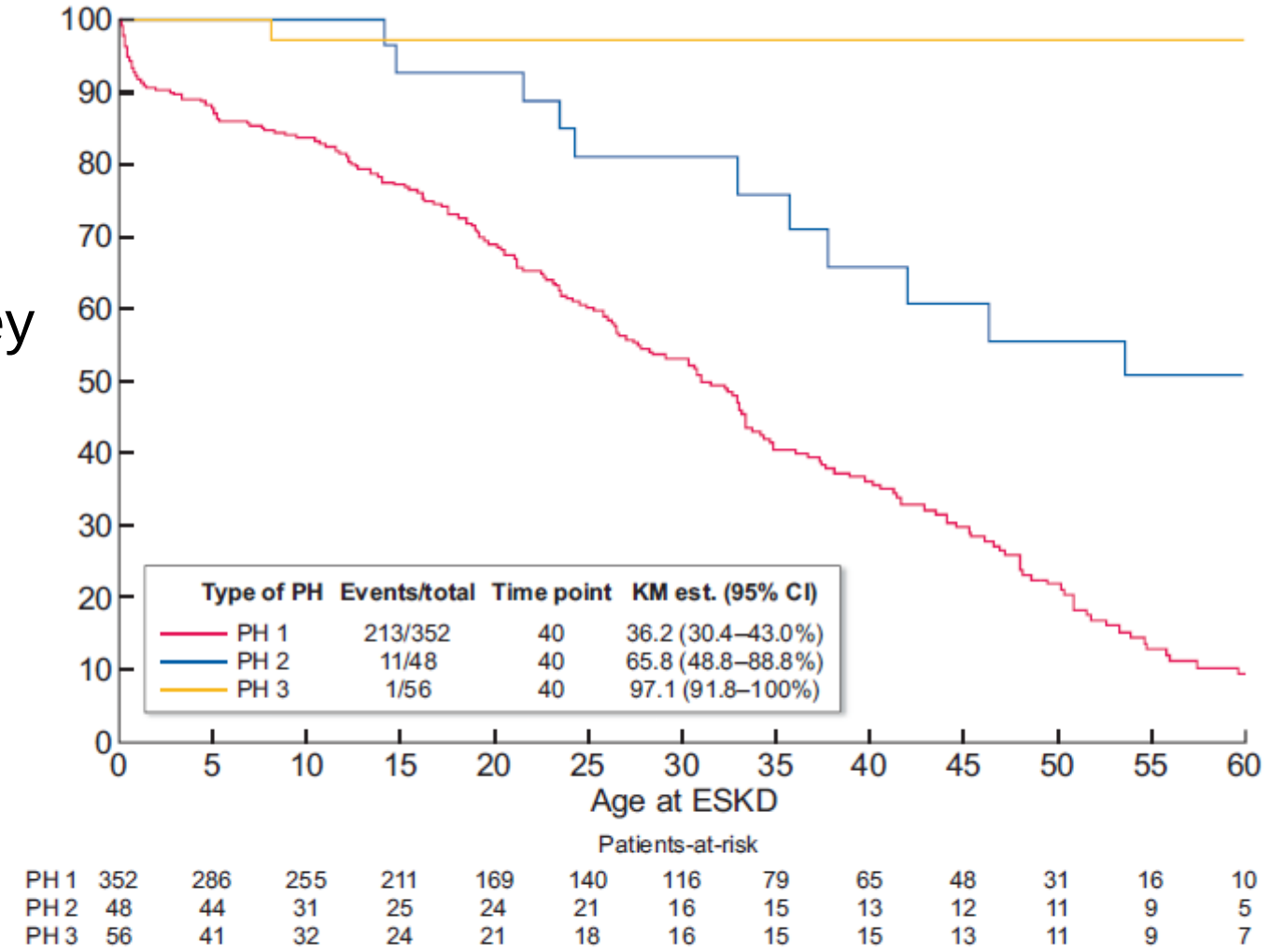
Urine oxalate	Survival estimate, % (number at risk)			
<1.1	100 (42)	96 (7)	96 (1)	–
1.1–<1.6	100 (42)	95 (8)	95 (5)	95 (2)
1.6–<2.4	100 (42)	91 (19)	73 (10)	65 (6)
≥2.4	100 (42)	85 (19)	42 (6)	23 (2)

MAYO CLINIC

Zhao et al Clin J Am Soc Nephrol 11: 119–126, 2016

Kidney failure is common in PH 1 and PH2, especially in PH1

Percent without kidney failure



····· PH3

--- PH2

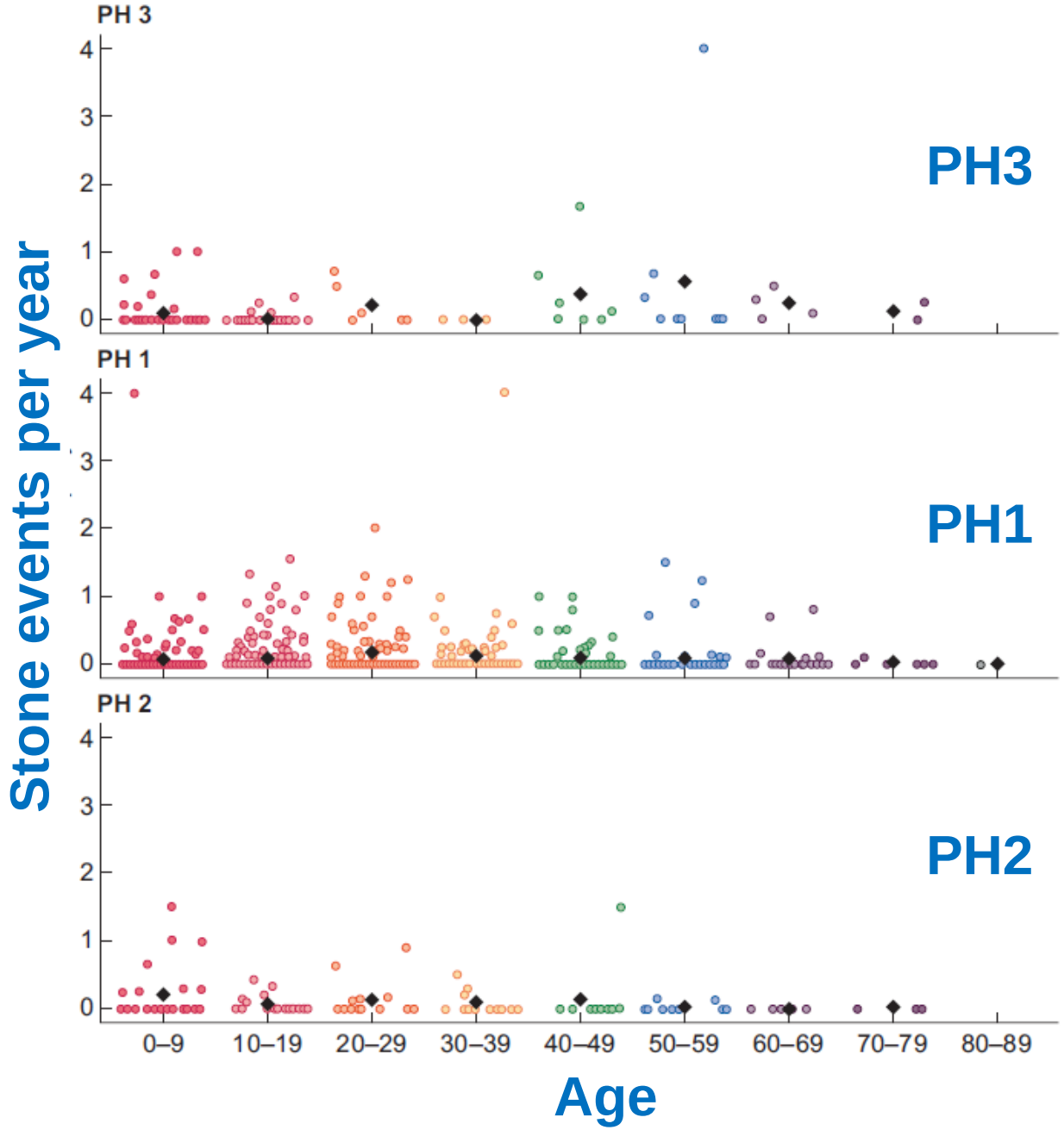
— PH1

RARE KIDNEY STONE CONSORTIUM

MAYO CLINIC

Zhao et al Clin J Am Soc Nephrol 11: 119–126, 2016

Kidney stones are equally common in all PH types and across the decades

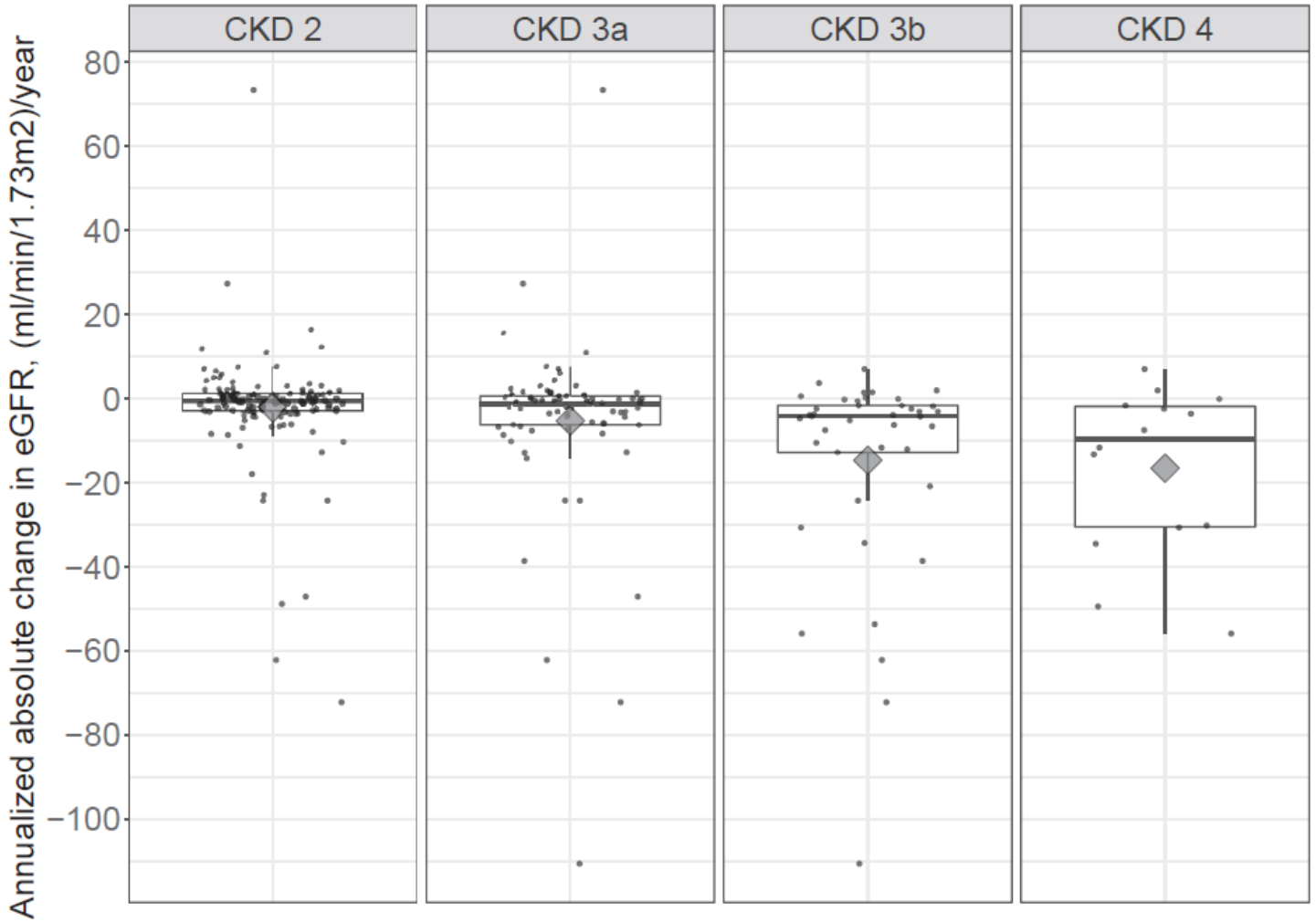


RARE KIDNEY STONE CONSORTIUM

MAYO CLINIC

Singh P et al Nephrol Dial Transplant. 2022 37(5):869-875.

eGFR declines more dramatically at lower CKD stages

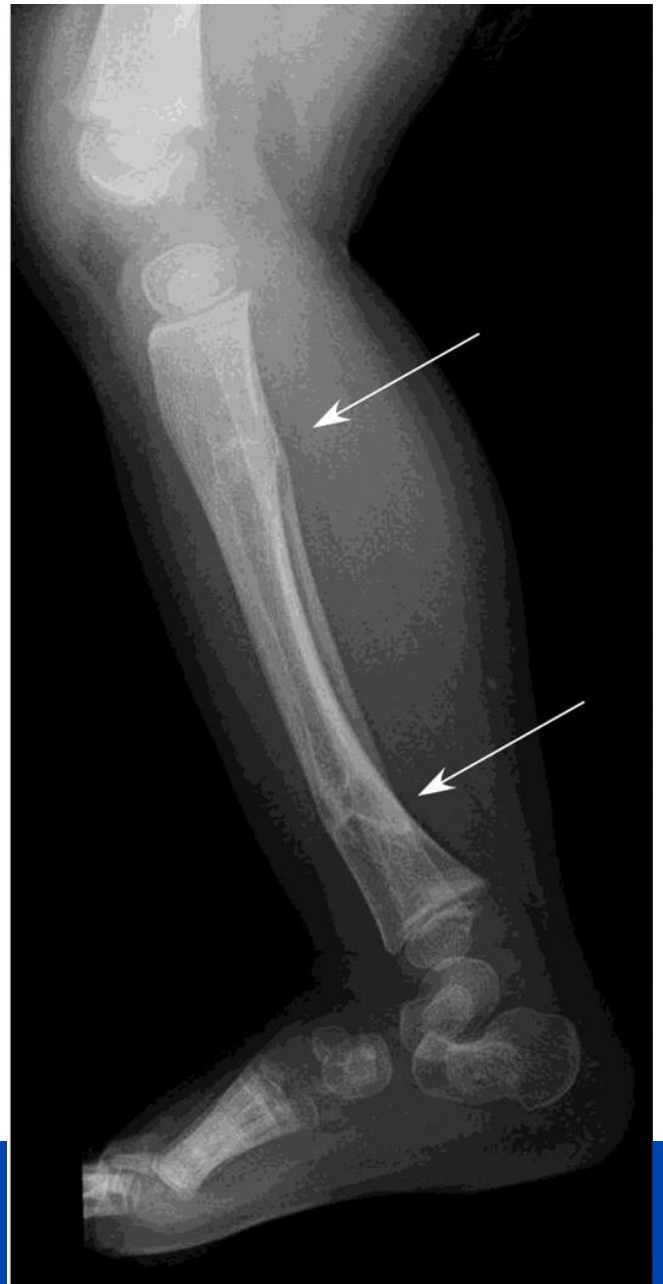


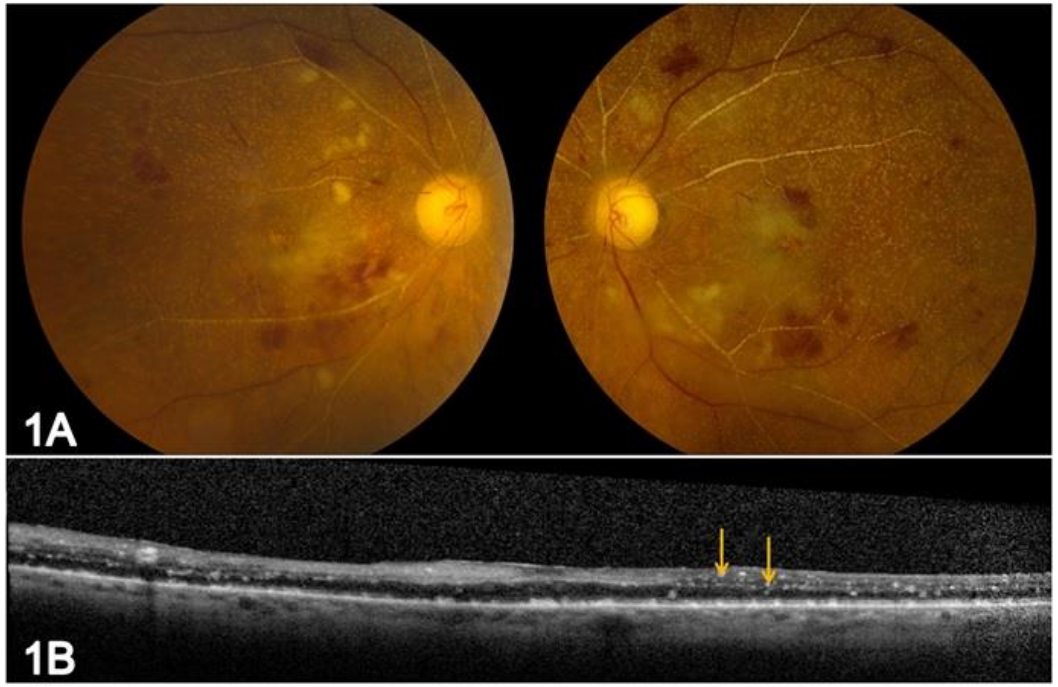
RARE KIDNEY STONE CONSORTIUM

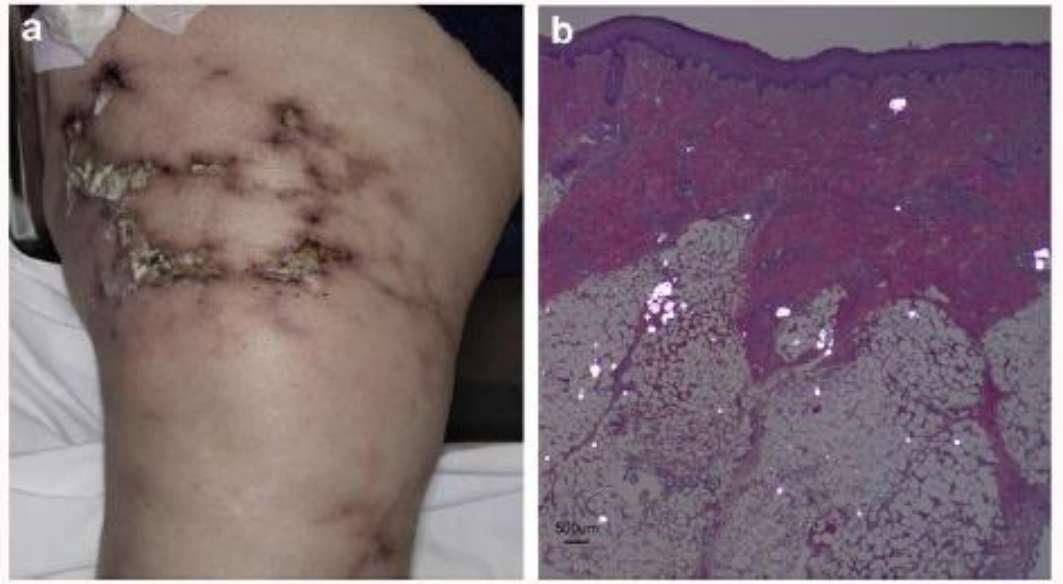
MAYO CLINIC

Singh P, et al: Am J Kidney Dis. 2022; Sep;80(3):373-382

Oxalosis



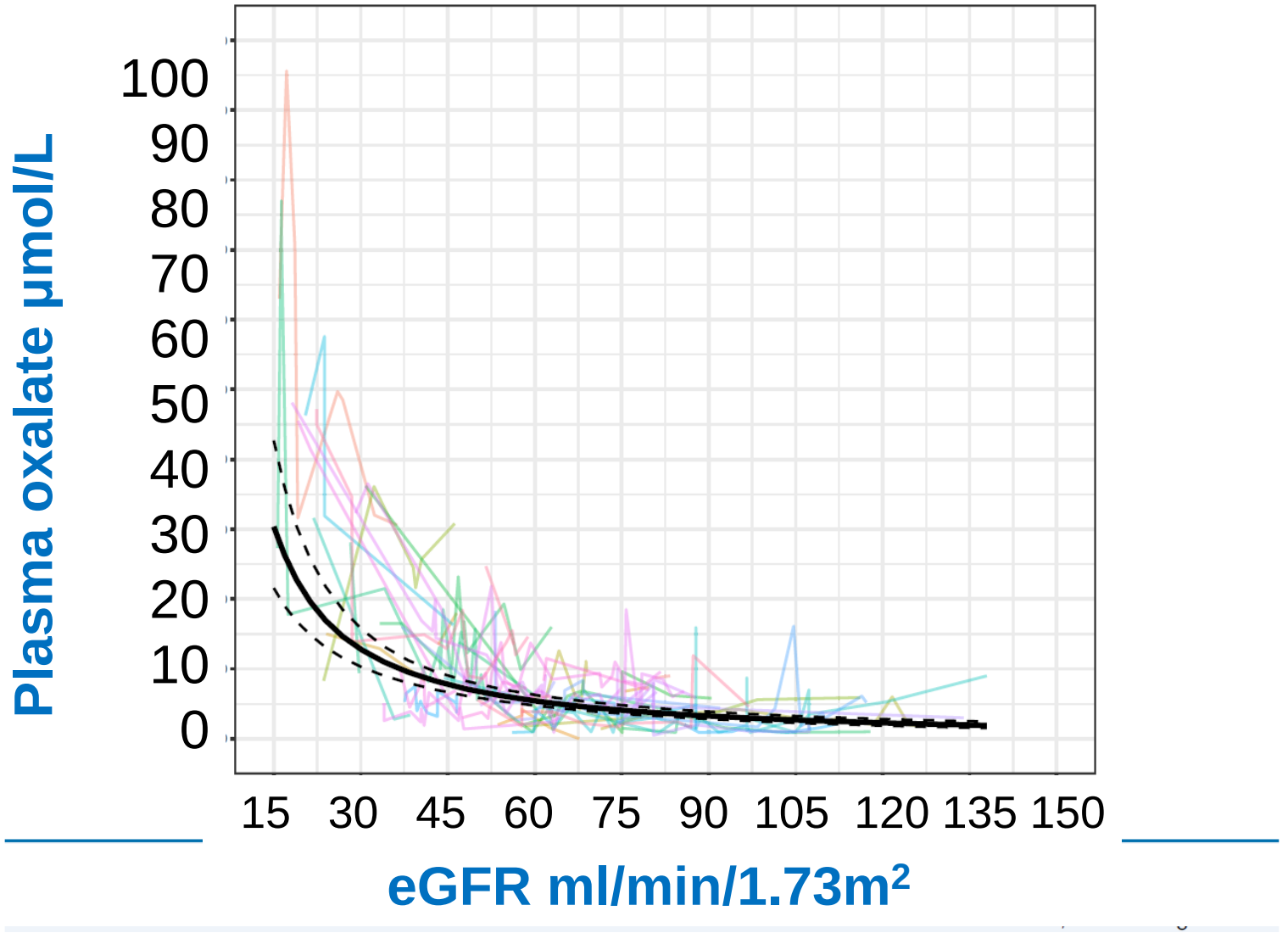




RARE KIDNEY STONE CONSORTIUM

MAYO CLINIC

Plasma oxalate increases markedly at low eGFR in PH1

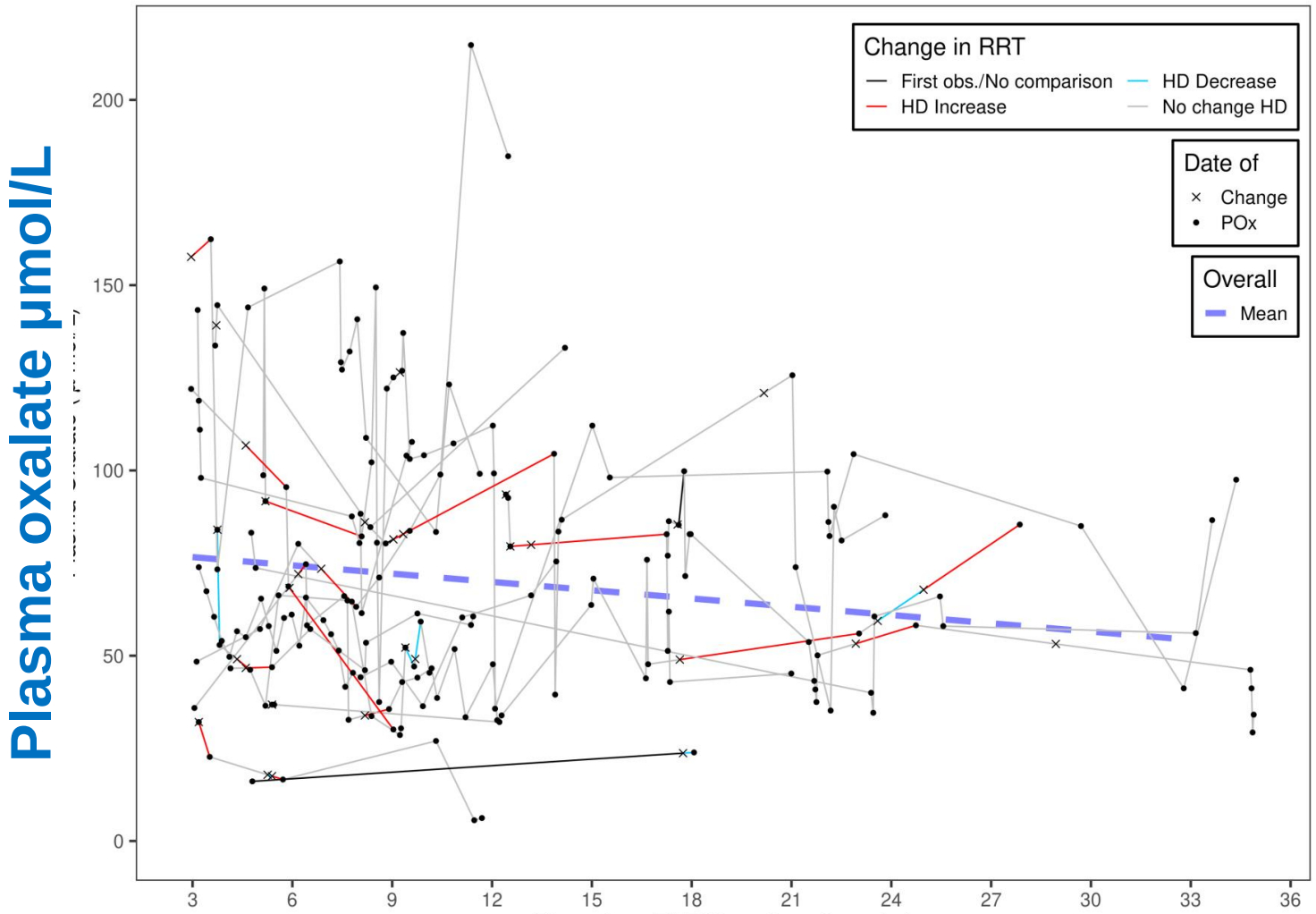


RARE KIDNEY STONE CONSORTIUM

Singh P, et al: Am J Kidney Dis. 2022; Sep;80(3):373-382

MAYO CLINIC

Plasma oxalate over time on dialysis in PH1



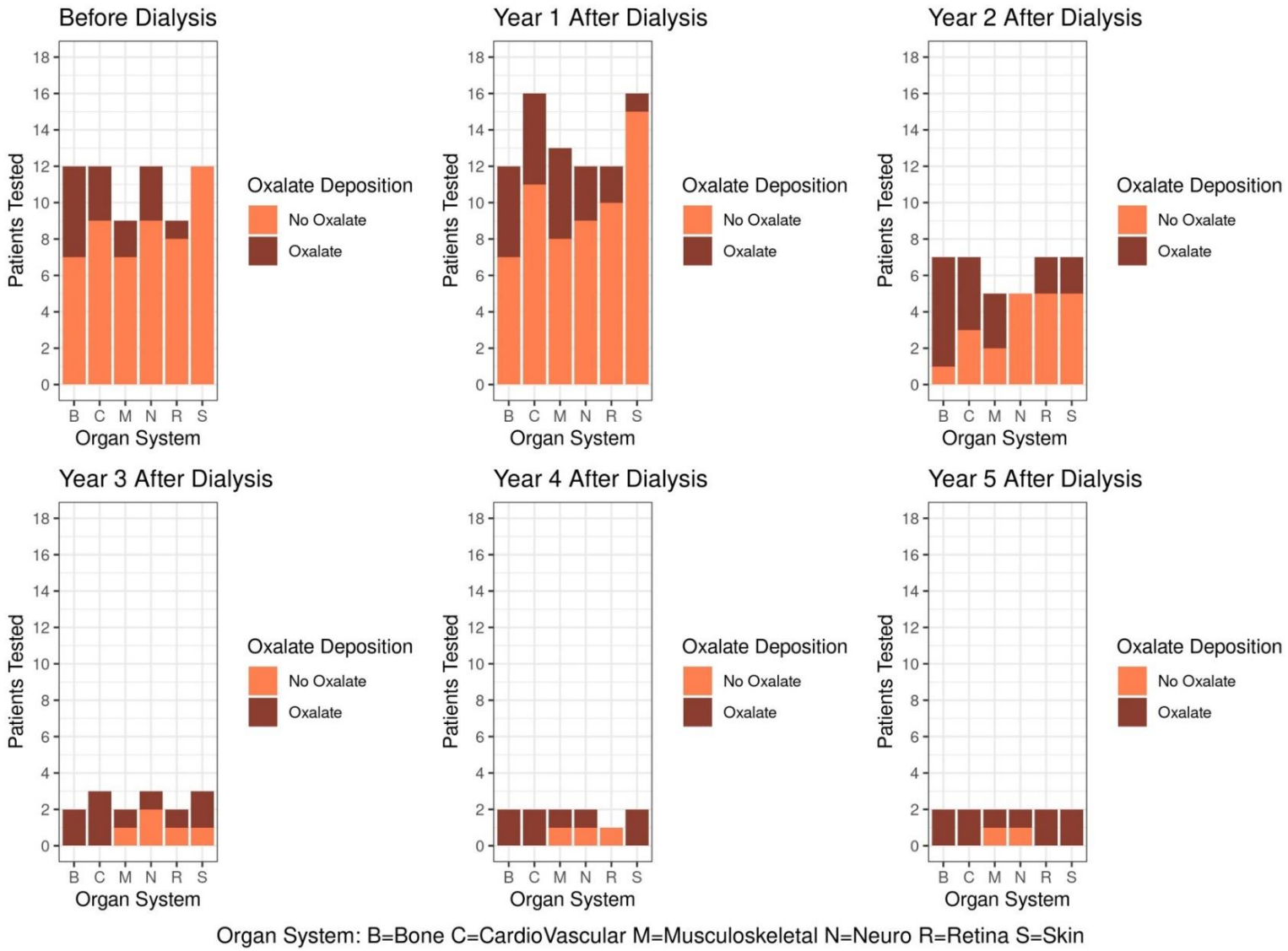
RARE KIDNEY STONE CONSORTIUM

MAYO CLINIC

Oxalosis over time on dialysis

RARE KIDNEY STONE CONSORTIUM

Bone
Cardiovascular
Musculoskeletal
Neuro
Retina
Skin



Sas DJ et al. Front Med (Lausanne). 2021 Apr 9;8:592357.

KHI Endpoints for Clinical Trials in Hyperoxaluria: Outcomes

- A group of candidate markers compiled for evaluation.
- Promising candidates underwent rigorous examination via detailed literature review
- Biomarkers/endpoints evaluated sequentially on biweekly calls
- **Several remained as viable candidates**
  - **Plasma oxalate**
  - **Urine oxalate**
  - **Change in eGFR**
  - **Stone events**
- Workgroups summarized reviews
- Compiled into a draft report
- Paper draft Back and forth with FDA: published 2020
- PH patient group building on white paper, sought experience of others re: patient/family risk tolerance for clinical trials, new therapies.

Endpoints for Clinical Trials in Hyperoxaluria: KHI PH deliverables

PatientVoice

Feature

End Points for Clinical Trials in Primary Hyperoxaluria

Dawn S. Milliner,[1] Tracy L. McGregor,[2] Aliza Thompson,[3] Bastian Dehmel,[4] John Knight,[5] Ralf Rosskamp,[6] Melanie Blank,[3] Sixun Yang,[7] Sonia Fargue,[5] Gill Rumsby,[8] Jaap Groothoff,[9] Meaghan Allain,[10] Melissa West,[10] Kim Hollander,[11] W. Todd Lowther,[12] and John C. Lieske[1]

Abstract

Patients with primary hyperoxaluria experience kidney stones from a young age and can develop progressive oxalate nephropathy. Progression to kidney failure often develops over a number of years, and is associated with systemic oxalosis, intensive dialysis, and often combined kidney and liver transplantation. There are no therapies approved by the Food and Drug Association. Thus, the Kidney Health Initiative, in partnership with the Oxalosis and Hyperoxaluria Foundation, initiated a project to identify end points for clinical trials. A workgroup of physicians, scientists, patients with primary hyperoxaluria, industry, and United States regulators critically examined the published literature for clinical outcomes and potential surrogate end points that could be used to evaluate new treatments. Kidney stones, change in eGFR, urine oxalate, and plasma oxalate were the strongest candidate end points. Kidney stones affect how patients with primary hyperoxaluria feel and function, but standards for measurement and monitoring are lacking. Primary hyperoxaluria registry data suggest that eGFR decline in most patients is gradual, but can be unpredictable. Epidemiologic data show a strong relationship between urine oxalate and long-term kidney function loss. Urine oxalate is reasonably likely to predict clinical benefit, due to its causal role in stone formation and kidney damage in CKD stages 1–3a, and plasma oxalate is likely associated with risk of systemic oxalosis in CKD 3b–5. Change in slope of eGFR could be considered the equivalent of a clinically meaningful end point in support of traditional approval. A substantial change in urine oxalate as a surrogate end point could support traditional approval in patients with primary hyperoxaluria type 1 and CKD stages 1–3a. A substantial change in markedly elevated plasma oxalate could support accelerated approval in patients with primary hyperoxaluria and CKD stages 3b–5. Primary hyperoxaluria type 1 accounts for the preponderance of available data, thus heavily influences the conclusions. Addressing gaps in data will further facilitate testing of promising new treatments, accelerating improved outcomes for patients with primary hyperoxaluria.

CJASN 15: 1056–1065, 2020. doi: https://doi.org/10.2215/CJN.13821119

Due to the number of contributing authors, the affiliations are listed at the end of this article.

Correspondence: Dr. Dawn S. Milliner, Division of Nephrology, Mayo Clinic Rochester, 200 First Street SW, Rochester, MN 55905. Email: Milliner.Dawn@mayo.edu

Primary Hyperoxaluria
The Patient and Caregiver Perspective

Jennifer E. Lawrence and Debra J. Wattenberg

CJASN 15: 909–911, 2020. doi: https://doi.org/10.2215/CJN.13831119

Introduction

Living with primary hyperoxaluria—a rare genetic disease with excess oxalate production leading to frequent kidney stones, kidney impairment, and oxalosis—presents many challenges to patients, caregivers, and their families. Although the progression and severity of primary hyperoxaluria is variable, care for any child or adult with primary hyperoxaluria is an unusual strain to the family due to intensity of required medical care and associated financial hardship. To identify the concerns of the primary hyperoxaluria community, multiple in-person meetings were con-

experience interruptions in school and work, and loss of sleep.

"It is a daily challenge to make sure our son is drinking constantly throughout the day. He visits the school nurse every day who gives him one of his four daily doses of medication through his (gastrostomy) mickey button. As a 12-year-old, he misses sleepovers, sleep away camp, and overnight school trips."

Oxalosis and Hyperoxaluria Foundation, New York, New York

Correspondence: Dr. Jennifer E. Lawrence, Valdosta Specialty Clinic, 2418 North Oak Street, Valdosta, GA 31602. Email: jenlawtidmore@gmail.com

Editorial › Am J Kidney Dis. 2021 Oct 8;S0272-6386(21)00895-7. doi: 10.1053/j.ajkd.2021.09.005. Online ahead of print.

End Points for Clinical Trials in Hyperoxaluria: Case Study of Patient-Focused Drug Development in a Rare Disease

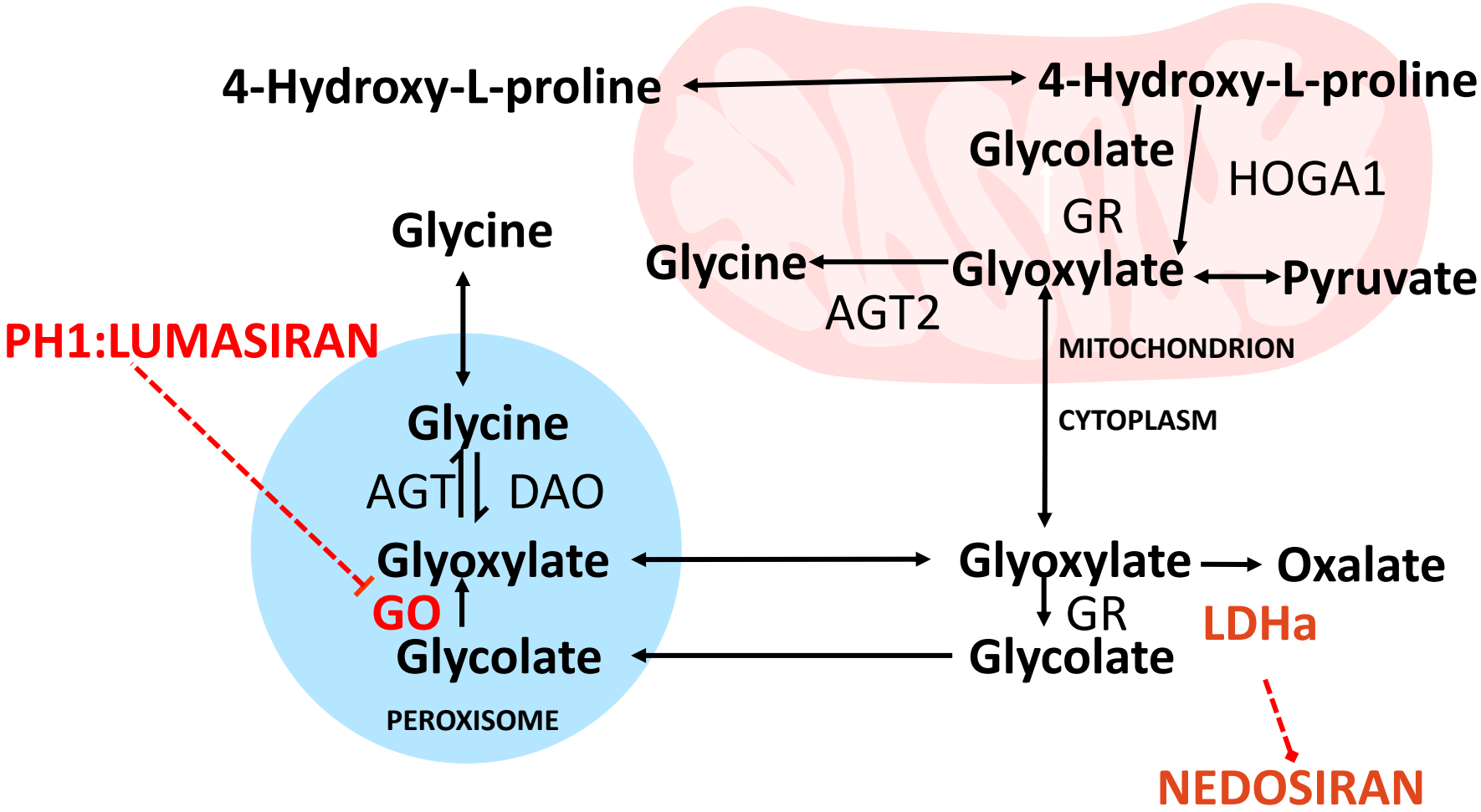
John C Lieske [1], Meaghan A Malley [2], Melissa West [2], Kim Hollander [3], Dawn S Milliner [4]

Affiliations + expand

PMID: 34634431 DOI: 10.1053/j.ajkd.2021.09.005

MAYO CLINIC

siRNA Place in PH1 Therapy



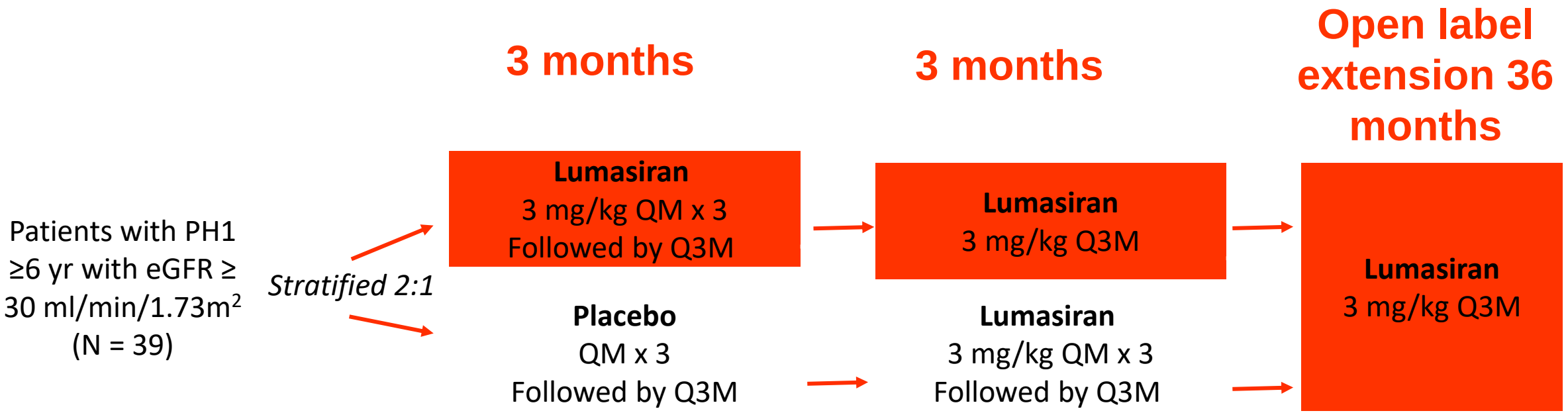
Bacchetta. Clin Kidney J. 2022;15:i17.

PH1, (??? PH2, and PH3):

MAYO CLINIC

ILLUMINATE A

- **Ongoing, phase III trial of subcutaneous lumasiran (small interfering RNA (siRNA silences *HAO1* gene encoding glycolate oxidase)**

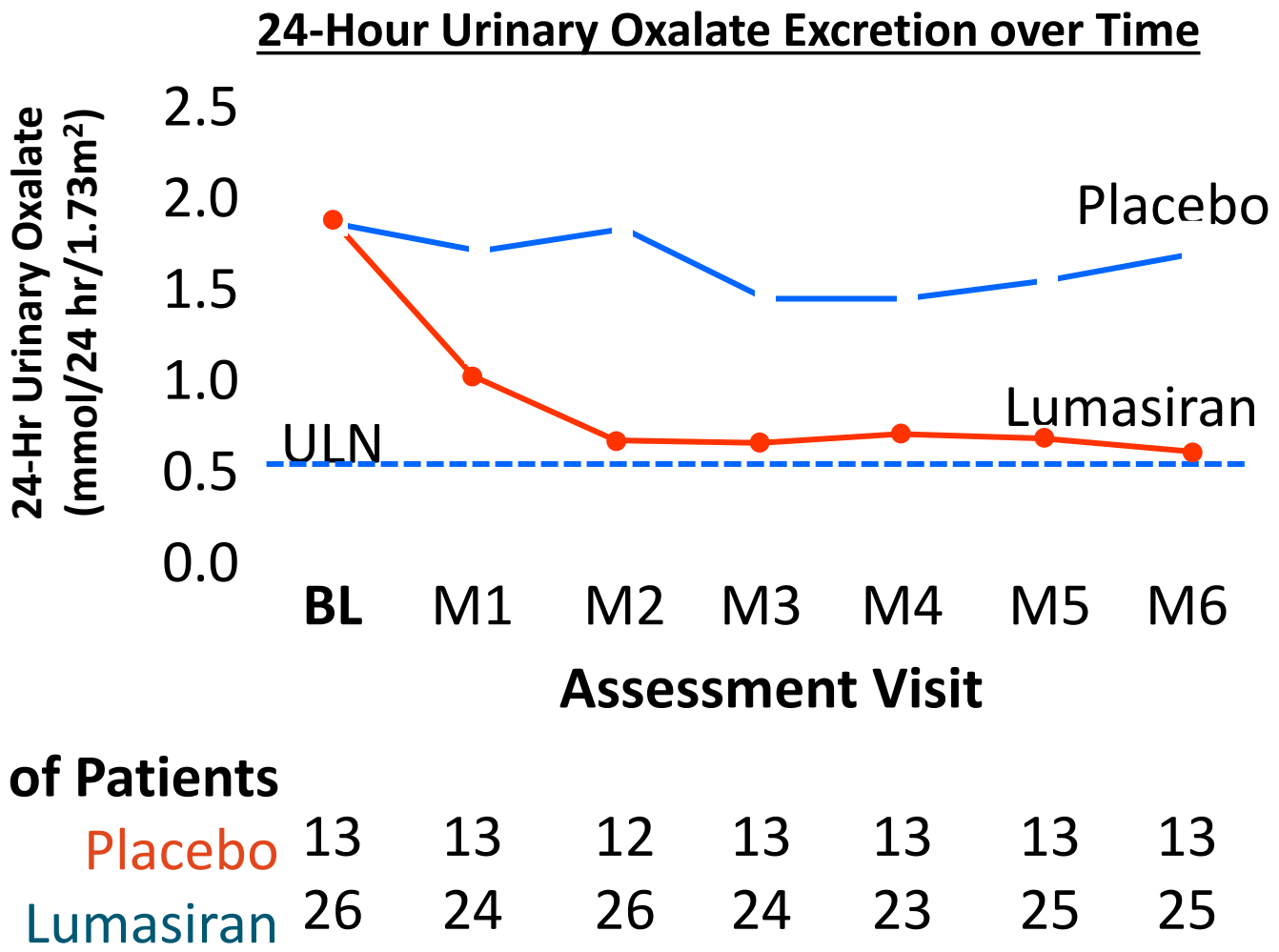


Garrelfs. NEJM. 2021;384:1216

MAYO CLINIC

ILLUMINATE A

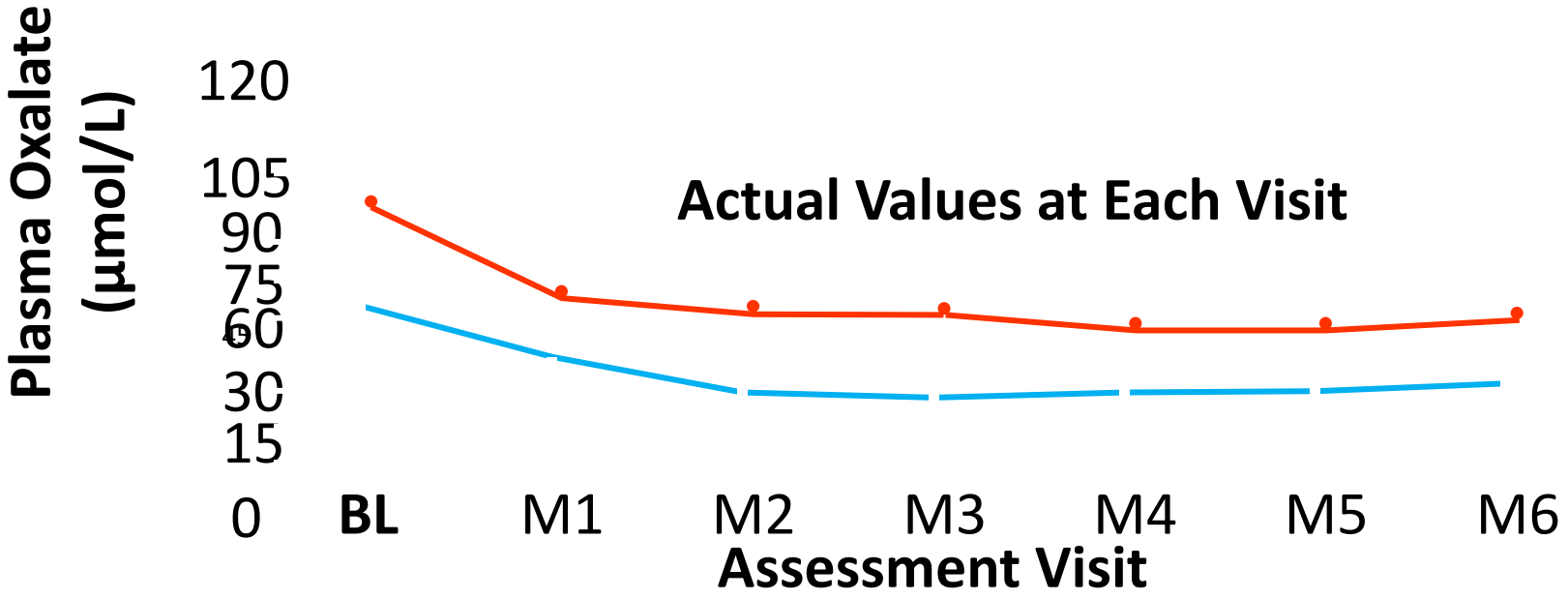
- Mean reduction in urinary oxalate excretion: 65% lumasiran vs 11% placebo (*P* < .001) at 6-mo primary analysis period
- Only transient injection-site reactions reported
- Approved as an Orphan drug 11/2020!



Garrelfs S. N Engl J Med. 2021;384:1216

MAYO CLINIC

ILLUMINATE C (CKD)



Cohort B (ESKD; N=15)

Cohort A (CKD4/CKD5; N=6)

No. of Patients	BL	M1	M2	M3	M4	M5	M6
Cohort A	6	6	6	6	6	6	6
Cohort B	15	15	15	15	13	14	15

Michael M AJKD 2023 81(2):145-15

MAYO CLINIC

Nedosiran

- **Nedosiran: GalNAc-conjugated RNAi treatment that targets hepatic lactate dehydrogenase (LDHa)**
- **RNAi therapy approved for PH; PHYOX program**
  - **PHYOX1 and PHYOX2: completed**
  - **PHYOX3: ongoing; extension trial of PHYOX2 in all types of PH**
  - **PHYOX4: ongoing; phase 1, single dose study in PH3**
  - **PHYOX7: ongoing; safety and efficacy in PH1 or PH2 with severe renal impairment with or without dialysis**
  - **PHYOX8: ongoing; safety, pharmacokinetics, and efficacy in children 0-5 yr with PH and intact kidney function**
  - **PHYOX-OBX: ongoing; natural history in PH3**
- **Approval in US for PH1 in late 2023!**

Goldfarb DS. Urolithiasis. 2023:51:80. Hoppe B. Kidney Int. 2022;101:626. Baum M. Kidney International. 2023;103:207. Coenen M. Abstract Poster1625. Haagensen A. Absract INFO22

MAYO CLINIC

PHYOX2 Results

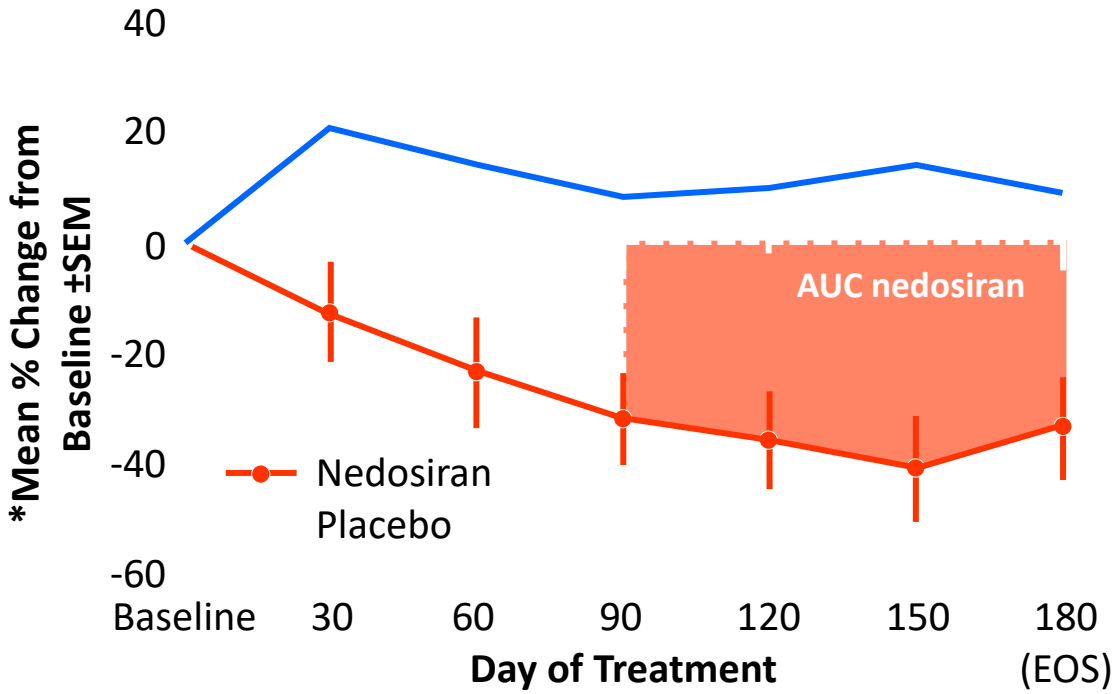
PHYOX2 Met Primary Endpoint Achieving a Significant Reduction in Uox

Mean $AUC_{24\text{-hour Uox}}$ (day 90 to day 180)

Overall mITT Population[1] (PH1 + PH2)

Standardized AUC24-hour Uox from Day 90 to Day	Nedosiran (n = 22)	Placebo (n = 12)
n	22	12
LS Mean (SE)	3507.4 (788.49)	-1664.4 (1189.96)
95% CI for LS Mean	(1961.7, 5053.1)	(-3997.2, 668.4)
LS Mean Difference from Placebo (SE)	5171.7 (1144.07)	
95% CI for Difference from Placebo	(2929.3, 7414.2)	
P-value for Difference from Placebo (2)	**<.0001**	

(1) mITT population = All participants in the ITT population who have at lease one efficacy assessment after the Day 90 dosing visit.
(2) P-value for testing difference from placebo



*LS means from MMRM model using time point estimates
**Multiple imputation (MI) under the missing at random (MAR) assumption was used to handle missing 24-hr Uox data

Baum. Kidney International. 2023;103:207.

MAYO CLINIC

Endpoints for Clinical Trials in Hyperoxaluria: PH Progress to Date

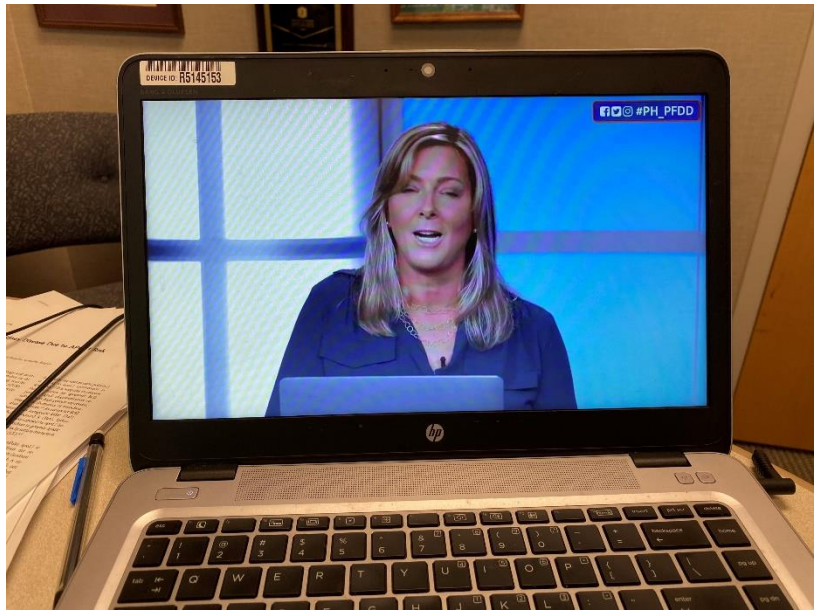
THE VOICE OF THE PATIENT REPORT: PRIMARY HYPEROXALURIA

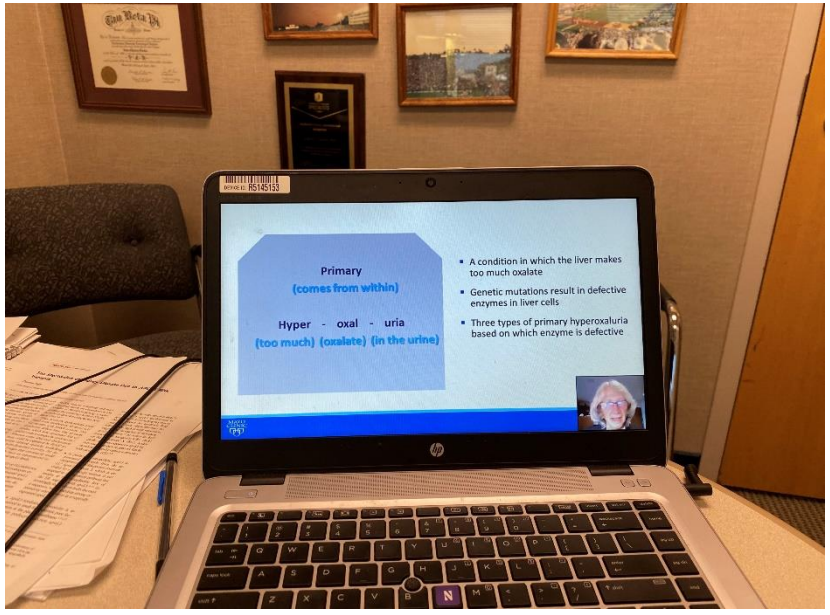
A Report on the Externally Led Patient-Focused Drug Development Meeting Corresponding to FDA's Patient-Focused Drug Development Initiative

Externally Led Public Meeting: October 5, 2020
Report Date:
Hosted by: The Oxalosis & Hyperoxaluria Foundation

Submitted to:
Center for Drug Evaluation and Research (CDER) &
Center for Biologic Evaluation and Research (CBER)
U.S. Food and Drug Administration (FDA)

Oxalosis & Hyperoxaluria Foundation
STEPPING STONES TO A CURE





Quality of Life
Collaboration with Dicerna/ Novo Nordisc

- Survey Tools
  - **PH survey** adapted from our Voice of the Patient meeting
  - **The Wisconsin StoneQOL (WisQOL)**
    - The Wisconsin StoneQOL underwent reliability and validity testing in 248 stone formers and demonstrated good internal consistency.
    - This instrument is currently undergoing further testing in a large multicenter trial.
    - Wisconsin StoneQOL scores are expressed on a scale between 0 and 100, with a higher number indicating a better QoL.
  - **Work Productivity and Activity Impairment Questionnaire (WPAI)**
- Administered electronically via REDCAP
- Promoted in OHF sponsored Webinar

Recent PH-related health event

	Living with PH	Parent or caregiver
Kidney stone	14	8
Decreased Kidney function	6	5
Failure to thrive	0	3
Hematuria	3	4
UTI	3	3
Fatigue	5	5
Bone fractures	0	1
Bodily pain	9	7
Nausea or vomiting	2	6
Chills/fever	1	2
Heart or eye problems	0	1
Anxiety or depression	11	8

What outcomes are most meaningful

	Living with PH	Parent or caregiver
Slowing formation of stones	10	7
Stopping formation of stones	14	15
Regaining energy	5	0
Lessening pain	2	0
Improving kidney function	6	5
Decreasing need for superhydration	6	5
Deceasing UTIs	1	0
Stopping disease progression	8	11
Eat what I want	4	1

PH treatment landscape

- **Lumasiran (GO) and Nedosiran (LHDa) seem equally effective for PH1**
  - Unclear why an LDHa approach did not initially work for PH2 or PH3
    - ?Dosing
    - ?pathway nuances
    - ? Genotype: phenotype
- **Other approaches under consideration**
  - Gene therapy
  - Small molecule
  - Multiple targets at once
- **Use of siRNA may allow kidney alone transplant in kidney failure** (without liver transplant)
- **Registries still essential to answer these questions; develop long term outcomes**

Conclusions

- **KHI project has worked as envisioned**
  - Stakeholder identified and engaged
  - ASN staff were instrumental for organizing the group, identifying next steps
  - Robust FDA involvement along the way
- **Project was “ripe” for this process**
  - Strong industry pipeline
  - Pressing need for consensus regarding trial designs for this rare disease population since standard double blind trials with hard endpoints may not be feasible or timely
- **Pooling data in retrospective registries was crucial to understand this monogenic disease**
  - define natural history and disease surrogates
  - Attract industry and technology
  - Support regulatory approval
- **In 2024 there are 2 approved therapies for the devastating disease PH1!**

Hard work towards newer treatments

Oxalosis & Hyperoxaluria Foundation

STEPPING STONES TO A CURE

RARE KIDNEY STONE CONSORTIUM

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www.rarekidneystones.org
1-800-270-4637

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Case Example Reactor Panel

Reactor Panel

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Kirtida Mistry, MBBCh, DCH, MRCPCH, Center for Drug Evaluation and Research, FDA
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Thank You!

Meeting materials will be posted on:
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