NORD
National Organization for Rare Disorders

Rare Disease Scientific Symposium

Data for Endpoint Selection

Craig Lipset
Decentralized Trials & Research Alliance, Buffalo Initiative
(Moderator)

Gabrielle Conecker, MPH
Decoding Developmental Epilepsies

Gerald F. Cox, MD, PhD, FACMG
Gerald Cox Rare Consulting, LLC; Boston Children's Hospital, a NORD Rare Disease Center of Excellence

Amena Fine, MD, PhD
Kennedy Krieger Institute, a NORD Rare Disease Center of Excellence

Amy Raymond, PhD, PMP
Worldwide Clinical Trials

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Data for Endpoint Selection

Gerald F. Cox, Md, PhD

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The Art and Science of Selecting Endpoints in Rare Disease Clinical Trials

Gerald F. Cox, MD, PhD, FACMG
Staff Physician in Genetics, Part-time
Boston Children's Hospital

Endpoint Objectives

Target Engagement	Pharmacodynamics	Clinical Benefit
• Is the drug active?	• Is there a biological effect?	• Is the drug effective?
• Proximal biomarker tied to MoA of drug	• Downstream biomarkers from MoA of drug	• Feels, functions, or survives

MoA, mechanism of action

PathMap for Gaucher disease type 1

Level	Gene	Protein	Biochemical	Cell	Organ	Early Clinical	Late Clinical
Feature	Biallelic *GBA* mutations	GCase deficiency	Increased GL-1, and lysoGL-1 substrates	Accumulation of substrate leads to lysosomal expansion and dysfunction, transforming macrophages into Gaucher cells	Infiltration of liver, spleen and bone marrow by Gaucher cells	• Hepatomegaly • Splenomegaly • Hypersplenism • Anemia • Thrombocytopenia • Low BMD • Delayed growth and puberty	• Splenic rupture • Bleeding • Blood & platelet transfusions • Skeletal pain, infarcts, and fractures • Fatigue • Low QoL • Disability
Assay	• DNA sequence	• Activity assay	• Plasma LC-MS/MS	• Lysosomal volume (IFM) and substrate (LC-MS/MS) in PBMCs	• Tissue levels of Gaucher cells (IFM) and substrates (LC-MS/MS) • Chitotriosidase • CCL-18	• Liver& spleen volume (MRI) • Hemoglobin • Platelets • BMD (DXA) • BMB (MRI) • AGV/Tanner Stage • Gaucher DSS	• # transfusions • # fractures • Pain, fatigue scores • SF-36, EQ-5D • ADL score • Ht, Wt Z-scores • Gaucher DSS

AGV, annualized growth velocity; BMB, bone marrow burden; BMD, bone mineral density; DSS, disease severity score; IFM, immuno-fluorescence microscopy; LC-MS/MS, liquid chromatography-tandem mass spectrometry; PBMC, peripheral blood mononuclear cells

Endpoint Development

Concept of Interest (COI)

- What domain is being measured?
- What is the desired outcome?

Clinical Outcome Assessment (COA)

- How is it being measured?
- Is it subjective or objective?
- What is clinically meaningful?

Context of Use (COU)

- Why, where, when, and in whom is it being measured?
- Intended claim?
- Geography, language, culture, clinical practice SoC?
- Central reader?
- Frequency?
- Patient subset?

Endpoint Alignment with Disease Stage and Drug Effect

- Disease course
  - Rapid vs slow progression
  - Frequency of events vs continuous change
  - Responders vs non-responders
  - Single vs co-primary vs composite vs multi-domain endpoints

- Drug effect – dictates disease stage and trial designs
  - Improvement vs stabilization
  - Prevention vs reversal
  - Transient effect – cross-over, N-of-1
  - Durable effect – parallel group

Endpoint Attributes – Validation

Validation Element	What It Answers	Type	When Established
Face	Does it look appropriate?	Qualitative	Early
Content	Does it cover the domain?	Qualitative	Early–mid
Sensitivity	Can it distinguish groups?	Quantitative	Mid
Analytical	Is it technically reliable?	Quantitative	Mid
Change	Can it detect within-person change over time?	Quantitative	Late

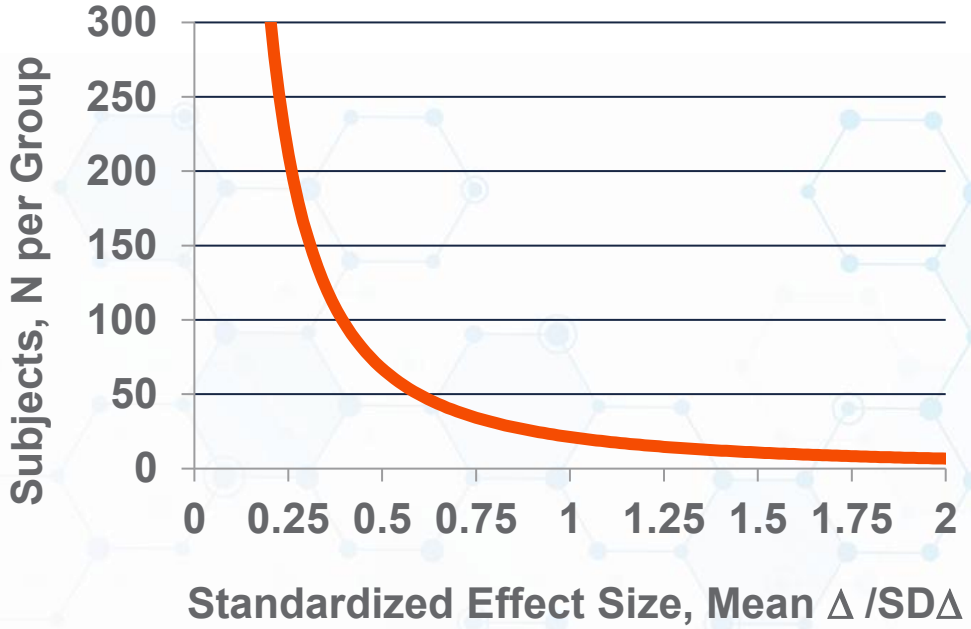
Endpoint Attributes – Feasibility

- For the Subject & Family
- Study burden fatigue
  - Duration of assessment
  - Frequency of assessment
  - Travel to clinic for assessment
  - Invasiveness of assessment
  - Risks of assessment

- For the Sponsor
- Logistical complexity and cost
  - Ensure availability at all clinical sites
  - Validate translation of questionnaires
  - Assay development and validation
  - Disease-specific assessment development and validation
  - Training of assessors
  - Standardization of assessments
  - Central labs and readers

Endpoint Attributes – Effect Size

- Intended treatment effect must be statistically significant and clinically meaningful
- Effect size (mean change/SD change) is inversely proportional to sample size
- Sample size is determined by power (80-90%), statistical significance (p< 0.5), and effect size



SES	N per Group
1.5	7
1	16
0.8	26
0.5	63
0.25	251

Sample size calculations based on 80% power and P <0.05 (two-tailed)

Cox GF, Am J Med Genet A. 2018;176:759-772

Endpoint Attributes – Interpretation

- Clinically meaningful change is recognized by the patient and/or clinician as providing clinical benefit

- Clinical benefit can be interpreted in complementary ways:
  - Minimum (clinically) important difference (MCID or MID) – mean change
  - Cohen's effect size (Cohen's *d*) – 0.2 (small); 0.5 (medium); 0.8 (large)
  - Responders – % of subjects who achieve MCID/MID
  - Number needed to treat – number of subjects required to produce one responder
  - Statistical rationale – change exceeds assay variability (e.g., 3 SD)

Endpoint Attributes – Natural history

- Characterizing potential endpoints for a clinical trial (desired outcome)
  - How many patients have abnormal values? (higher prevalence)
  - How abnormal are the values? (moderate to severe)
  - How fast does the disease change? (faster rate of progression)
  - How often do events occur? (higher frequency)
  - How predictable is the change over time? (lower standard deviation)
  - How homogeneous are the patients? (responsive sub-population)
  - Are there known disease modifiers? (stratify or exclude sub-populations)
- Understanding these characteristics aids in endpoint selection and sample size determination

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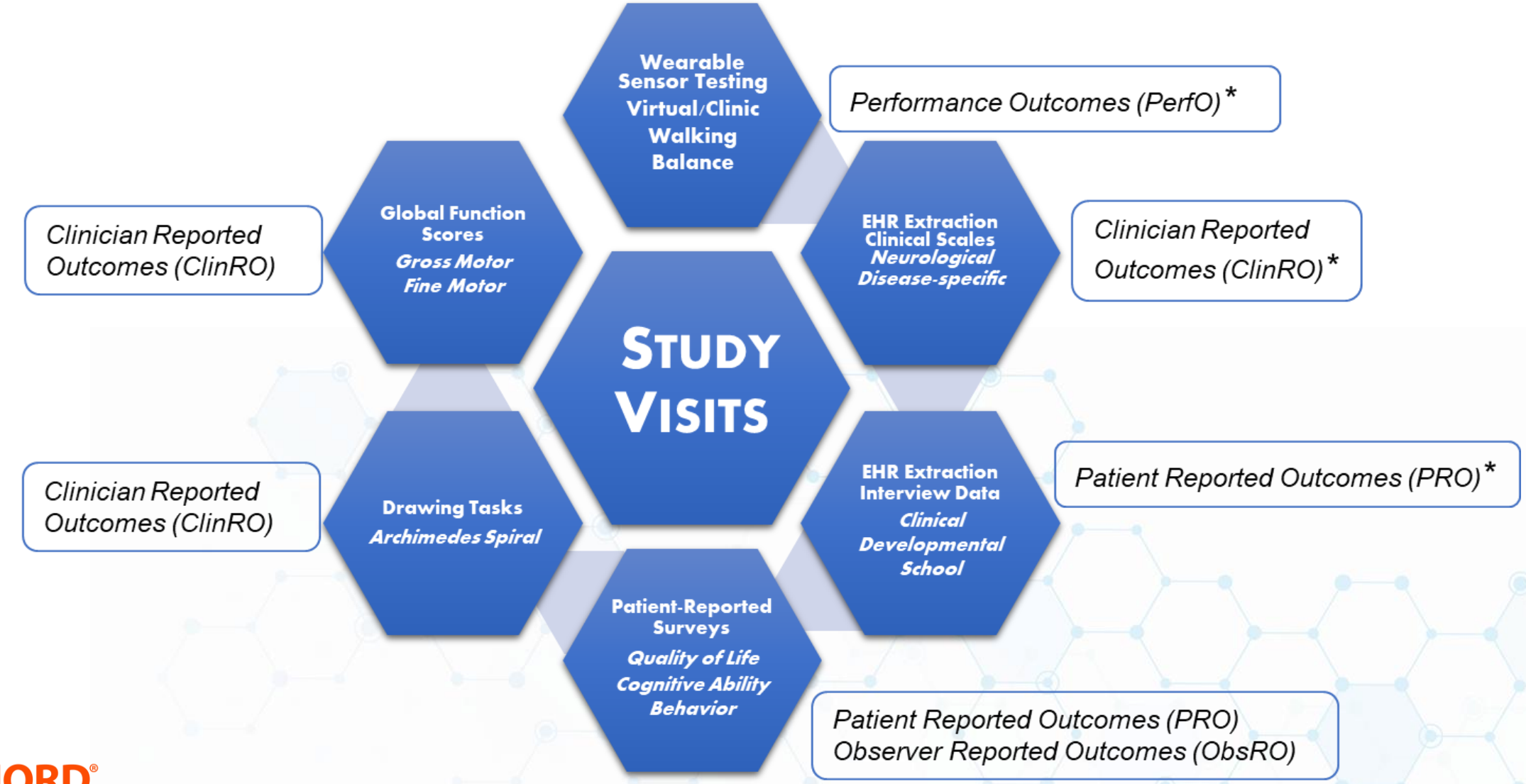
Data for Endpoint Selection

Amena Smith Fine, MD PhD

Assistant Professor Neurology

Kennedy Krieger Institute

Clinical Outcome Assessments for Endpoint Selection

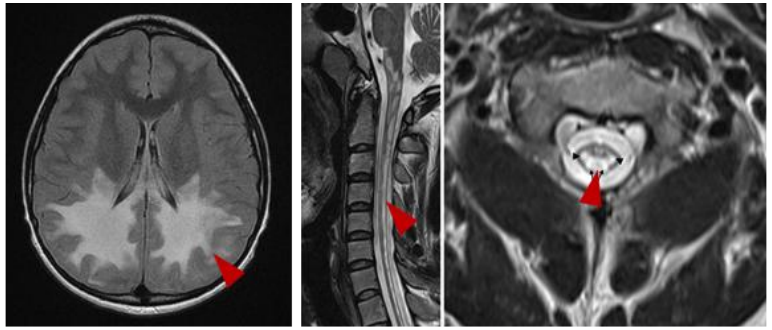


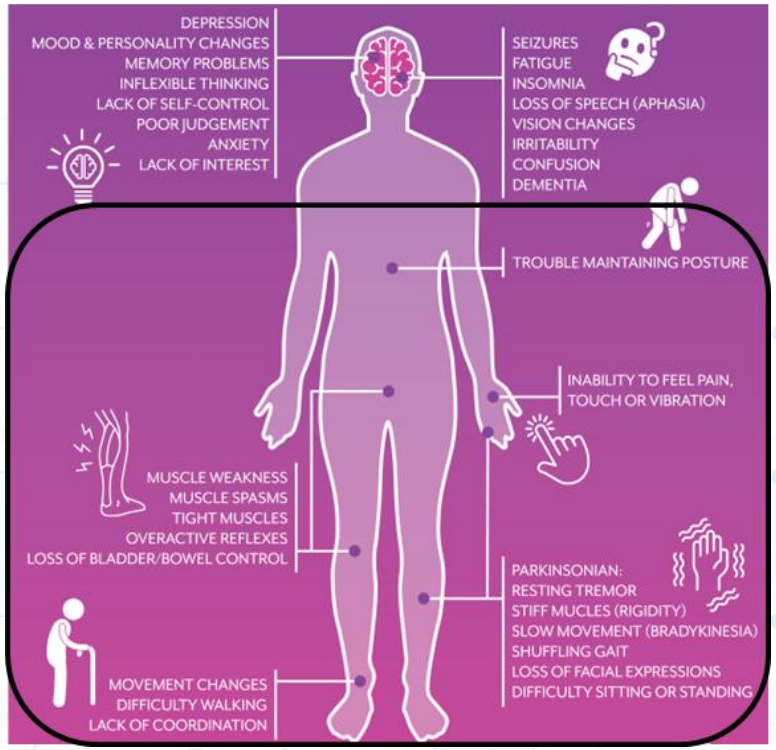
Endpoint Selection Approaches in Leukodystrophies

- Diverse group of rare genetic disorders that affect CNS myelination (1:7,000)

- *Broad* spectrum of neurologic and medical problems
  - Motor dysfunction, impaired feeding, orthopedic complications, respiratory failure, seizures, cognitive and/or developmental delays
  - Present across the **entire** lifespan

How do we determine clinically meaningful endpoints across a large, heterogeneous group of conditions?





EHR Data Extraction to Determine Endpoints in LDs

- 2025 LD consortium cohort study of >1000 patients (42 LDs)
- Automated EHR extraction queries of structured and unstructured data
- **Motor severity was the most important driver of complications**
  - Mortality was *highest* in patients with *lowest* motor milestone attainment
  - Many lose walking ability and require extensive physical assistance and adaptive equipment
  - Wide range of physical disabilities, high healthcare costs and patient/caregiver burden

Potential generalizability of clinical management, monitoring and treatment strategies across LDs

GLOBAL
LEUKODYSTROPHY
INITIATIVE

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Kotes E, Smith Fine A, Vanderver A, *et al*. ACNS 2025

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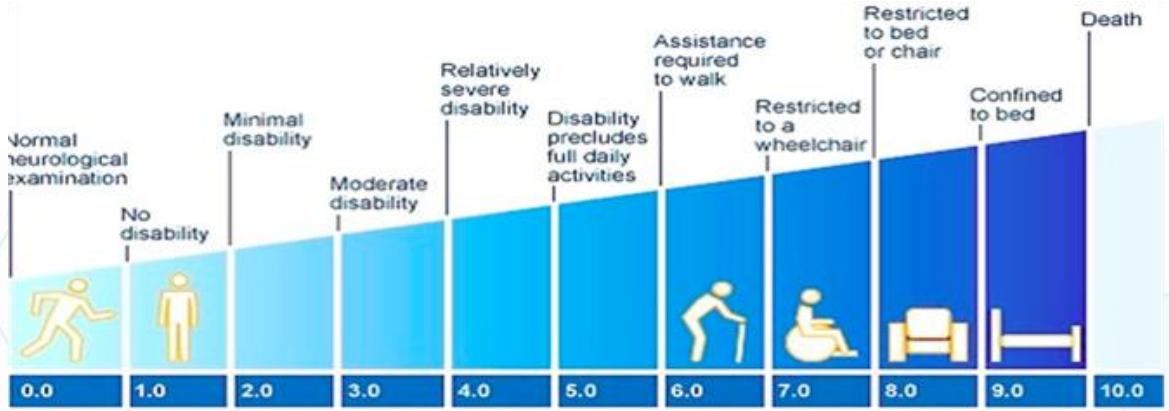
Approaches to Monitor Motor Disease Progression

- **Importance of monitoring disease severity and progression**
  - Patient perspective
  - Pharmaceutical trials perspective
- **Challenge of variable progression**
  - Clinical Scales
    - e.g. EDSS (Expanded Disability Status Scale)
    - Validated
    - Commonly used
    - *Not susceptible to small changes*
- **Need for sensitive, accessible outcomes**
  - Quantify brain and spinal cord neurodegeneration
    - Balance and gait disturbance



van Ballegoij WJC, Engelen M, *et al.* Front Physiol, 2020
Yan C, Smith Fine A, Pierpont R, *et al*. ACTN, 2026

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Wearable Sensors: In Person or Remote Data Collection

- **Wearable triaxial accelerometers**
  - *Collect data on physical activity using non-invasive sensors*
  - Watch sized battery-based accelerometers
  - Validity established in comparison with motion lab equipment
  - Placed on waist, feet, +/- chest, wrists for a series of tests
    - Pre-defined tasks (e.g. walk and balance tests) vs. dynamic movement vs. general activity tracking or step counts

- **Advantages of a wearable system**
  - Sensors can be used in-person or at home during virtual visits
  - User friendly for the participant and new staff
  - Allows more frequent collection of data points
  - Tests are directly supervised in real-time by research staff

Horak FL, *et al*. J Bioeng Biomed Sci 2014
Dewey DC, *et al*. J Neurol Sci 2017
Zesiewicz TA, *et al*. Gait and Posture 2017
Smith Fine A, *et al*. ACTN 2022
Yska H, *et al*. JIMD 2024

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Wearable Devices for Sensorimotor and Activity Assessment

Stride velocity
Foot Angles
Postural sway

Sit to stand
Turning
Leaning

Steps (temporal symmetry, stride variability)

Calories
Activity counts
(over minutes, hours, days)

Sleep
Circadian Rhythmicity

Opal V2

Actigraph

Fitbit

Opal V2C

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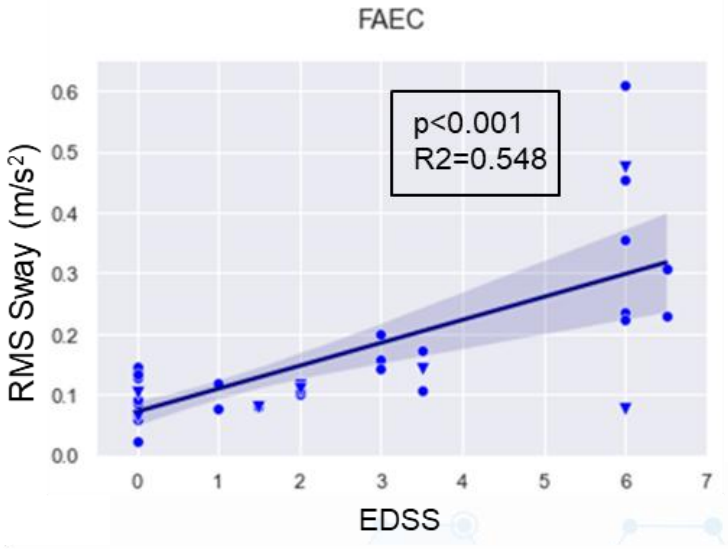
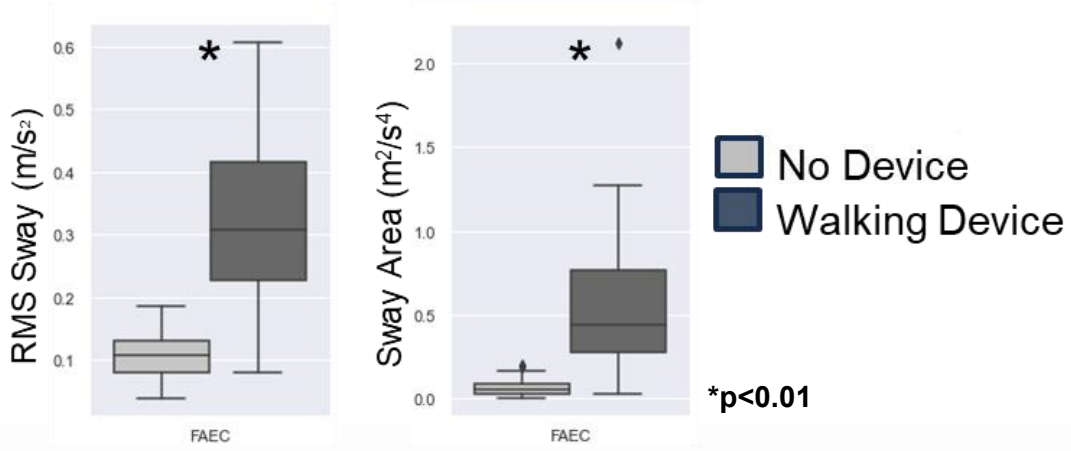
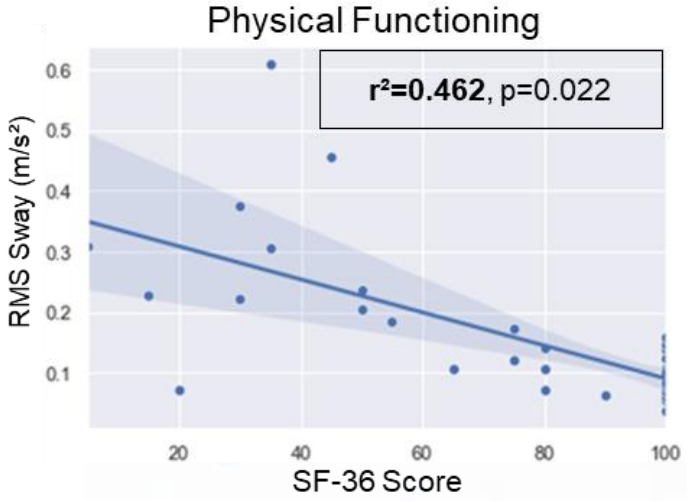
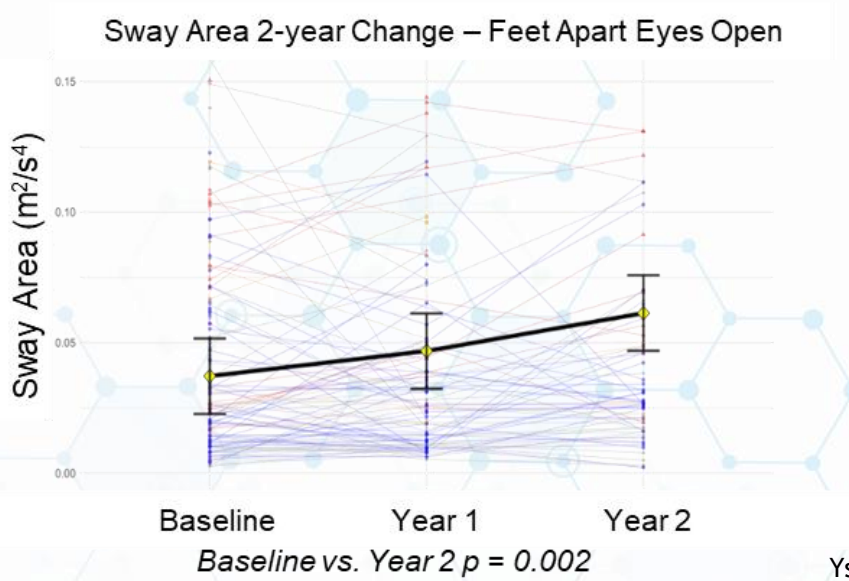
Clinically Meaningful Outcomes Identified in X-ALD - *Sway*









Yska H, Smith Fine A *et al*. JIMD 2024

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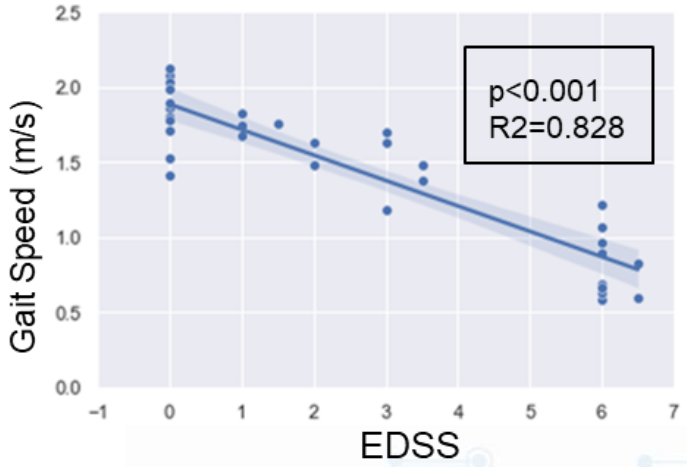
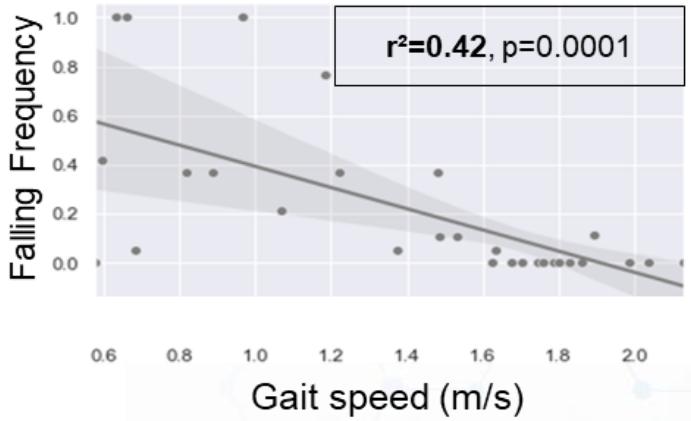
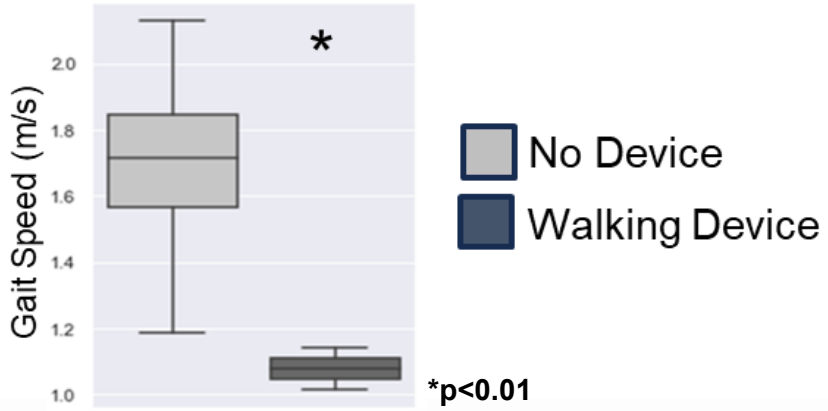
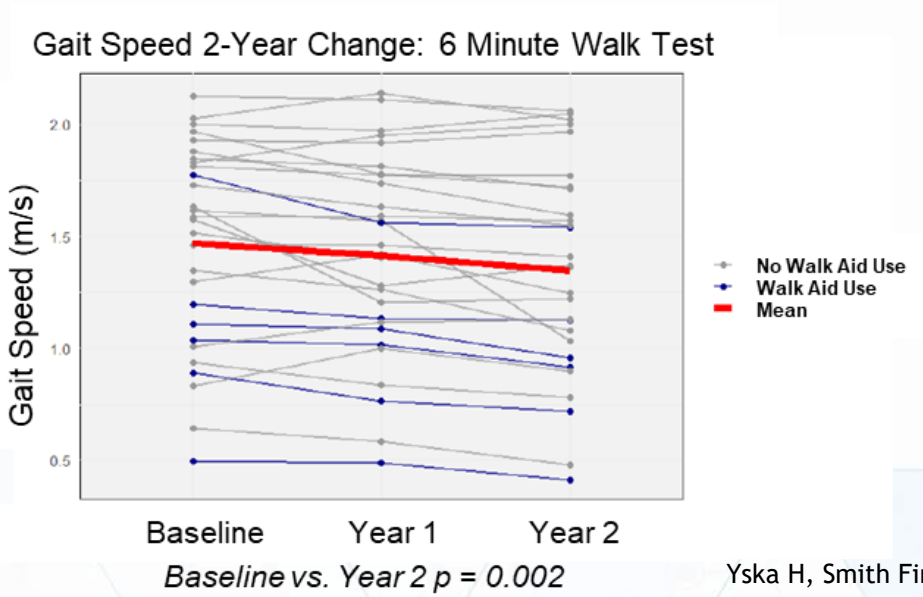
Clinically Meaningful Outcomes Identified in X-ALD - *Gait*









Yska H, Smith Fine A *et al*. JIMD 2024

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Thank You

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Assistant Professor of Neurology

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Data for Endpoint Selection: Caregiver-Led Efforts to Measure All

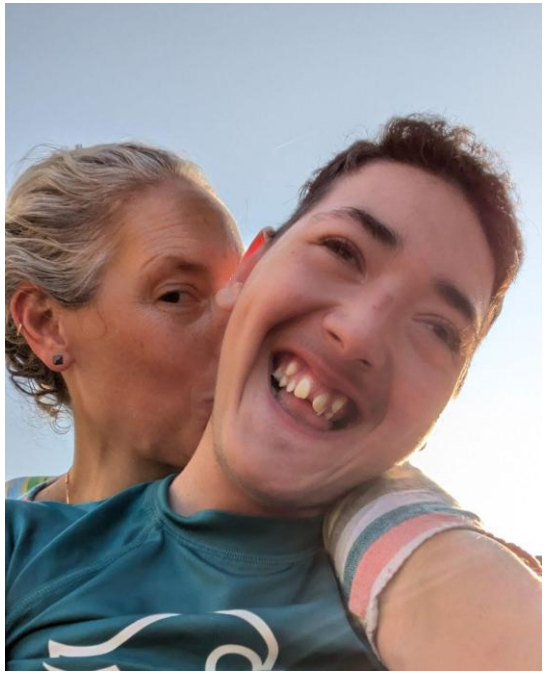
Gabi Conecker, MPH
Decoding Developmental Epilepsies

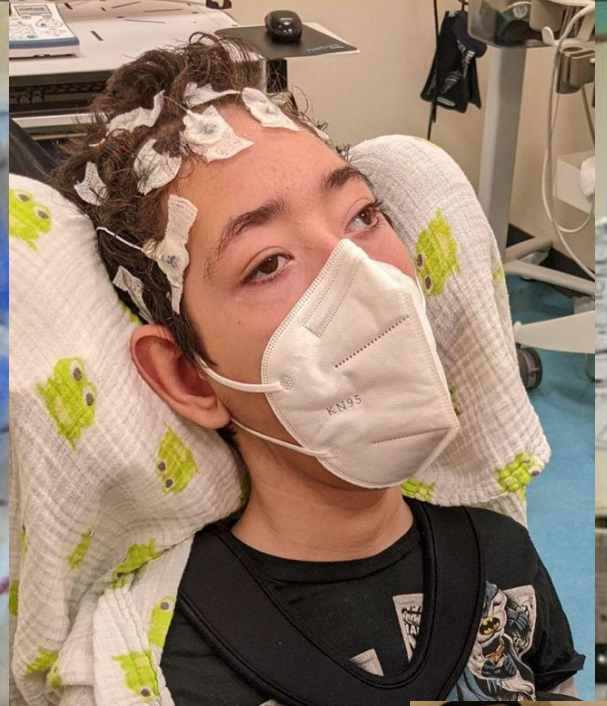
Decoding Developmental Epilepsies

DEE-P CONNECTIONS

About Me

- Background in Global Public Health
- 13 year old son with a severe pediatric-onset genetic epilepsy disorder - SCN8A-DEE
- Isolated caregiver with no information on best care and treatments on a newly discovered disorder





KN95

PUSH
DOWN
& TURN

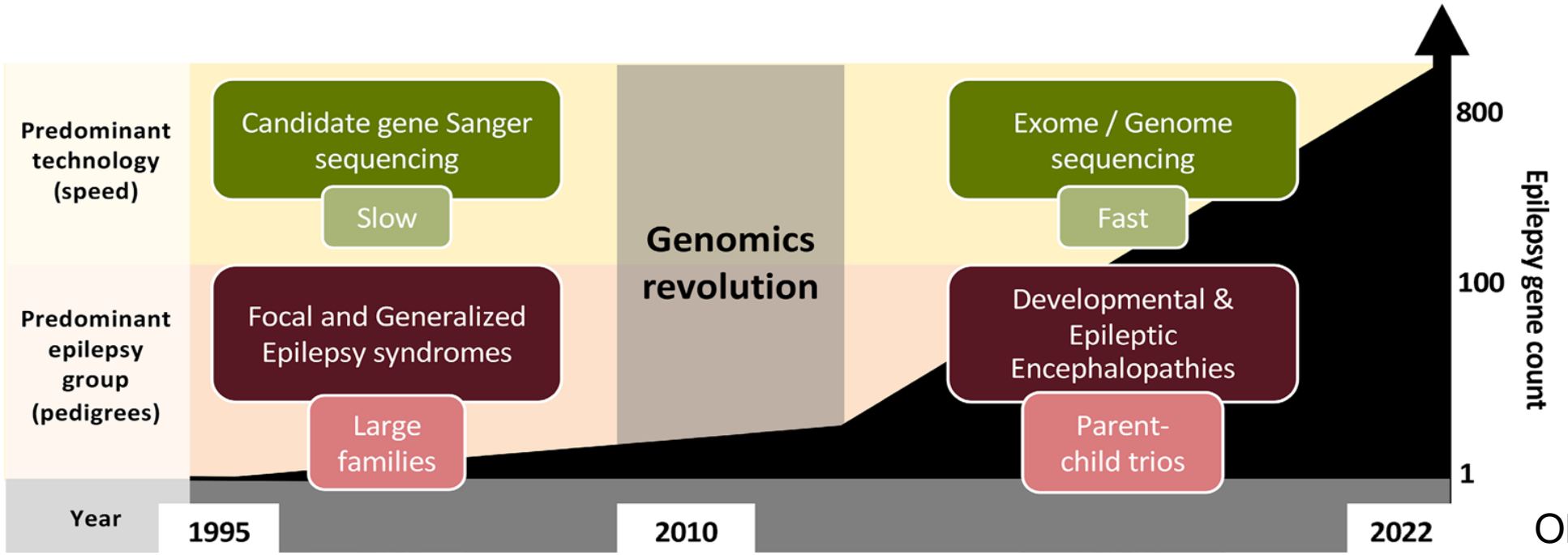




PHILIPS

NEOTECH VeoGrip®

There is Exponential Growth in Gene Discovery



Oliver et al 2023

Nearly 1000 monogenetic conditions causing a DEE condition have been identified.

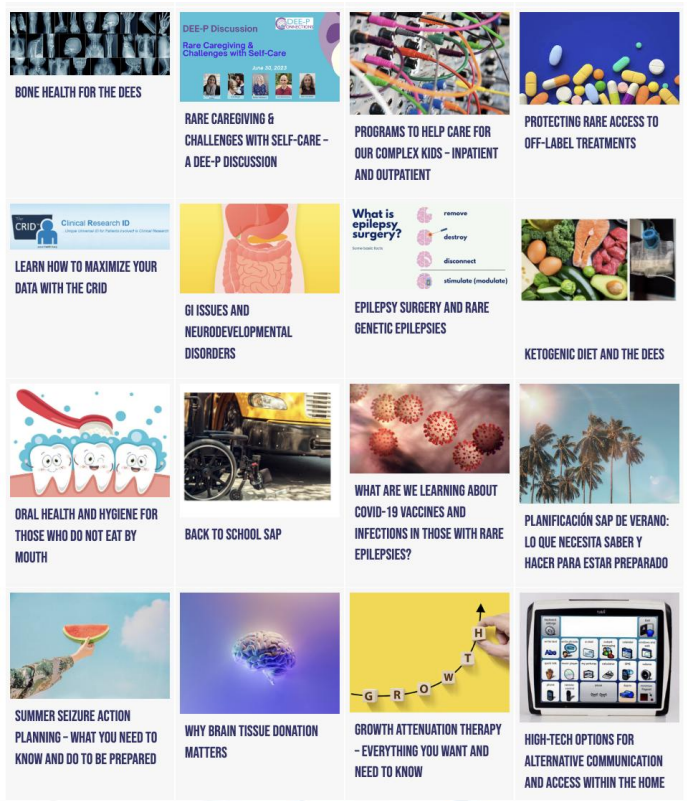
➔ **We cannot only pursue clinical trial readiness one disorder at a time.**

Building DEE-P Connections

DEE-P CONNECTIONS

Collaboration

Resource Center Hub



Multi-layered Approach

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Guidance on Endpoints

21st Century Cures Act

Provides the impetus for robust inclusion of and reliance on patient experience data when evaluating clinical benefits of new therapies.

This expansive definition of “patient experience data” includes a wide range of opportunities for the collection of information that might be used to inform and provide a greater patient focus in medical product development

The Food & Drug Administration (FDA) Patient-Focused Drug Development (PFDD) guidances

Issued in response to the Act to aid researchers and drug developers in designing clinical outcome assessments (COA) that provide optimal tests of a therapy's benefits.

These guidances focus exclusively on clinical outcomes and emphasize the essential and extensive role of patient-caregiver involvement in most aspects of COA development

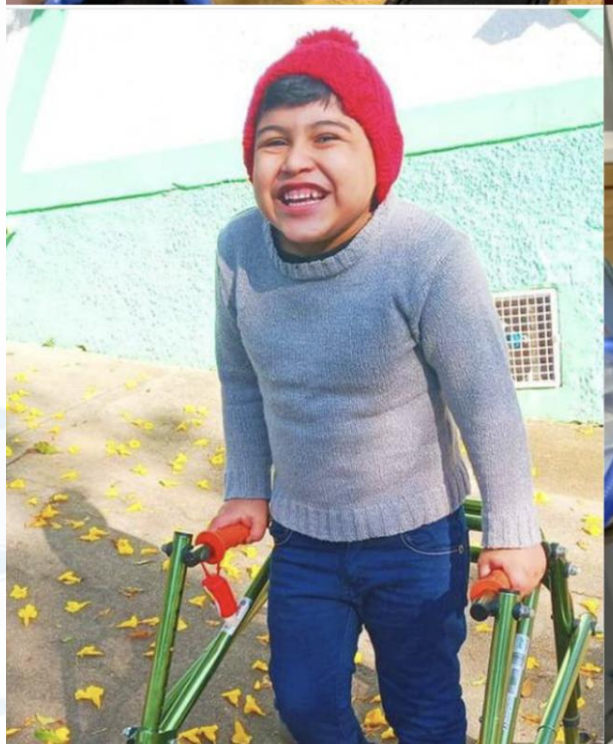
The Inchstone Project

Children with profound developmental impairments have **severe challenges**.

YET they **can do some critically important things**.

BUT **skills acquisition is slow** and takes small steps.

AND available measures **do not capture what they can do, growth and regression**.



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THE INCHSTONE PROJECT

Our Goals

THE INCHSTONE PROJECT

1. To advance neurodevelopmental measures for individuals with profound ID and severe neurological impairment (SNI) that are
   - family-centered, strengths-based, can capture meaningful change.
   - have capacity for use in clinical trials and clinical practice.

1. To facilitate their utilization in clinical practice and trials.

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Measuring What Matters Most in the DEEs and those with Severe Neurological Impairment (SNI)

THE INCHSTONE PROJECT

Communication is a top priority, regardless of etiology.

Motor and challenging behavior were also top priorities.

What counts as meaningful change depends on level of functioning

Small improvements in alertness and ability to use a touch screen help quality of life

CVI was common and we need to understand more and find the best way to measure it.

Current measures have potential for use in clinical trials, but they need modifications.

The Inchstone Approach to Suit Clinical Complexities in SNI

THE INCHSTONE PROJECT

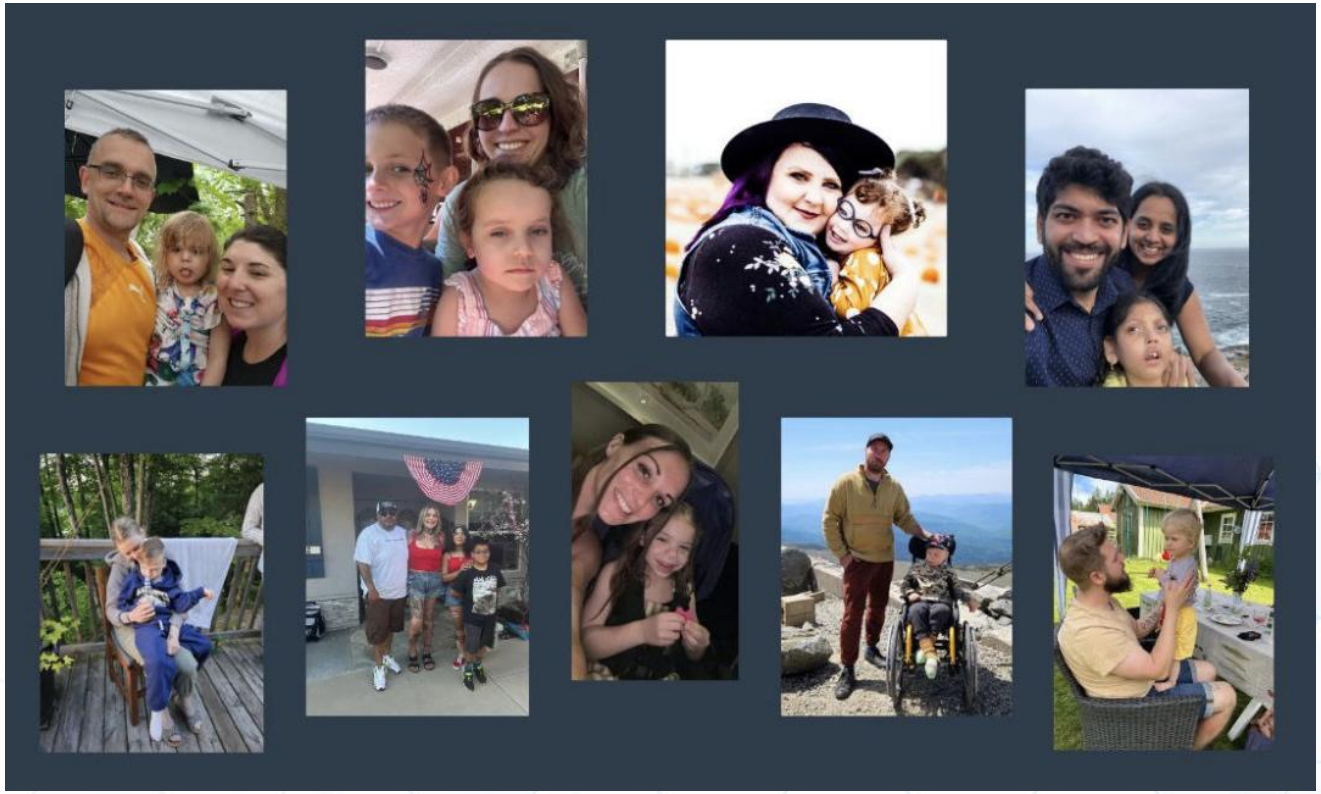
Functional impairments	1. Developmental Profile - 4 (DP-4) 2. BSID-IV - cognition domain 3. Awareness and responsivity
Associated neurological conditions	1. Cortical visual impairment - based on CVI Range assessment 2. Motor impairments
Treatment progress	1. Goal Attainment Scaling 2. Meaningful change
Quality of life	1. Quality of Life Inventory-Disability (QI-Disability)

Parents Speak Survey II

Achieving fit-for-purpose measures and endpoints for clinical trials

We MUST Embrace Data NOW to Find Cures Tomorrow

- The COG Model
- HIV Investments



Path to Meaningful Endpoints

- Engage Patient Communities from **Day 1**
- Patient priorities need to underpin pre-clinical research and development
- Unreliable measurement instruments undermine both NHS and assessment of trial outcomes
- Collaborative effort needed across disorders with similar (profound) impacts to validate FFP outcome measurement tools
- New DMT are at risk of failure without appropriate measurement tools and endpoints

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The Answers Are Waiting for Us

"Radically new science demands radically new thinking about how we regulate, manufacture, pay for and deliver treatments. Ten years from now, if children are still dying of conditions we know how to correct, it will not be because the science wasn't ready. It will be because we lacked the imagination to build a system worthy of it. KJ's story is a miracle. But it should not remain a miracle. It should become a model."

- Dr. Jeff Coller, NYTimes OpEd, April 9th 2026


OPINION
GUEST ESSAY

This May Be the Most Important Medical Story of the Decade

April 9, 2026

Matt Chase

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Decoding Developmental Epilepsies

International SCN8A ALLIANCE
Collaborating for a cure

DEE-P CONNECTIONS

THE INCHSTONE PROJECT

Be in touch

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Data for Endpoint Selection

Amy Raymond, PhD, PMP

Therapeutic Strategy Lead

Worldwide Clinical Trials

Goal: Safe, Effective, Meaningful Therapeutic Solutions

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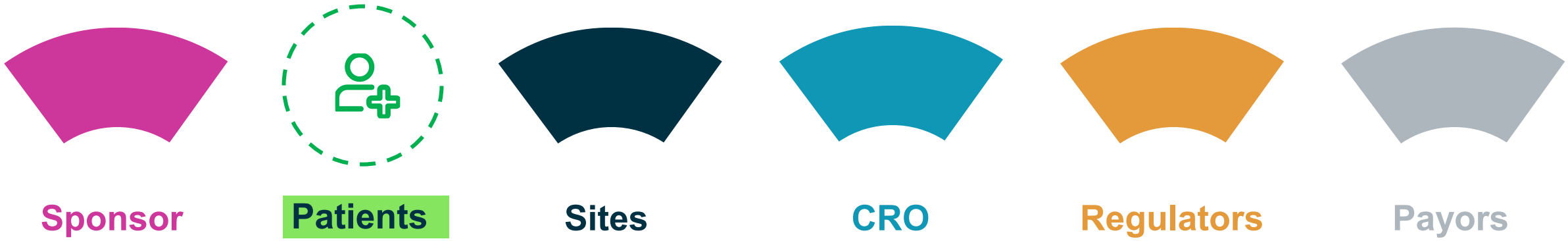
Shared Goal: Safe, Effective, Meaningful Therapeutic Solutions



Submissions

Approval

Patient Access

Pre-Clinical	Clinical Development			Regulatory Review	Post-Marketing/LTFU
	Phase I	Phase II	Phase III		Phase IV

Product Development Lifecycle

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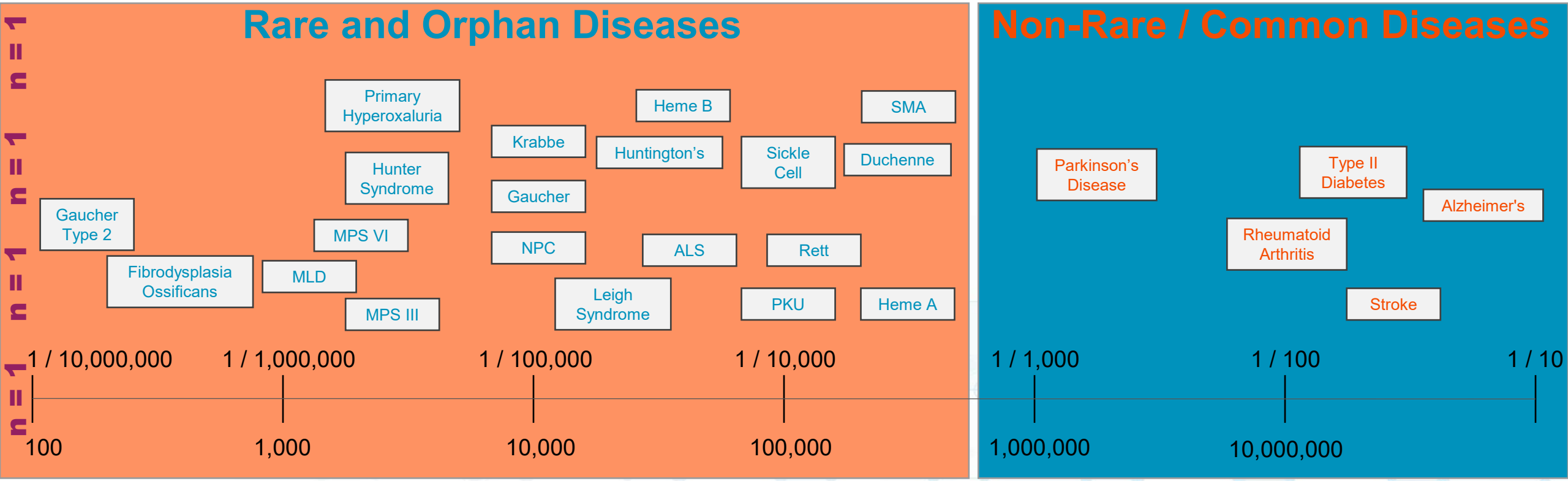
Rarity of Disease is a Spectrum



5-6 per 10,000

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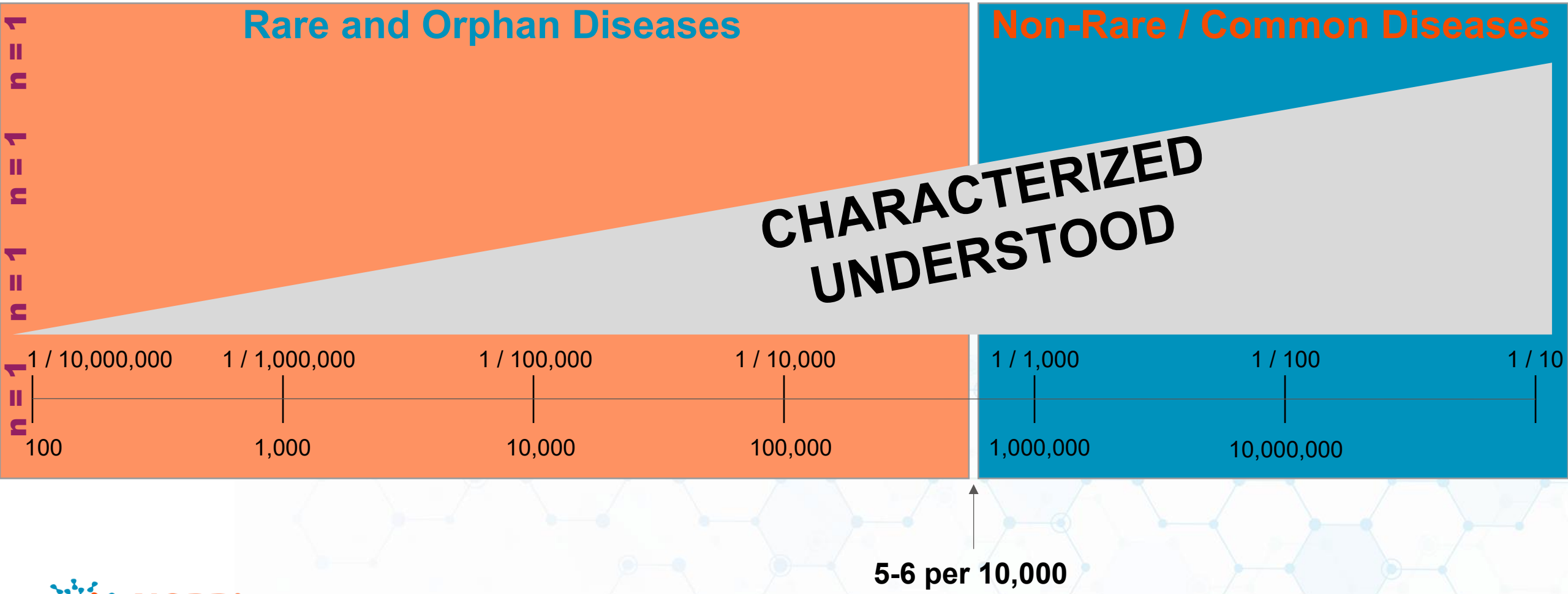
Rarity of Disease is a Spectrum



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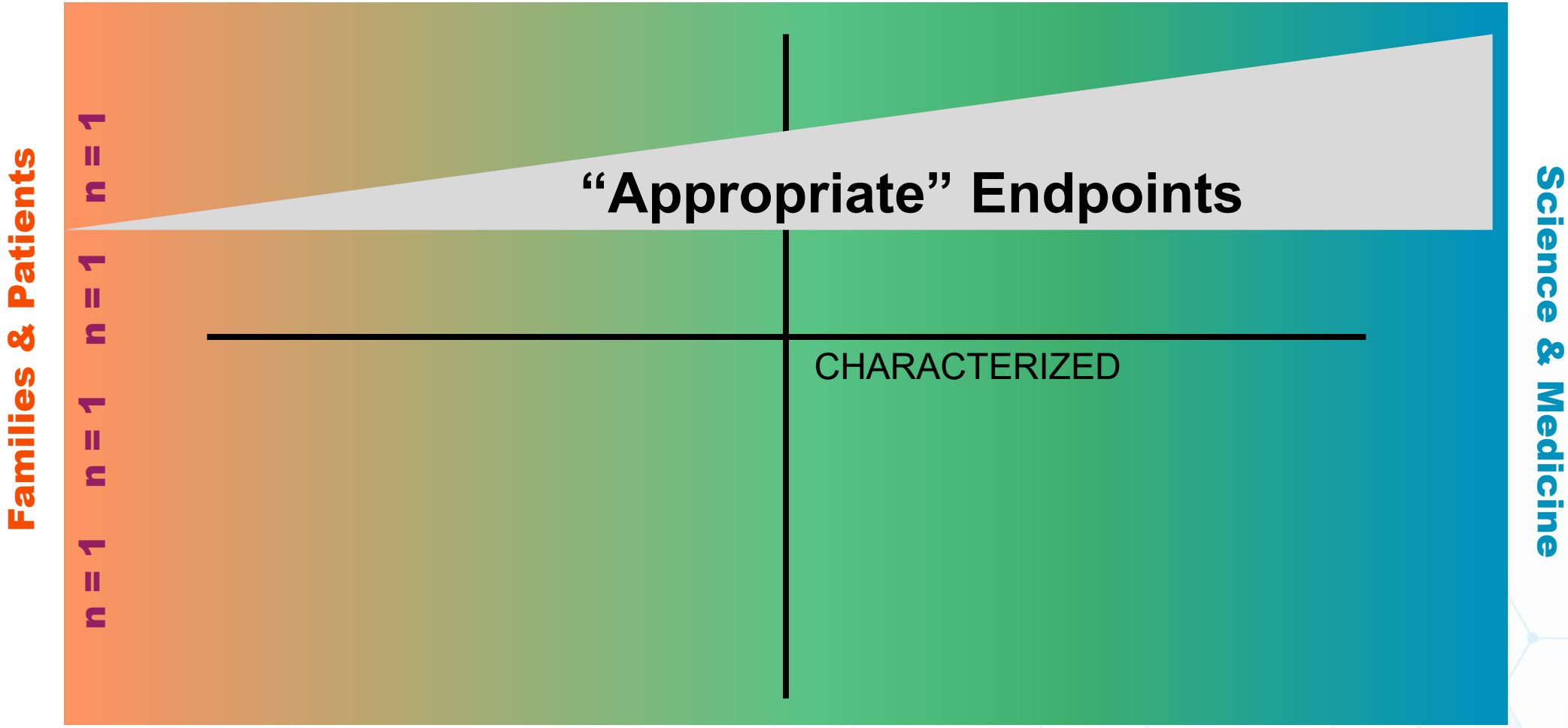
Expertise Anchored On Spectrum of Rarity



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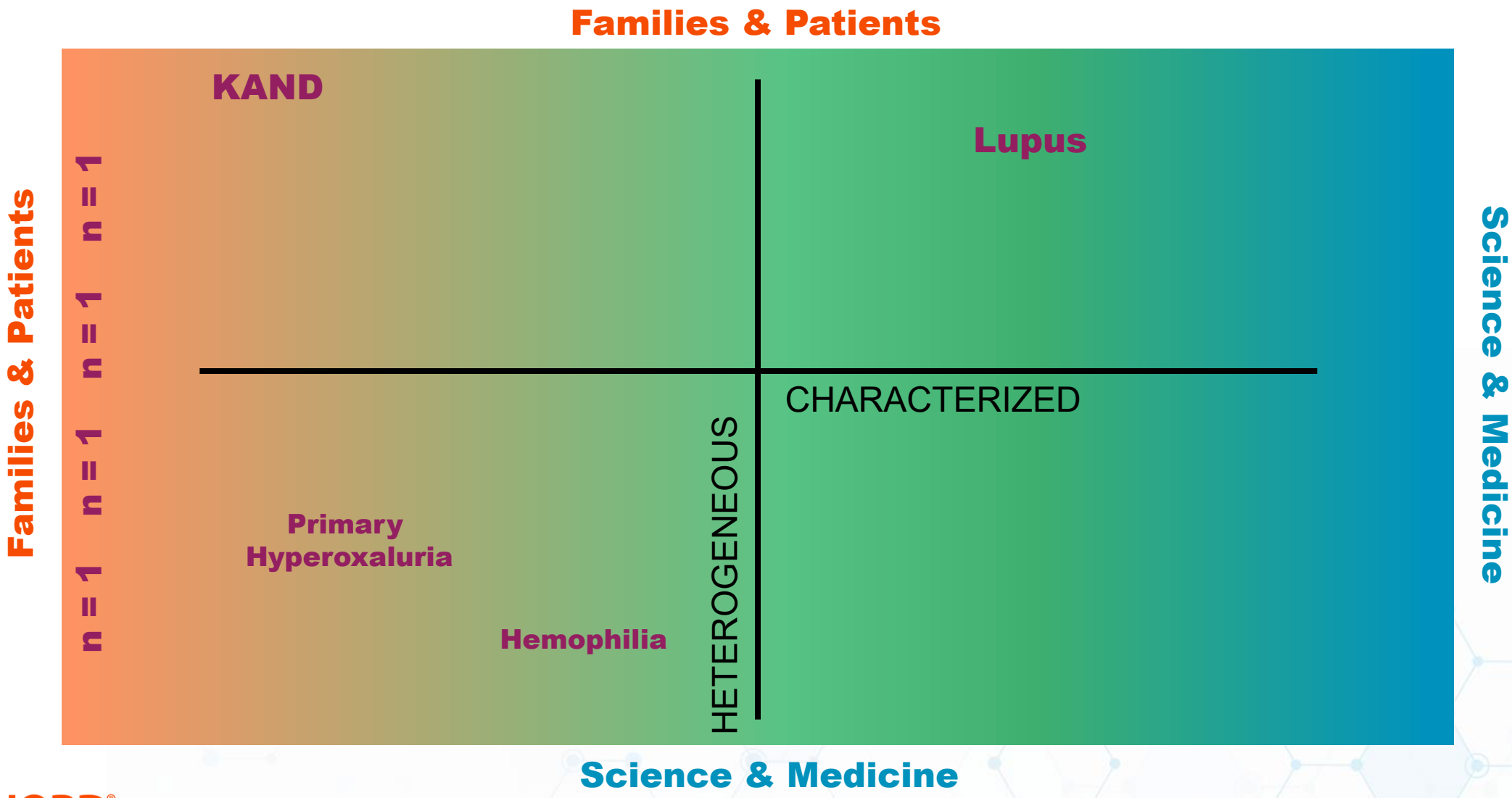
Expertise Anchored On Spectrum of Rarity X Heterogeneity



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With Each Decision, What Problem(s) Are We Solving/Making?

	Sponsor	Patients	Sites	CRO	Regulators	Payors
Goal:	relief	RELIEF	relief	relief	relief	

With Each Decision, What Problem(s) Are We Solving /Making?

	Sponsor	Patients	Sites	CRO	Regulators	Payors
Goal:	relief	RELIEF	relief	relief	relief	
Constraint:				No Constraints		No Role in Trial Design
Driver:		RELIEF				

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Endpoints: Key Attributes

Sponsor	Patients	Sites	CRO	Regulators	Payors
Valid Interpretable High-Signal Low-Noise	Matter	Measurable	Valid Interpretable High-Signal Low-Noise	Valid	Value

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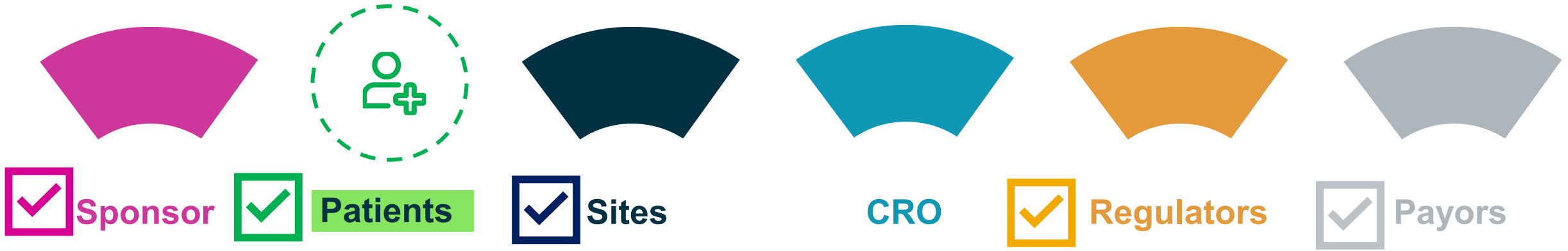
Endpoints: Key Attributes



Shared Goal: Safe, Effective, Meaningful Therapeutic Solutions

Sponsor Patients Sites CRO Regulators Payors

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Shared Goal: Safe, Effective, Meaningful Therapeutic Solutions

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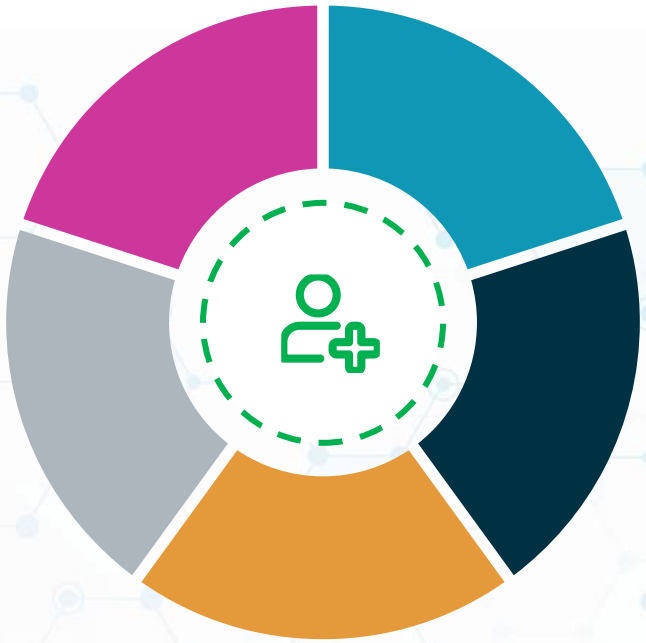
Submissions

Approval

Patient Access

Pre-Clinical	Clinical Development			Regulatory Review	Post-Marketing/LTFU
	Phase I	Phase II	Phase III		Phase IV



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Thank You

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