Patient-Focused Outcome Measurement in Rare Neurogenetic Conditions: Measuring What Matters

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Disclosures

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ASXL RARE RESEARCH ENDOWMENT

Decoding Developmental Epilepsies

I am a clinical neuropsychologist, researcher, and sibling

Why do we need measures?

- Diagnosis/categorization
- Monitoring
- Clinical care (to treat and support the individual)
- Research studies (to understand the group)
  - *Natural history studies*
    - Collect health information to understand how a disease develops and progresses over time
  - *Clinical trials*
    - Individuals are assigned to one or more treatments to evaluate the effects of those treatments on outcomes.

Measures are important, but what should we measure?

What we measure should be patient-focused, meaning, we should measure what matters most to patients as these are the aspects of the condition that are important to treat and monitor.

Let’s focus on clinical trial readiness…

There are currently no FDA approved treatments for MED13L or CTNNB1, but therapies are on the horizon.

We need to have validated patient-focused outcome measures ready for use in clinical trials. This is important to test the efficacy of novel treatments.

← Home / Drugs / Development & Approval Process | Drugs / FDA Patient-Focused Drug Development Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making

FDA Patient-Focused Drug Development Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making

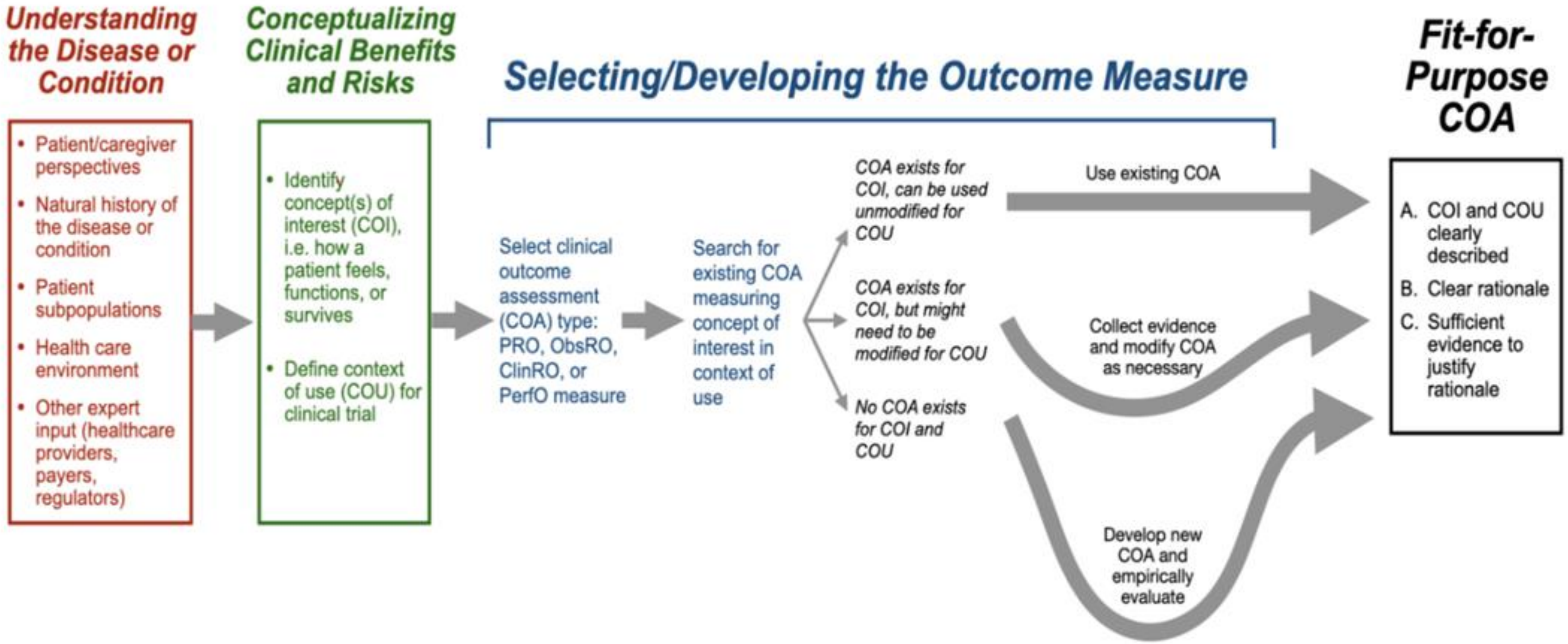
"Patient-focused drug development (PFDD) is a systematic approach to help ***ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated*** *into drug development and evaluation.*

As experts in what it is like to live with their condition, ***patients are uniquely positioned to inform*** *the understanding of the therapeutic context for drug development and evaluation."* - FDA

https://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-development

What is most important to patients and how do we measure those things?

Figure 2: Roadmap to Patient-Focused Outcome Measurement in Clinical Trials



Understanding the Disease or Condition

Understanding the Disease or Condition

- Patient/caregiver perspectives
- Natural history of the disease or condition
- Patient subpopulations
- Health care environment
- Other expert input (healthcare providers, payers, regulators)

QUANTITATIVE and QUALITATIVE approaches are critical to understand the patient experience

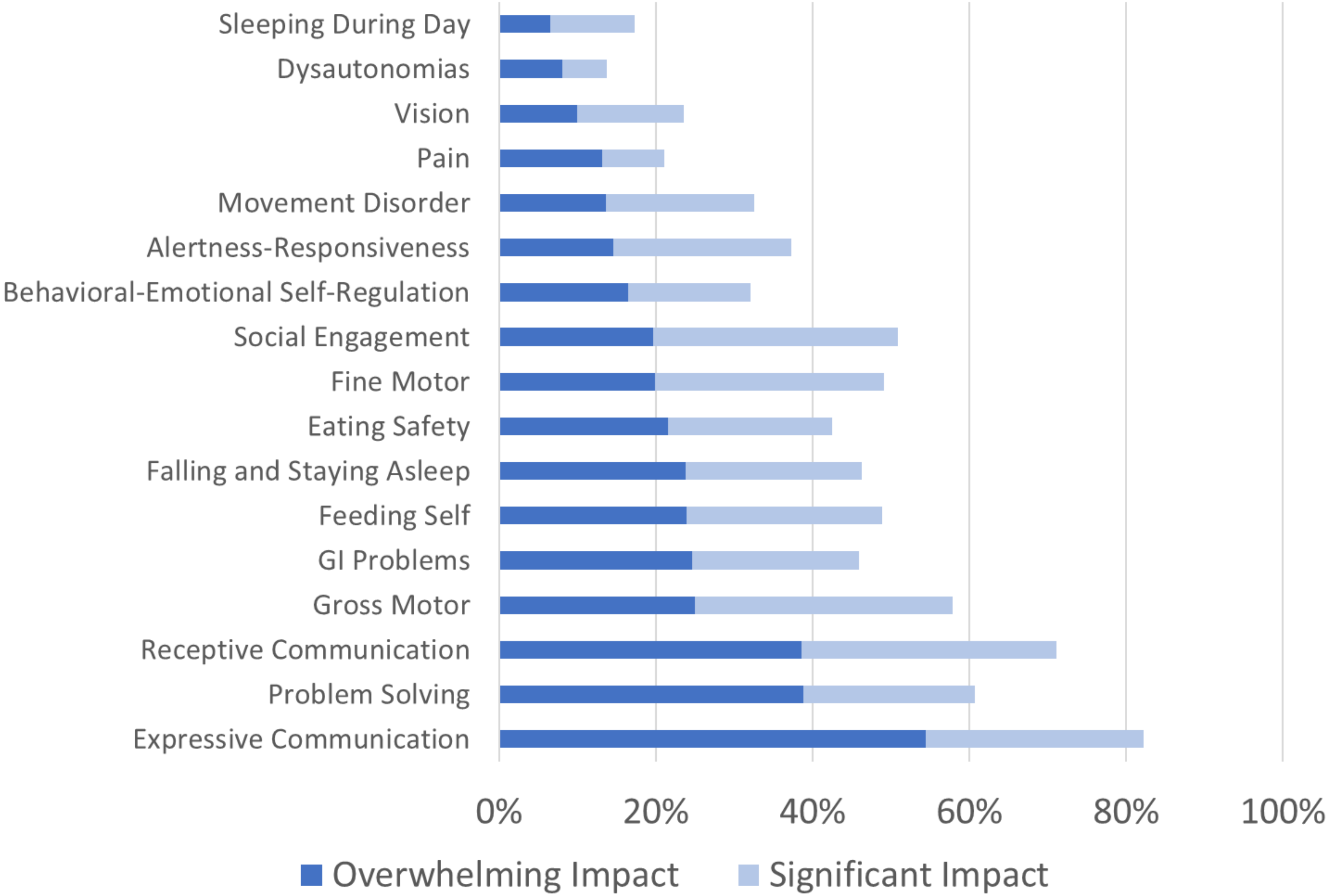
You must have good qualitative data. Good quantitative work will not solve the problems of poor qualitative work.

- Behavioral phenotyping
  - The characteristic cognitive, functional, behavioral, and psychiatric pattern that is typical in a disorder
- Natural history studies
- Conceptuel model of condition
- Understanding impacts and priorities

Some examples of ways to capture patient experience data about the condition to inform patient-focused outcome measure development…

Impact Survey: Structured, Quantitative

Caregiver survey of top impacts to quality of life in 267 individuals with severe impairments associated with rare neurogenetic conditions



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Good Day and Bad Day: Open-ended, Qualitative

How do you know your child is having a good day?

How do you know your child is having a bad day?

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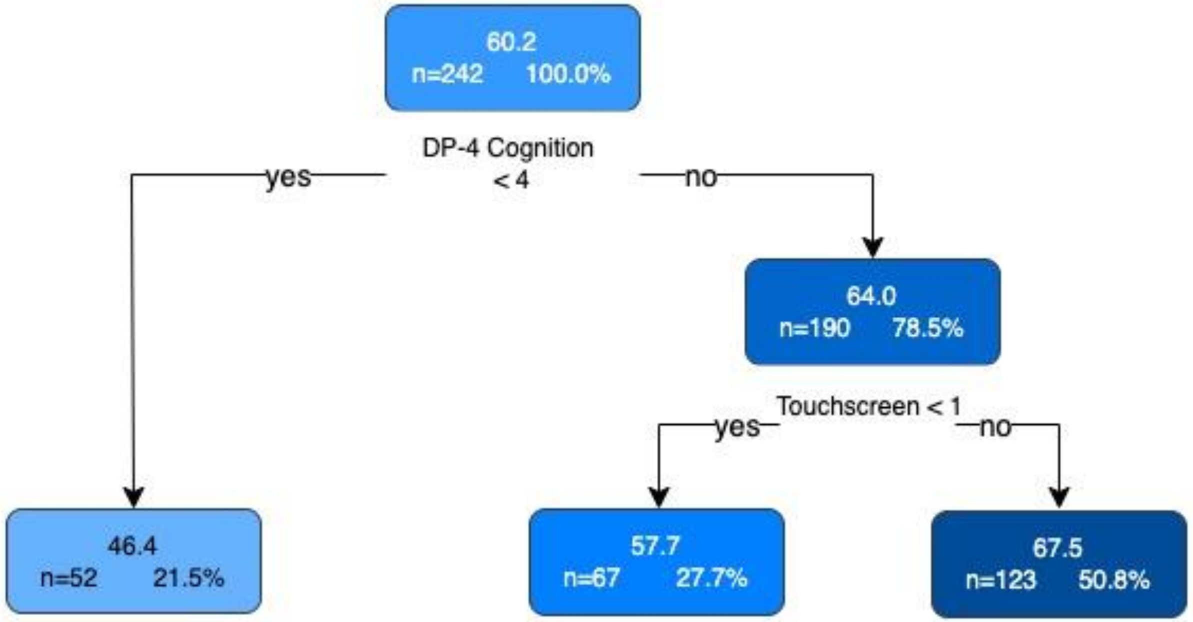
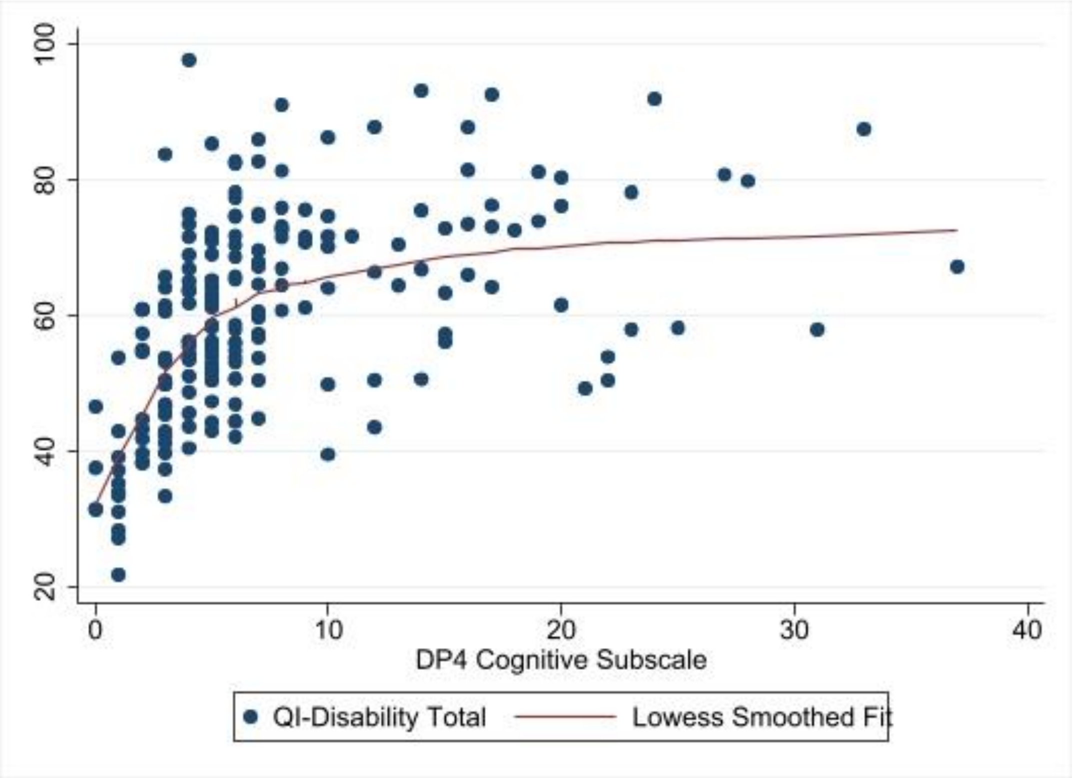
Predictors of Quality of Life: Quantitative





Ludwig, Downs et al., under review

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Priorities Survey: Open-ended, Qualitative

Building a Research Roadmap for ASXL-related disorders: Determining family research priorities

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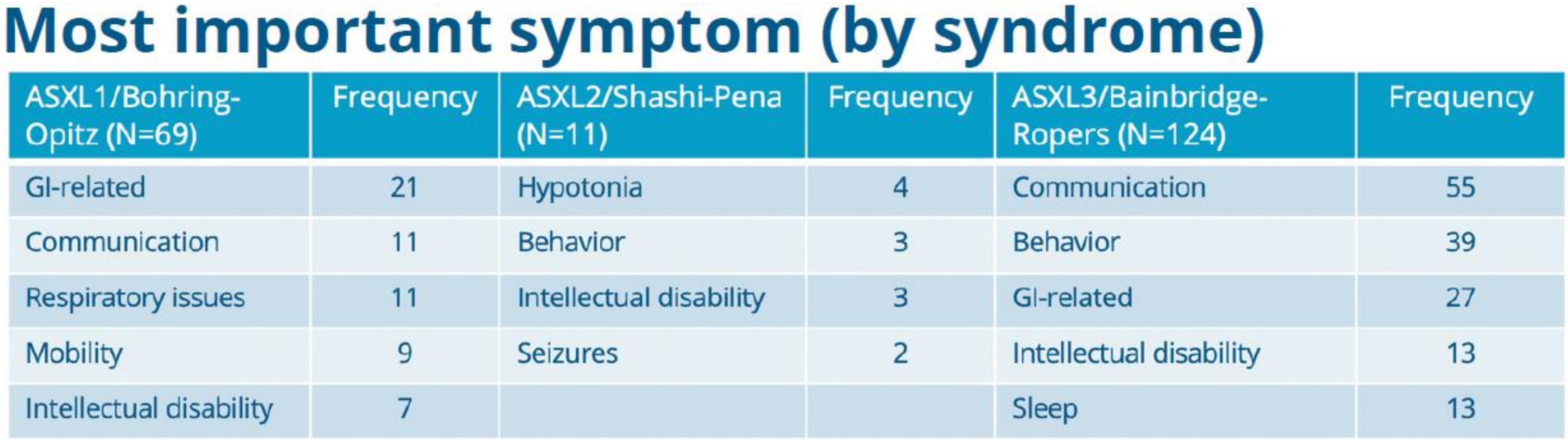

Most important symptom (by syndrome)

ASXL1/Bohring-Opitz (N=69)	Frequency	ASXL2/Shashi-Pena (N=11)	Frequency	ASXL3/Bainbridge-Ropers (N=124)	Frequency
GI-related	21	Hypotonia	4	Communication	55
Communication	11	Behavior	3	Behavior	39
Respiratory issues	11	Intellectual disability	3	GI-related	27
Mobility	9	Seizures	2	Intellectual disability	13
Intellectual disability	7			Sleep	13

Johnson et al., 2022

Priorities Focus Groups: Qualitative

- **40 participants in 15 focus groups**
  - *Lived experience of the symptoms*
  - *Impact of the symptoms*
  - *Meaningful change in the symptoms*

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Neurodevelopment

- Atypical trajectory of development
- Emotional/behavioral dysregulation and mental health
- Inadequacy of current assessments/ measurements

Gastrointestinal

- Approaches to management
- Interventions/ supports
- Recognizing/ communicating GI symptoms
- Feeding/mealtime challenges
- Healthcare experience

Behavior

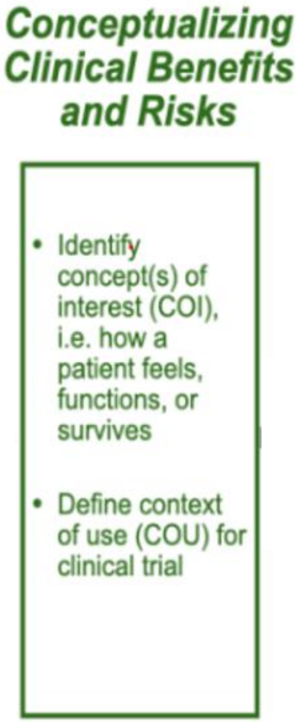
- Manifestation of problem behaviors
- Assessment and treatment of problem behavior
- Impact on the family

MED13L Priorities Survey is LIVE! Access here:

MED13L Disease Concept Map is being presented!

CTNNB1 Disease Concept Map is being finalized and next steps are to launch a priorities survey!

Concept of Interest (COI) = An outcome!

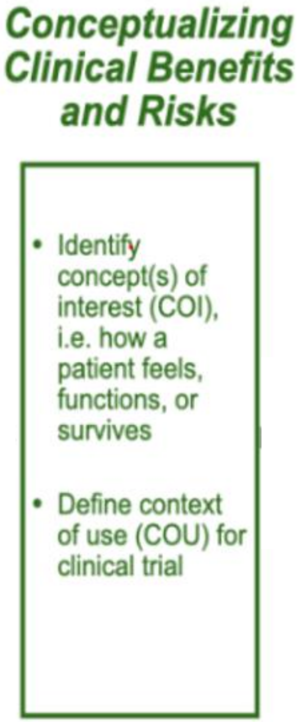


Conceptualizing Clinical Benefits and Risks

- Identify concept(s) of interest (COI), i.e. how a patient feels, functions, or survives
- Define context of use (COU) for clinical trial

- **Aspect of an individual's experience or clinical, biological, physical, or functional state that an outcome measure is intended to capture**
- FDA says that for clinical trials we should select COIs that:
  - Reflect an aspect of health that is **important to patients**
    - *The patient experience data collected informs this!*
  - Have the **ability to be modified** by the investigational treatment
  - Could demonstrate clinically meaningful differences between study arms within the **time frame** of the clinical trial

Concept of Interest (COI) = An outcome!



Conceptualizing Clinical Benefits and Risks

- Identify concept(s) of interest (COI), i.e. how a patient feels, functions, or survives
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What are the COI's for Med13L and CTNNB1?

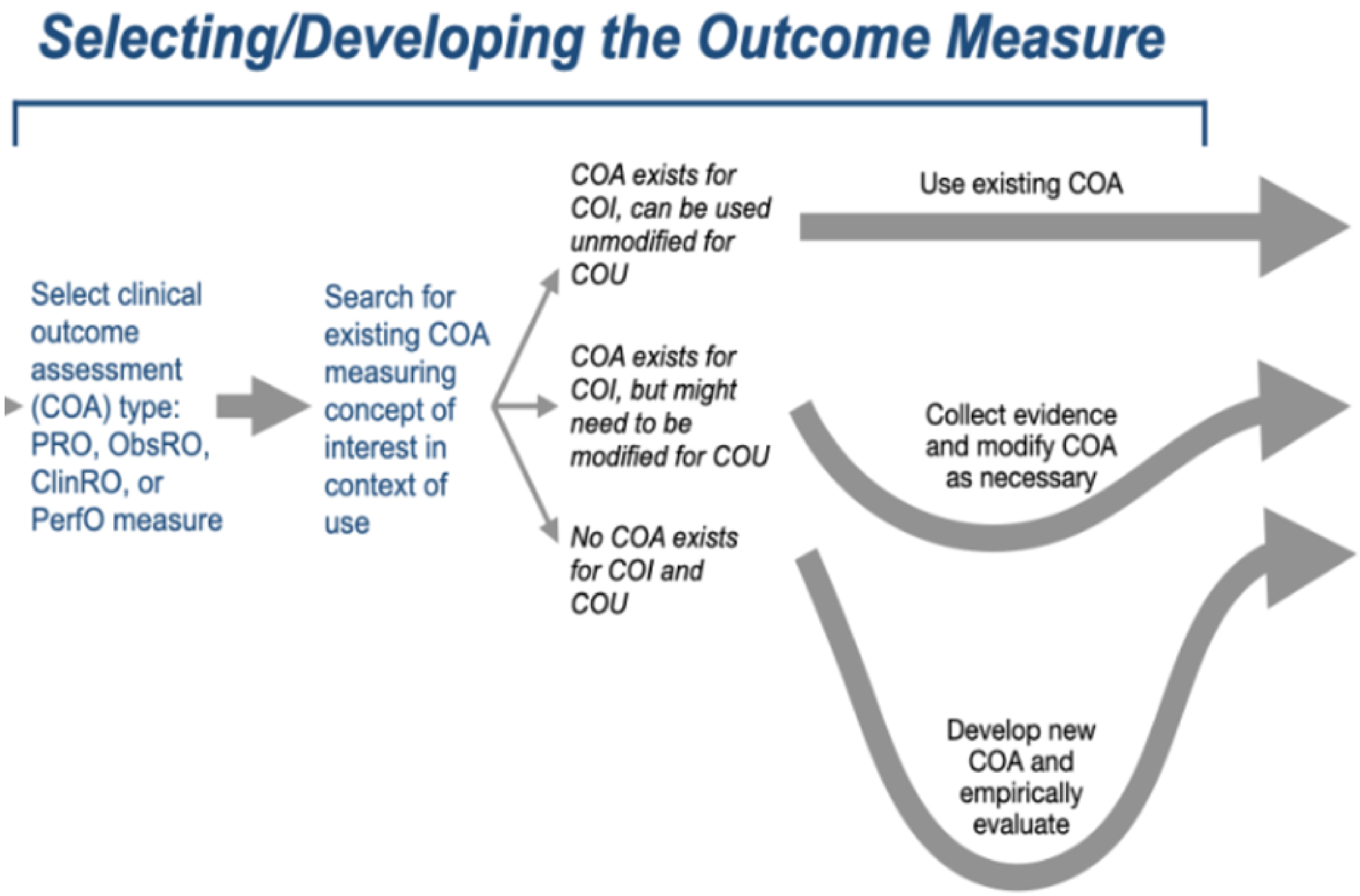
Challenge to consider in rare neurogenetic conditions: Relevant constructs may differ based on patient factors (e.g., age, ability level). Are there COI's that may span the population?

We need to measure COI’s that are important to patients and have potential to be modified in the timeframe of a trial, but are the outcome measures we have…

Relevant?
Understood?
Valid?
Sensitive to meaningful differences across groups?
Sensitive to meaningful change?

Clinical Outcome Assessment (COA)

- **In a clinical trial, COAs measure outcomes (COIs) that describe or reflect how a patient feels, functions or survives**
  - *Patient-reported outcomes*
  - *Observer-reported outcome*
  - *Clinician-reported outcome*
  - *Performance outcome*
- Potential COAs must be identified and evaluated for their potential to be valid for the context of how they will be used (i.e., **“fit for purpose”**)



Selecting/Developing the Outcome Measure

Select clinical outcome assessment (COA) type: PRO, ObsRO, ClinRO, or PerfO measure

Search for existing COA measuring concept of interest in context of use

COA exists for COI, can be used unmodified for COU

Use existing COA

COA exists for COI, but might need to be modified for COU

Collect evidence and modify COA as necessary

No COA exists for COI and COU

Develop new COA and empirically evaluate

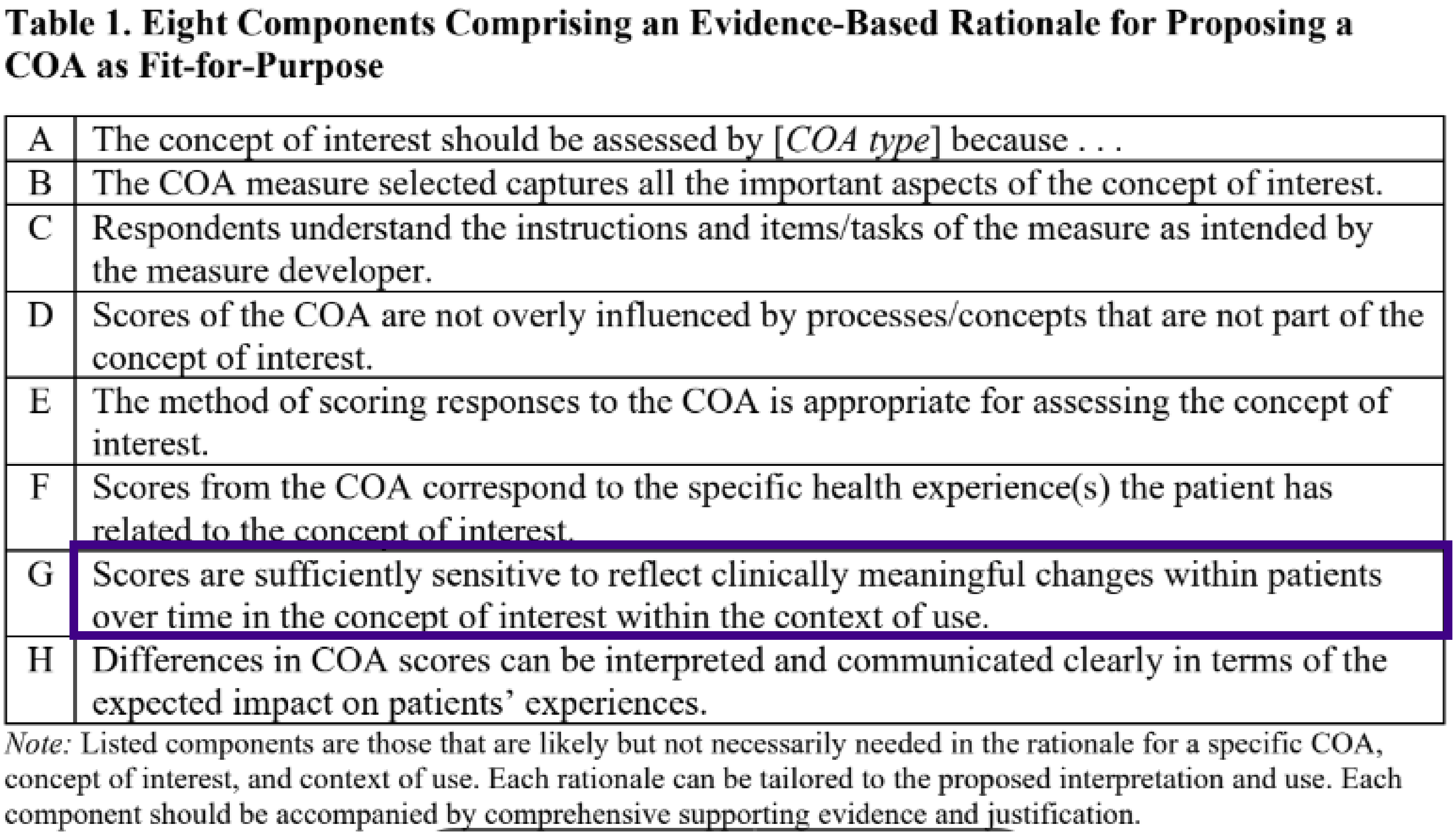


Table 1. Eight Components Comprising an Evidence-Based Rationale for Proposing a COA as Fit-for-Purpose

A	The concept of interest should be assessed by [*COA type*] because . . .
B	The COA measure selected captures all the important aspects of the concept of interest.
C	Respondents understand the instructions and items/tasks of the measure as intended by the measure developer.
D	Scores of the COA are not overly influenced by processes/concepts that are not part of the concept of interest.
E	The method of scoring responses to the COA is appropriate for assessing the concept of interest.
F	Scores from the COA correspond to the specific health experience(s) the patient has related to the concept of interest.
G	Scores are sufficiently sensitive to reflect clinically meaningful changes within patients over time in the concept of interest within the context of use.
H	Differences in COA scores can be interpreted and communicated clearly in terms of the expected impact on patients' experiences.

Note: Listed components are those that are likely but not necessarily needed in the rationale for a specific COA, concept of interest, and context of use. Each rationale can be tailored to the proposed interpretation and use. Each component should be accompanied by comprehensive supporting evidence and justification.

COAs need to capture meaningful change

- Measures must be sensitive enough to capture meaningful changes in the outcome
- ***Challenges to consider for rare neurogenetic conditions:***
    - **Development is often an outcome of interest, but many current measures are unable to capture small changes that may be meaningful for some patients (Downs et al., 2024).**

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Your voice matters!

We must bring together experts and patients/caregivers early (co-design methods) to maximize the likelihood of developing measures that are valid and will capture meaningful outcomes in clinical care and research contexts.

Thank you!

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

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