Rare Disease Natural History Studies: Experience from the GNAO1 Natural History study in a pre/postpandemic world

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Bow Foundation: gnao1.org

Washington University in St.Louis

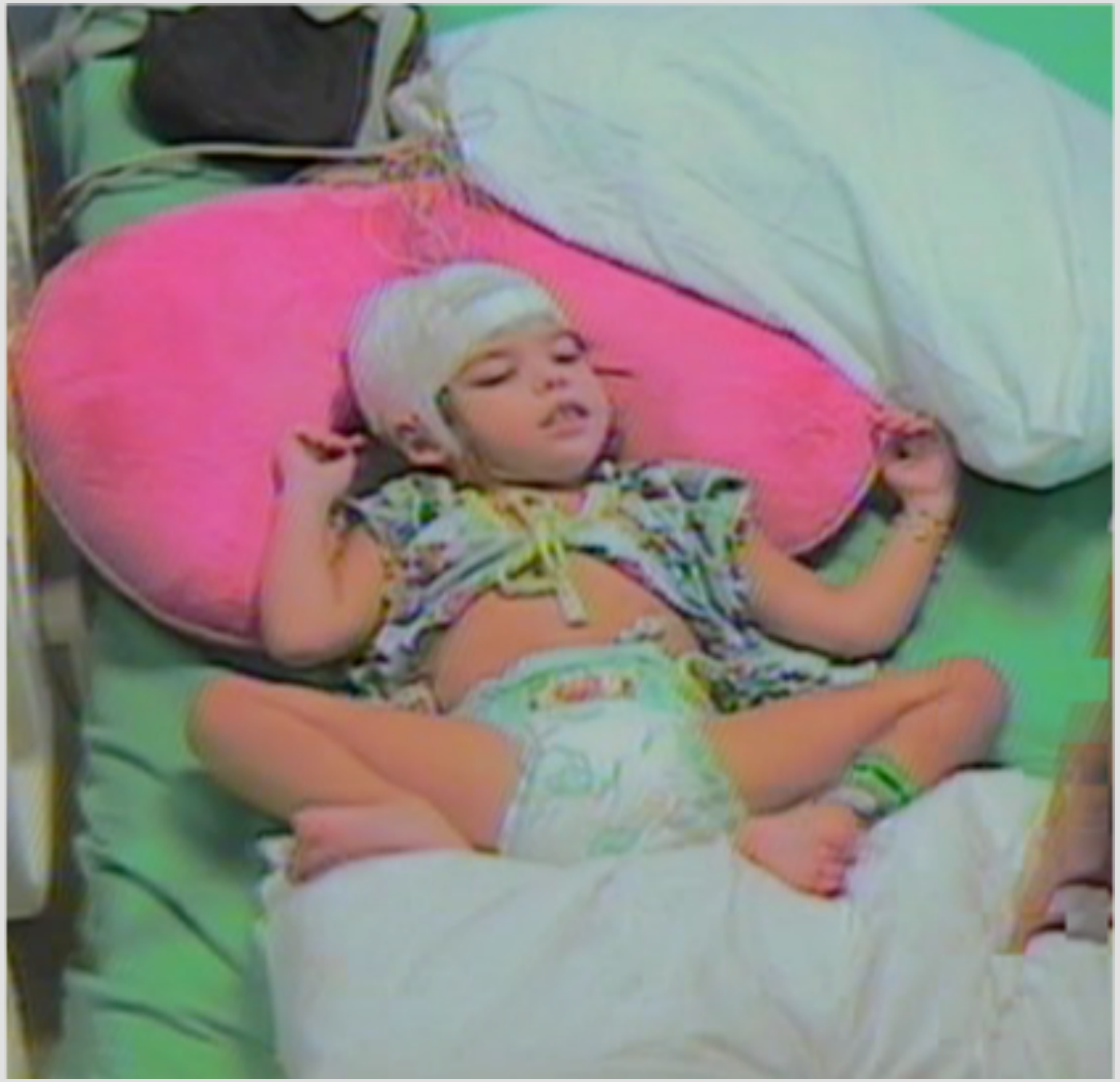
Learning Objectives

Primary: Understand the how, what and why of natural history studies in rare diseases

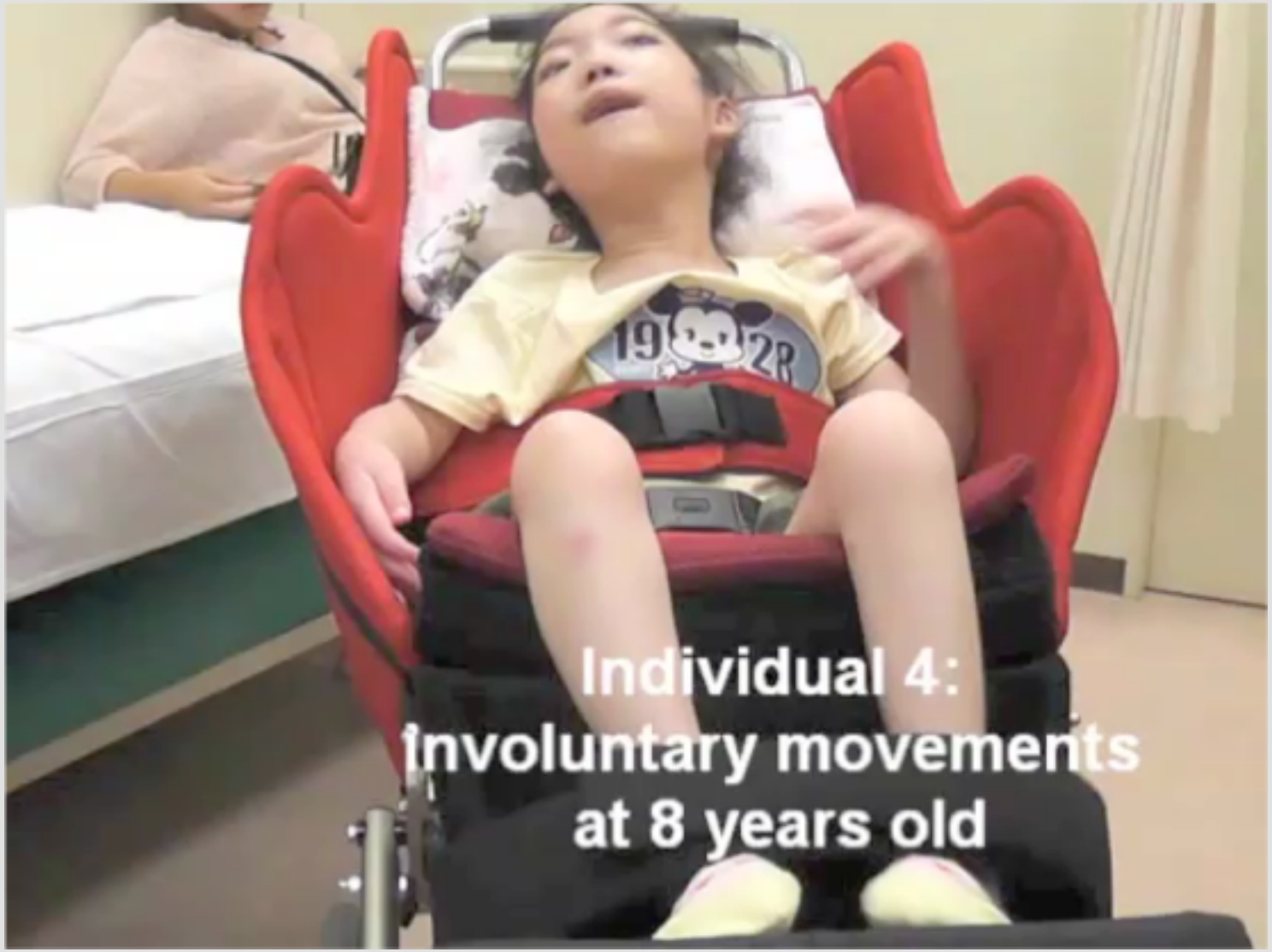
Explore process of taking single case → clinical research program

- Clinical features of GNAO1 neurological disease
- Types of natural history studies
- How to learn from other rare diseases
- Early results from GNAO1 natural history study

Case presentation



- Normal preg/delivery
- Global developmental delay from early infancy
  - 6 mo hypotonic
- Very extensive work-up unrevealing
- Chorea by age 4 – stable until age 8 when it became intractable
- Age 9: trach dependent due to chorea, multiple ICU stays
- Died age 10
- EIEE via whole exome: ?not causative


Individual 4:
involuntary movements
at 8 years old

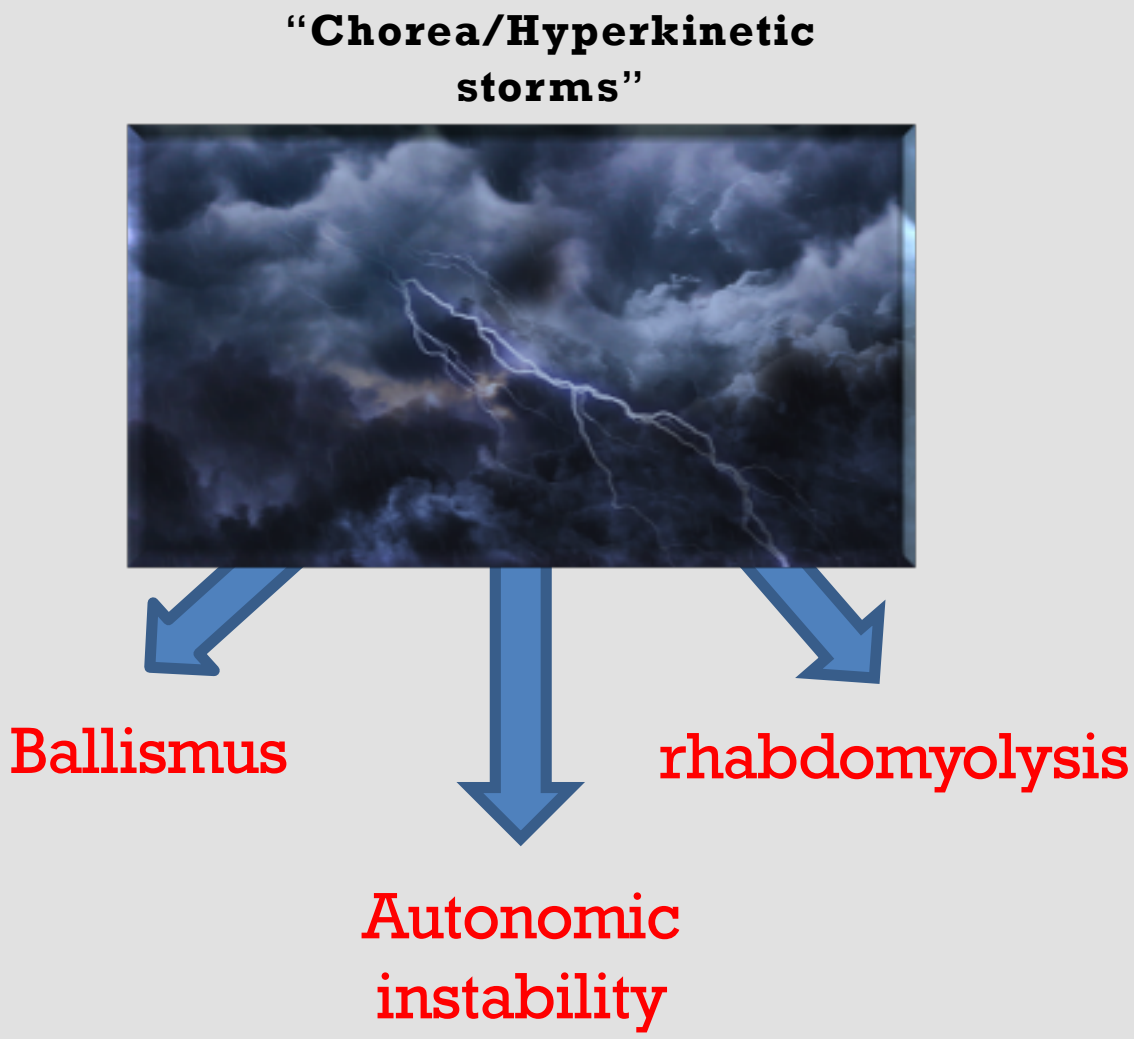
Question 1: How would you characterize the abnormal movements?

1. Dystonia
2. Chorea/ballismus
3. Myoclonus
4. Athetosis

"*GNAO1* Neurodevelopmental Disorder"

- Hypotonia
- Global Developmental Delay
  - preserved intellect
- Early infantile epileptic encephalopathy (EIEE) OR
- Movement disorder dominated by episodes of chorea/ballismus OR
- Both

- Emerging genotype/phenotype correlation
  - *GNAO1* encodes $G\alpha_o$, the α subunit of G_o heterotrimetric signal transducers.
  - loss of GNAO1 function →? epilepsy
  - gain of GNAO1 function →? chorea



The Bow Foundation

Their vision is to build a better tomorrow for GNAO1 patients and their families by fundraising to support medical research that leads to a more informed GNAO1 body of knowledge, better patient treatment options, and an eventual cure.

The Bow Foundation has three specific areas of focus:

1. Scientific research
2. GNAO1 family support
3. Awareness and Advocacy

(www.bowfoundation.org)

The Bow Foundation

- Nov 2017: Meeting at SFN
- April 2019: Launch of annual joint family and scientific conference + NHS
- April 2020: 2nd Annual ~~Conference~~
  - Virtual Symposium held on April 29, 2020
  - Conversion of in-person NHS to virtual collection of data
- Expansion of study to include more international families

(www.bowfoundation.org)

Problem

"Section 526(a)(2)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) defines a rare disease: condition that "affects less than 200,000 persons in the United States."

There are approximately 7,000 recognized rare diseases. Individually, each rare disease affects a small number of people, but cumulatively rare diseases affect about 1 in 10 people in the United States.

Most rare diseases have no approved therapies, and thus, overall, this presents a significant unmet public health need."

"Rare Diseases: Natural History Studies for Drug Development Guidance for Industry"
https://www.fda.gov/media/122425/download

Four Main Goals of Natural History Studies

1. Characterize the patient population

- Some rare diseases have substantial genotypic and/or phenotypic heterogeneity, and the natural history of each subtype may be poorly understood or inadequately characterized.
- Information is useful to decide:
  - inclusion criteria
  - stage of disease to treat
  - duration of a trial
  - frequency of data collection
  - specific endpoints.

"Rare Diseases: Natural History Studies for Drug Development Guidance for Industry"
https://www.fda.gov/media/122425/download

Four Main Goals of Natural History Studies

2. Identification or Development of Clinical Outcome Assessments

- Clinician-reported outcome → Movement Rating Scales
- Observer-reported outcome (e.g., reports by or from caregivers) → CP Child
- Patient-reported outcome
- Performance outcome (e.g., tests of memory or walking ability) → GMFM, Peabody

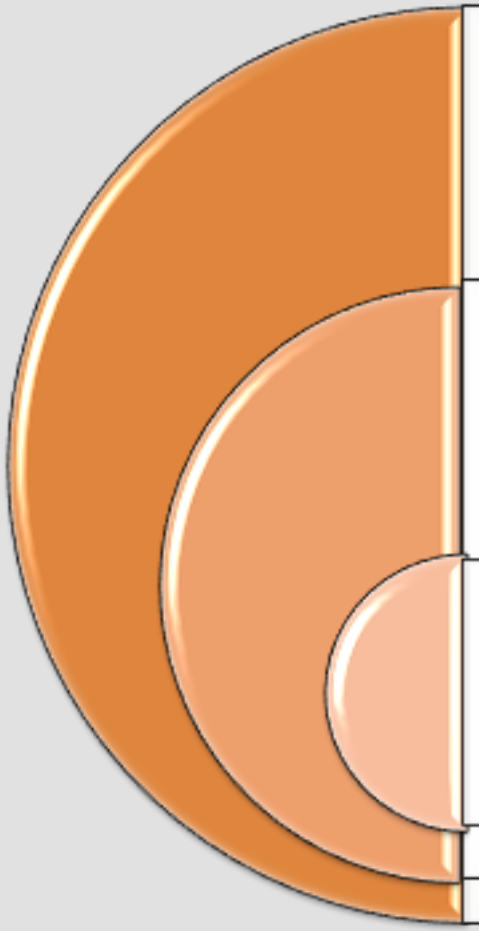
"A natural history study can help evaluate the ability of a new or existing clinical outcome assessment to detect change in a particular disease or a pattern of progression of a disease or symptoms of disease. Natural history studies also can be used to evaluate the performance and reproducibility of a clinical outcome assessment for use in a clinical investigation."

Four Main Goals of Natural History Studies

3. **Identification or Development of Biomarkers**
   - Objective measure of pathologic process or biological response to a therapeutic intervention.
   - Physiological measurements, blood tests and other chemical analyses of tissue or bodily fluids, genetic or metabolic data, and measurements from images.

4. Data and information from a Natural History Study may provide an untreated, external control group for use as the comparator to the treatment group(s) in an investigational drug trial.

Types of Natural History Studies



Retrospective studies: combine information from patient medical records, scientific literature reviews, and other existing sources of disease-specific information	• Pros: Cheapest, patients do not need to be present, can fill critical knowledge gaps and can set a course for future analysis • Cons: Information is often missing or inaccurate and variable between subjects
Cross-sectional studies: collect patient data at a specific time point	• Pros: relatively cheap and quick to conduct. • Cons: cannot develop 'cause and effect' relationship
Prospective (longitudinal) studies: collect data over time in a systemic fashion	• Pros: can greatly inform the development process, more suitable for use as an external control group • Cons: Expensive and require a longer time investment

"Rare Diseases: Natural History Studies for Drug Development Guidance for Industry"
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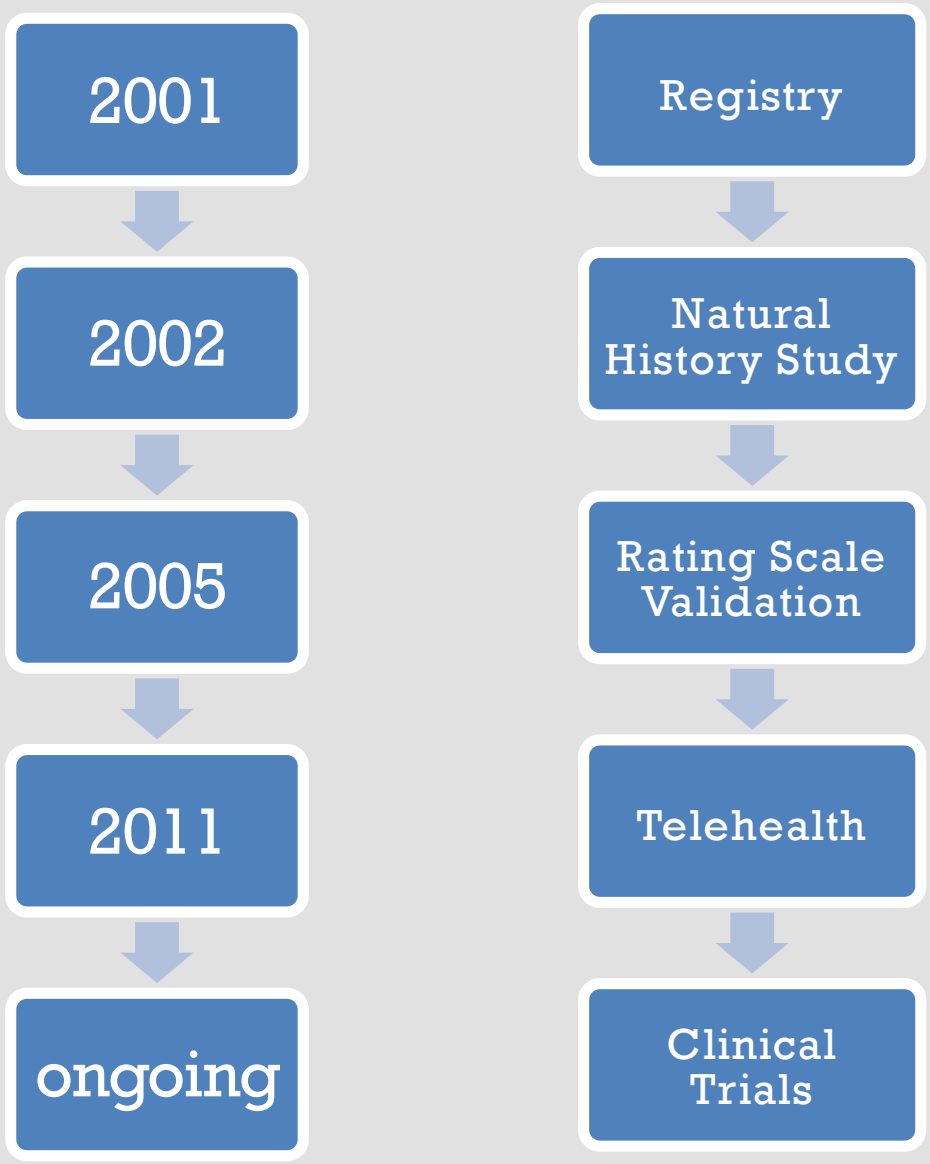
Batten Disease Model



Question 2: What type of natural history study would you prioritize?

1. Registry
2. Retrospective study
3. Cross-sectional study
4. Prospective study

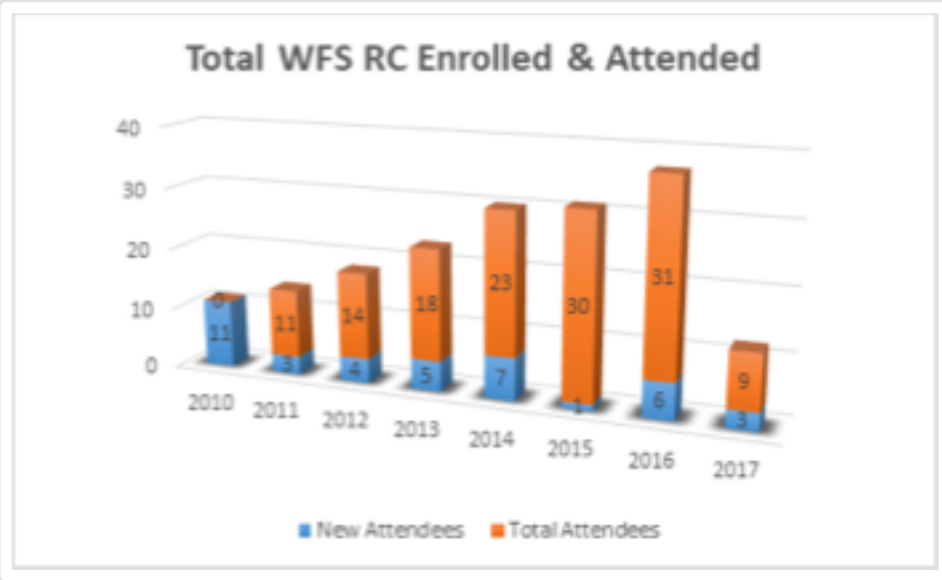
Wolfram Disease Natural History Study

Wolfram patients

- Genetically confirmed
- Ages 5-26 at entry
- N=40 total
- N=29 with MRI
- Annually

Controls*

- Age/sex matched
- N=28 healthy
- N=24 type 1 diabetic
- Annually for 3 yrs



Annual Assessments:

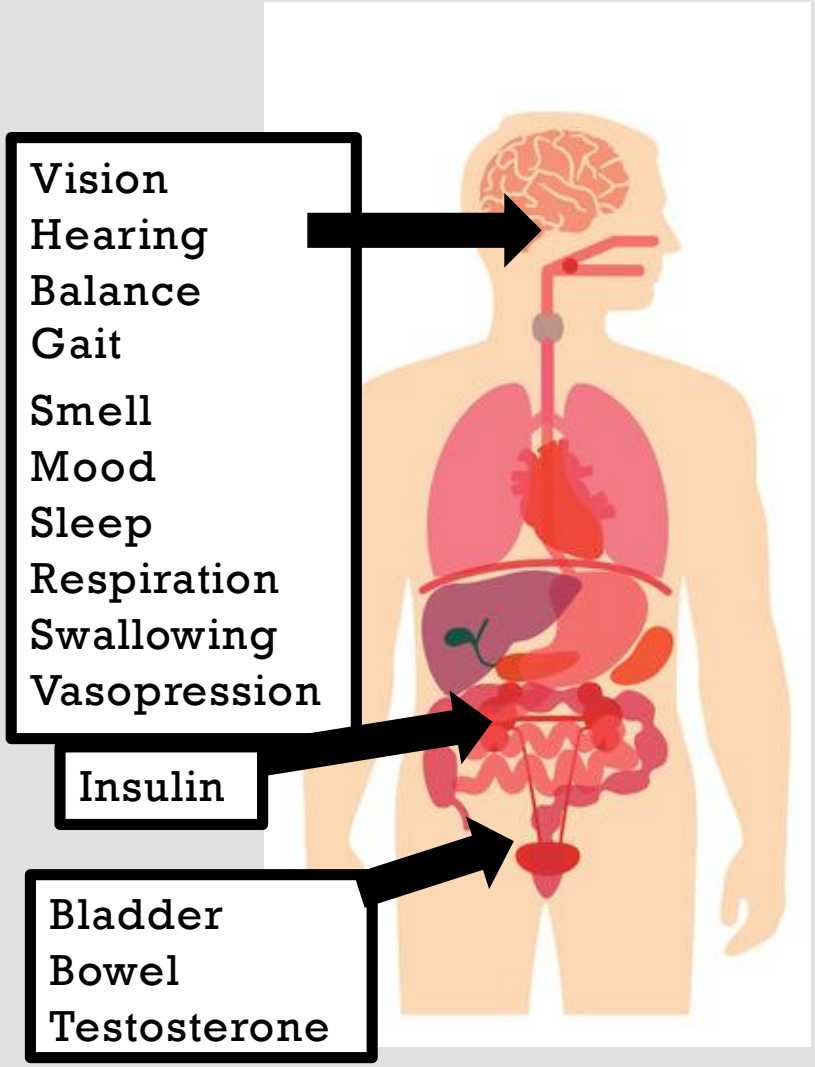
- Neuroimaging*
- Balance*
- Neuropsychology*
- Taste & Smell*
- Neurology
- Ophthalmology
- Audiology
- Psychiatry
- Endocrinology
- Urology

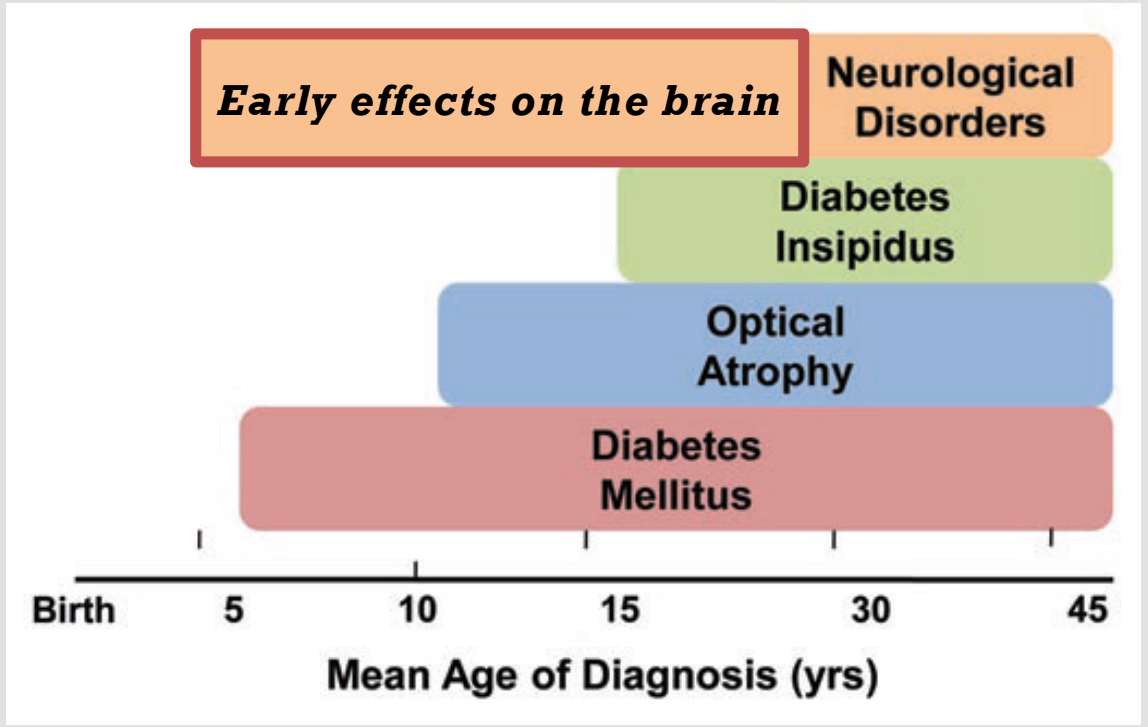
HD41890; Hershey

Lesson 1: Phenotype of genetically defined ≠ phenotype for clinically defined

Genetically defined patients	
n	40
Gender: M/F	17 / 23
Age range (years)	5.1 - 25.8
Age mean (SD)	13.5 (5.5)
Diabetes Insipidus	65%
Diabetes Mellitus	90%
Optic Atrophy	93%
Hearing Loss	68%
DIDMOAD	38%

Lesson 2: Wolfram is more diverse and has greater CNS involvement than originally thought.

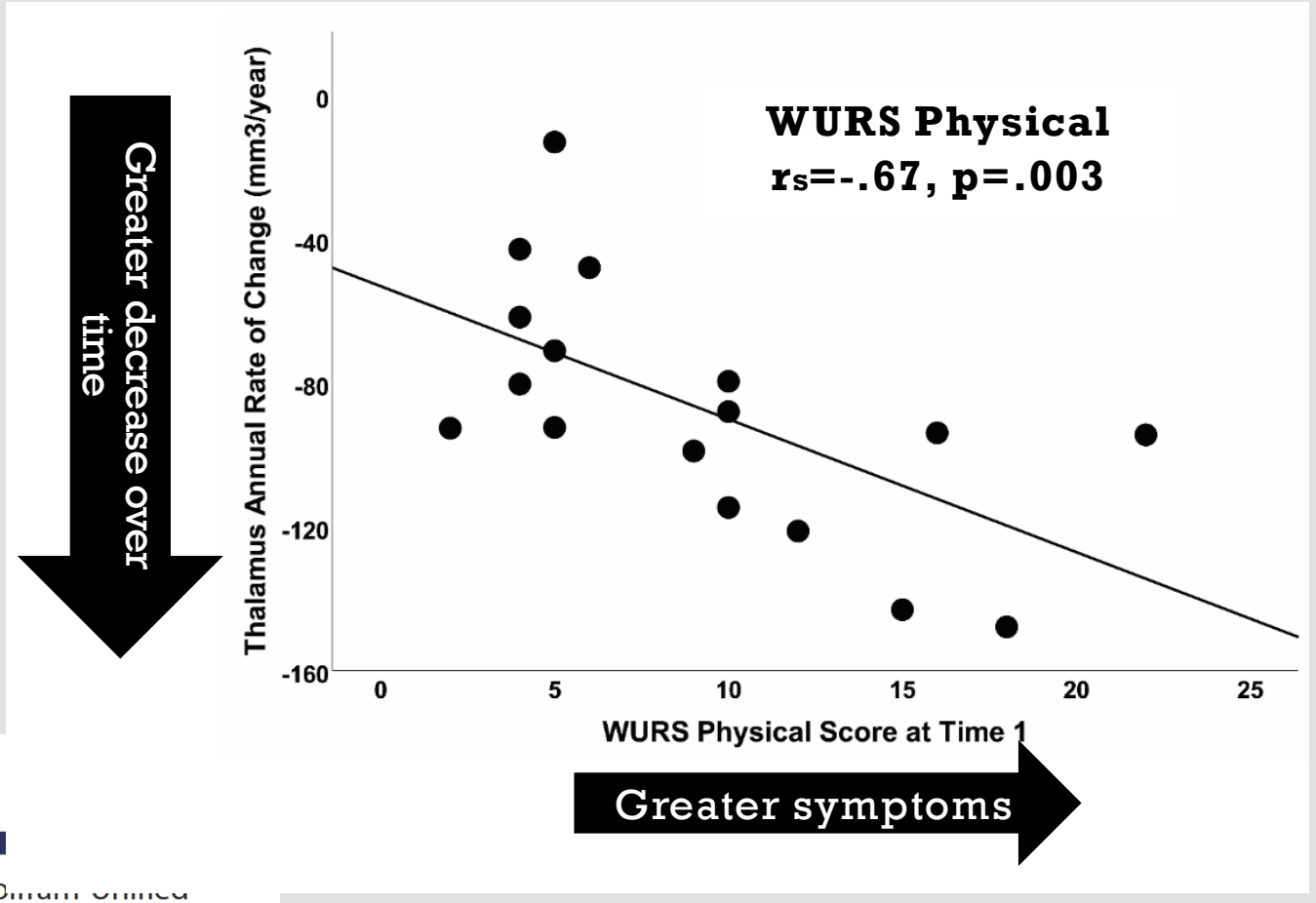




Lesson 3: Need for disease-specific rating scale

1) Batten disease rating scale (UBDRS) used as template given similarities.
2) Items adjusted to be more disease specific to Wolfram Syndrome → WURS
3) Reliability and validity tested with multiple raters
4) Instructions for rating clarified based on initial reliability testing
5) Continued assessment of scale performance and reliability with modifications as guided by the data

Symptoms at time 1 associated with thalamic rate of change



Nguyen et al. Orphanet Journal of Rare Diseases 2012, 7:89
http://www.ojrd.com/content/7/1/89

RESEARCH

Reliability and validity of the Wo... Rating Scale (WURS)

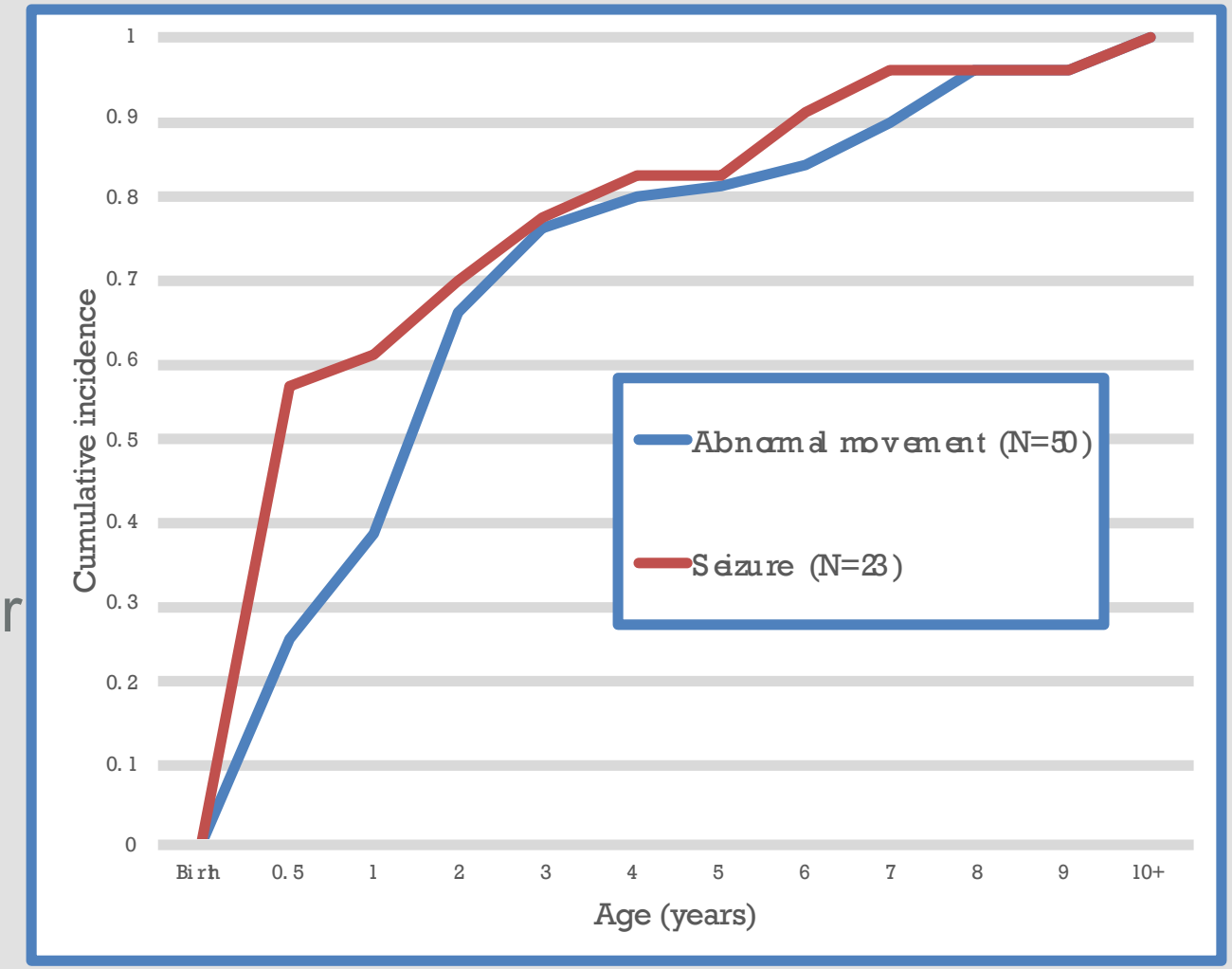
Chau Nguyen[1], Erin R Foster[1,3], Alexander R Paciorkowski[6], Amy Viehoever[3], Colleen Considine[2], Aidena Bondurant[2], Bess A Marshall[4], Tamara Hershey[2,3,5*] and Washington University Wolfram Study Group

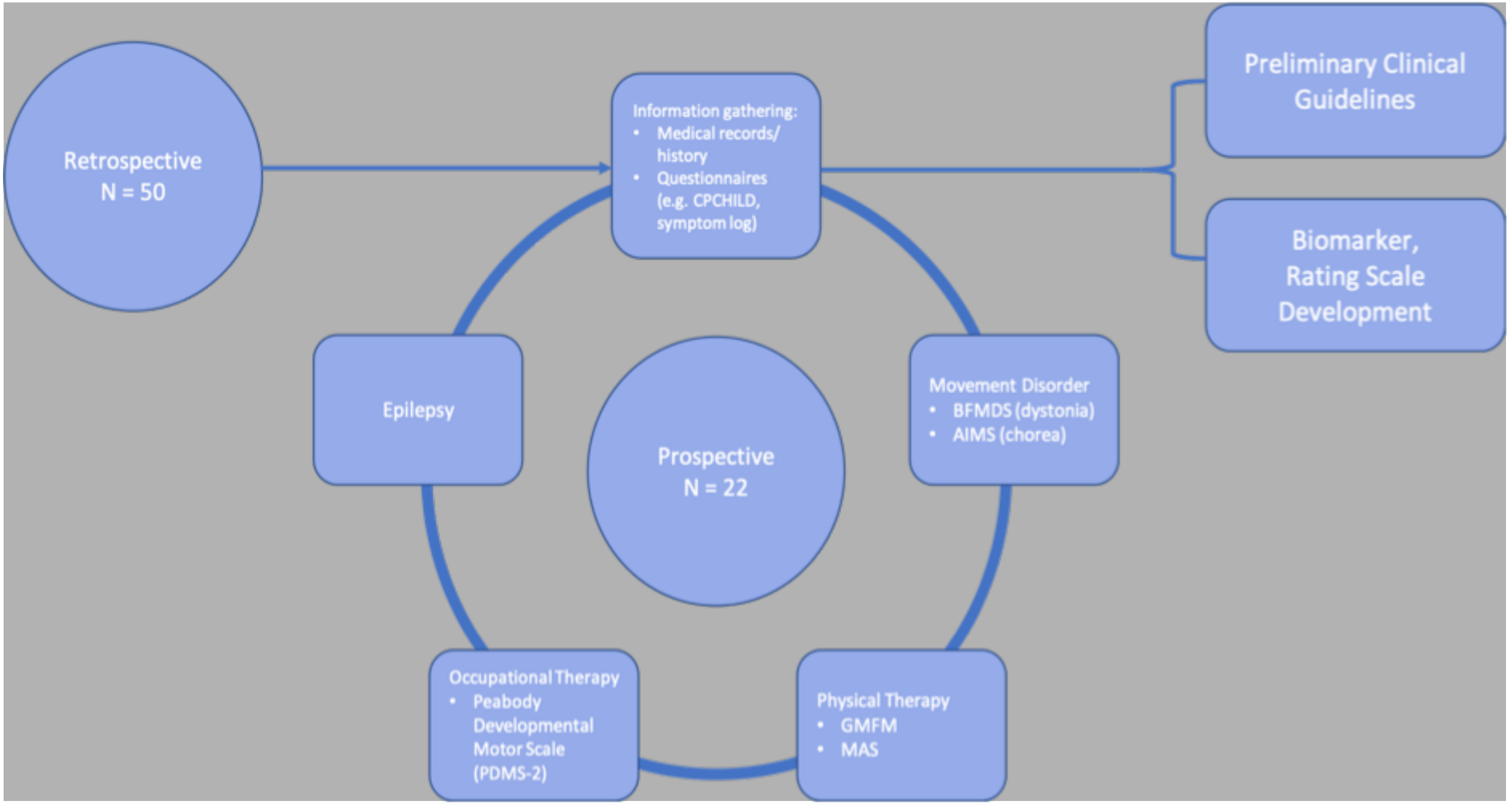
GNAO1 Natural History Study

1. **Define Clinical Phenotype of GNAO1 associated Neurologic Disease**
   Retrospectively assess the natural history of GNAO1 associated neurologic disease.
2. **Establish feasibility for a long-term prospective natural history study**
   Obtain pilot data for a large prospective natural history study of GNAO1 associated neurological disease.
3. **Develop a Rating Scale specific to GNAO1 associated neurologic disease**
   Identify clinically meaningful and quantifiable features of the disease to design a rating scale that captures the severity of the disease.
4. **Generate an initial set of best practice recommendations for local treating physicians and therapists**
   Develop a clinical resource for dissemination of information on the management of GNAO1 associated neurologic disease.

GNAO1 Registry

- Bow Foundation, PI: Erika Axeen
- 82 subjects
- Phenotypic spectrum
  - 62 (76%) movement disorder
  - 43 (52%) epilepsy
  - 27 (33%) overlapping disorder marked by both abnormal movements and epilepsy
  - 1 hypotonia only (age 4)




Retrospective
N = 50
Information gathering:
• Medical records/ history
• Questionnaires (e.g. CPCHILD, symptom log)
Preliminary Clinical Guidelines
Biomarker, Rating Scale Development
Epilepsy
Prospective
N = 22
Movement Disorder
• BFMDS (dystonia)
• AIMS (chorea)
Occupational Therapy
• Peabody Developmental Motor Scale (PDMS-2)
Physical Therapy
• GMFM
• MAS

Clinic, year 1

- 22 subjects scheduled
  - 1 withdrew due to illness

- All had hypotonia as infants
- Tremendous variability in ability levels and movement disorders
  - Mixed dystonia/chorea + hypotonia
  - Mixed dystonia/chorea + spasticity
  - Chorea only
  - Hypotonia + hypokinesia
- Most kids happy, infectious smiles
  - Anxiety
- New Symptoms
  - Temperature regulation (related to autonomic instability?)
  - Aversion to bright sunlight

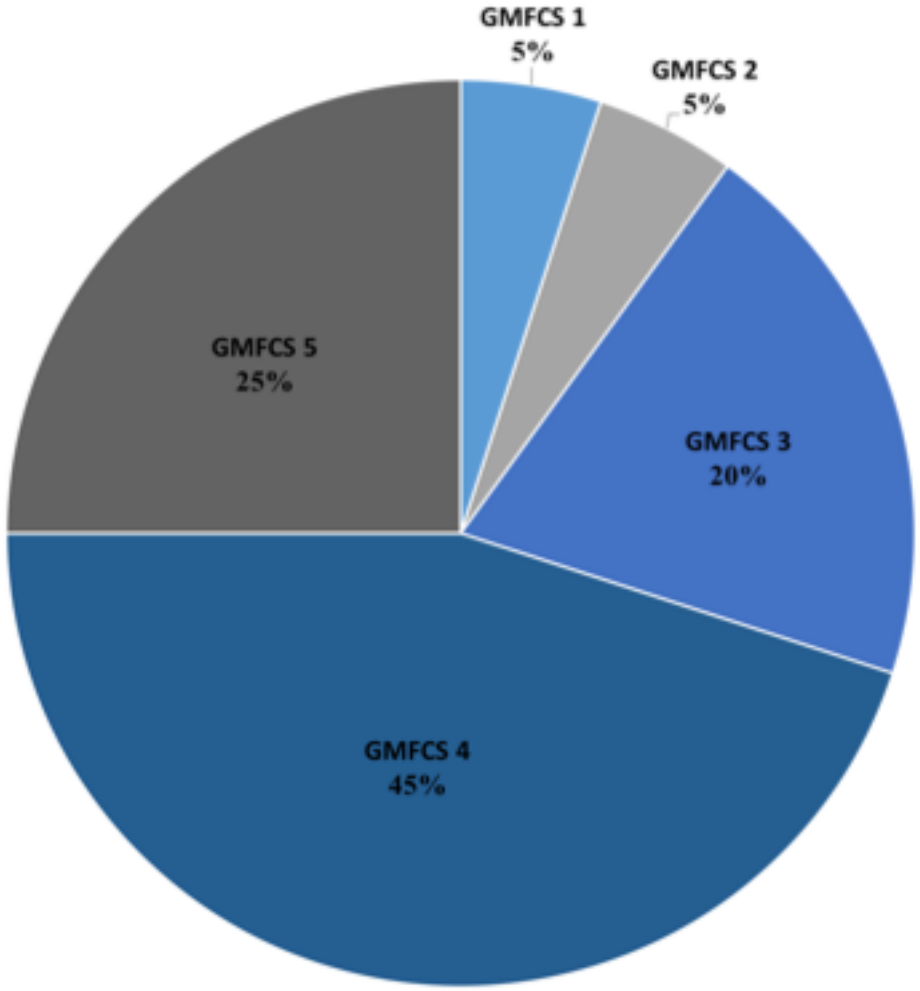

View site information

Children gather here for 1st-ever clinic

PHOTOS BY LAURIE SKRIVAN • lskrivan@post-dispatch.com

Physical therapist Erin Smith counts as Maria Emiliana Pincardini, 8, holds her balance and her father, Matias, cheers her on during an evaluation of her gross motor skills for her GMAOI on Thursday at St. Louis Children's Hospital.

Year 1 GNAO1 cohort: Genotype ≠ phenotype

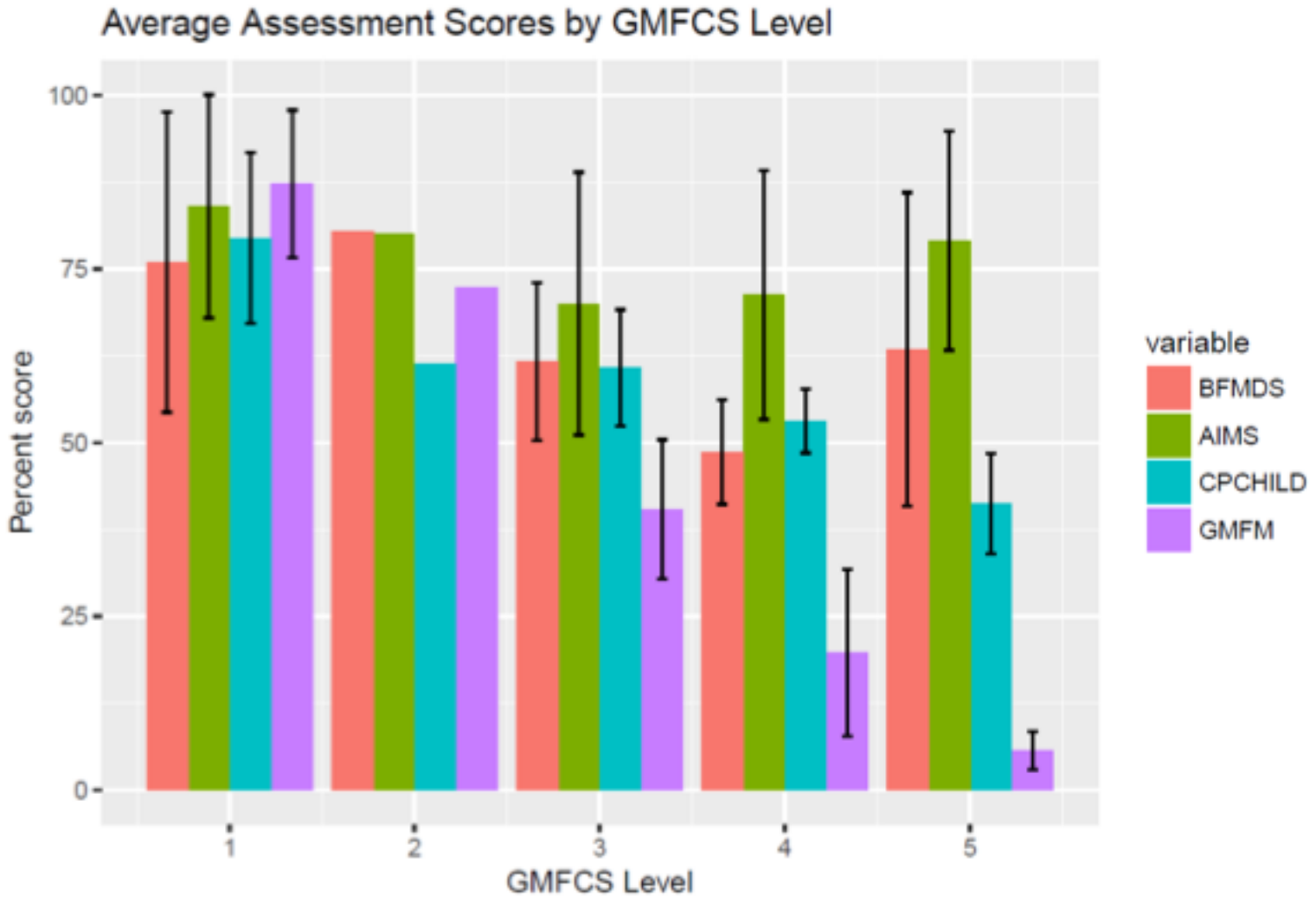


I (n = 1)	II (n = 1)	III (n = 4)	IV (n = 9)	V (n = 5)
p.E237K (23y)	p.A227V (4y)	p.E237K (8y)	p.E237K (3y)	p.E237K (3y)
		p.R209H (3y)	p.R209H (5y, 3y, 9y)	p.G40W (4y)**
		p.Y291 (7y)**	p.E246K (2y)	p.E246K (2y)
		p.I344del (15y)	p.R209C (3y, 4y)	p.R179G (1y)**
			p.Y231C (5y)**	p.G203R (2y)
			c.723+2T>C (4y)	

GNAO1 Natural History Study: Assessments

Assessment	Targeted Domain of Measurement
Abnormal Involuntary Movement Scale (AIMS)	Chorea
Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS)	Dystonia
Gross Motor Function Measure (GMFM-88)	Gross Motor Development, mobility
Modified Ashworth Scale (MAS)	Spasticity
Peabody Developmental Motor Scales 2nd Edition (PDMS-2)	Fine Motor Development
CPCHILD Questionnaire	Quality of Life, caregiver burden

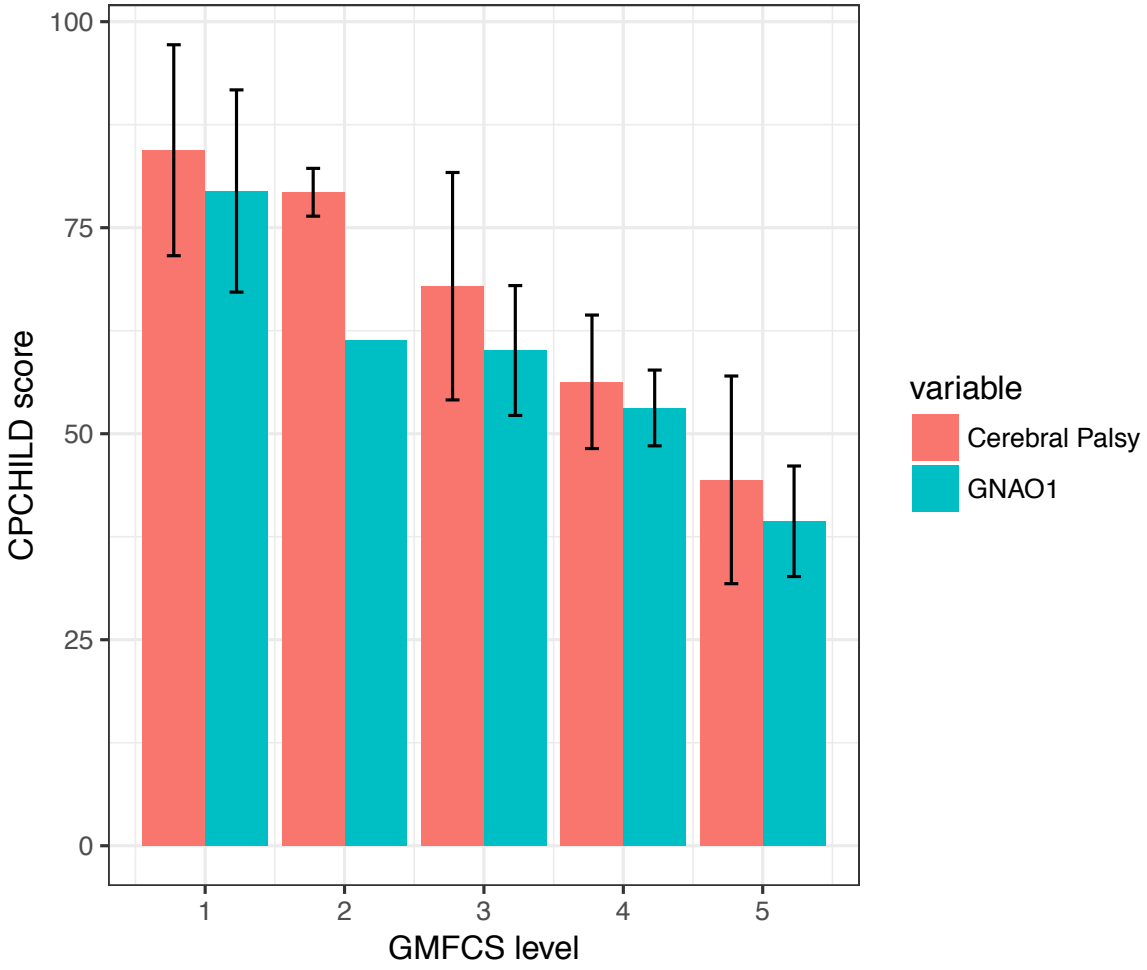
Assessment of Outcome Measures: rating Scales do not correlate with disability

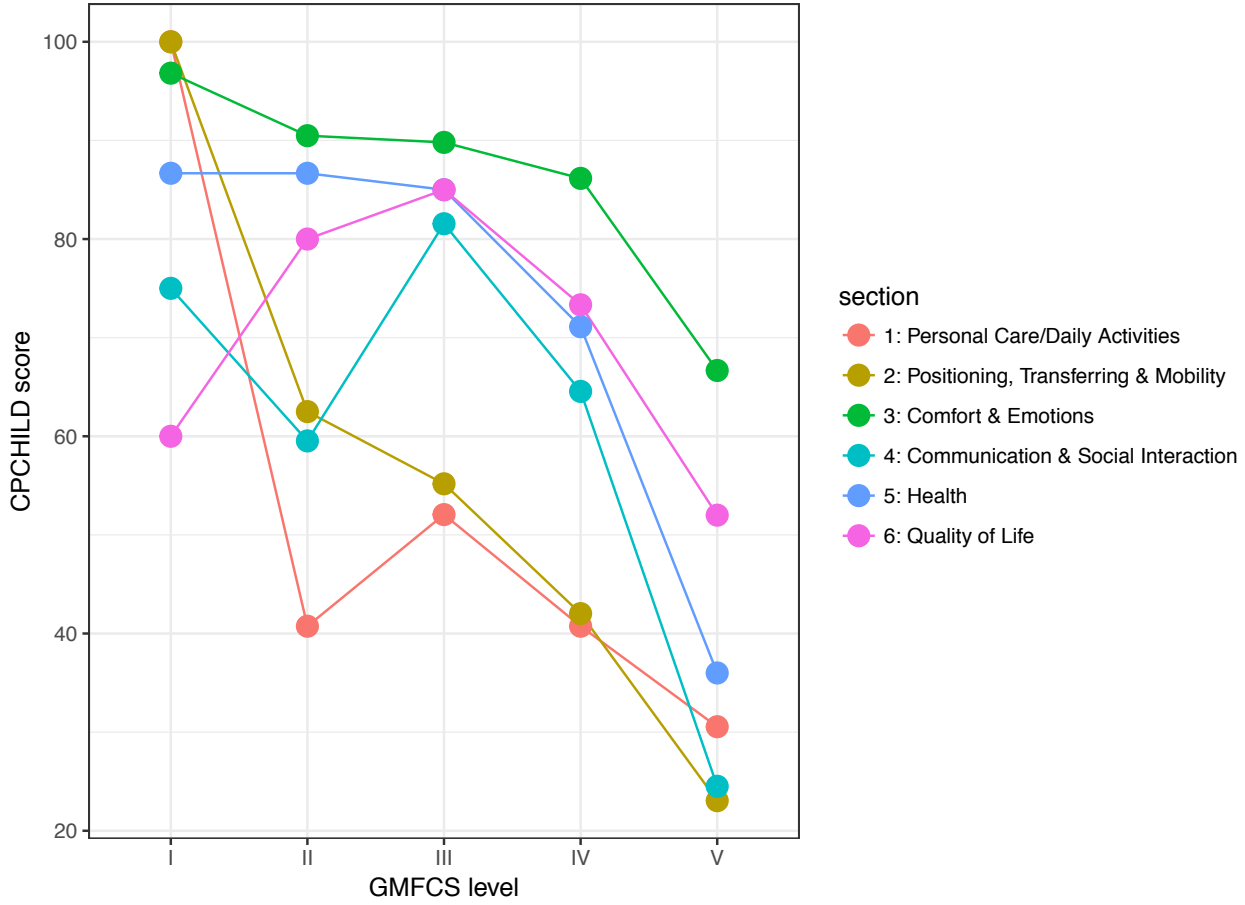


Question 3: What do you think the most important problem that the families reported?

1. Inability to walk/mobility
2. Seizures
3. Abnormal movements
4. Difficulties with communication

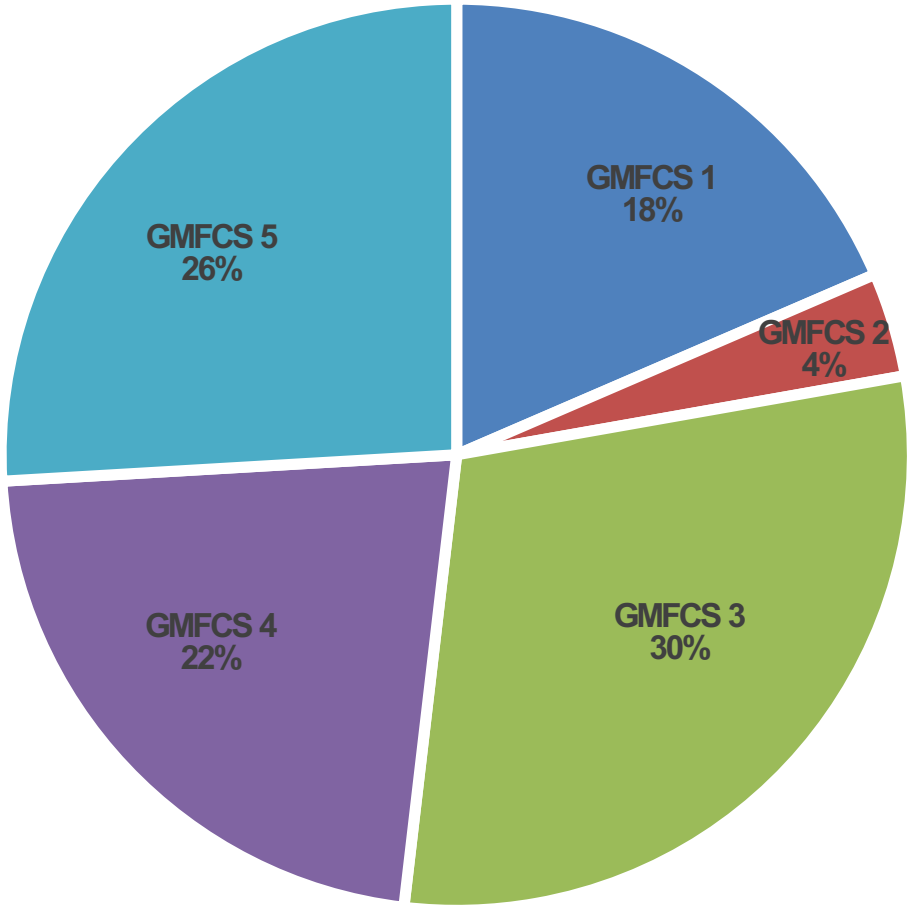
Quality of Life: CPChild





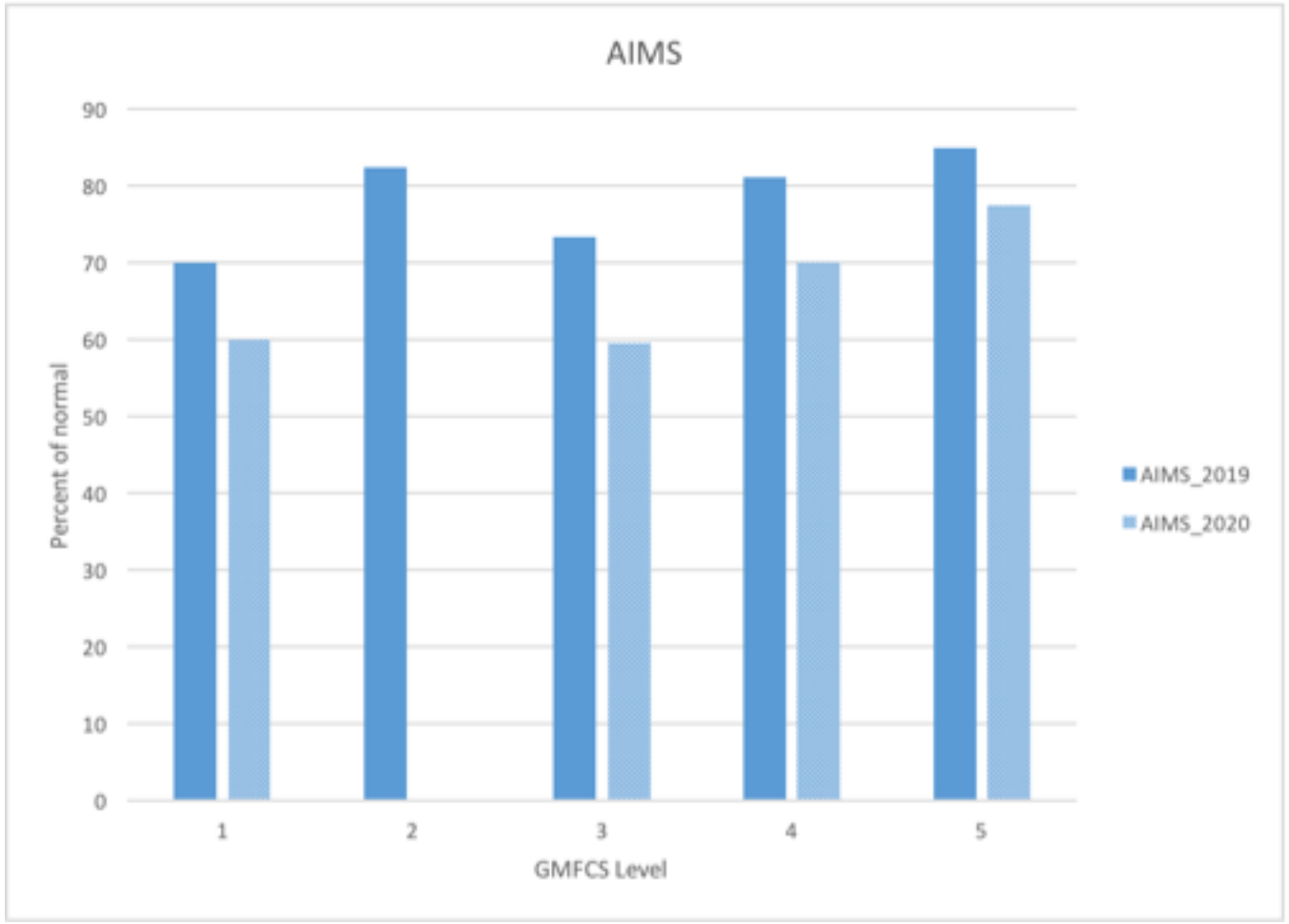
Transition to virtual data collection

Year 2 GNAO1 cohort (ongoing)



I (n = 5)	II (n = 1)	III (n = 6)	IV (n = 6)	V (n = 7)
p.I344del (16y, 4y)	p.R209H (3y)	p.E237K (9y)	p.E237K (4y)	p.E237K (4y)
p.L131P (4y)		p.R209H (5y, 6y, 4y)	p.R209H (10y)	p.G40W (5y)**
c.724-8G>A (18y)		p.R209C (4y)	p.R209L (4y)	p.R209C (20y)**
p.D174G (5y)		c.723+2T>C (5y)	p.D201V (2y)	p.S47N (2y)**
			p.Y231C (6y)	p.S47G (9y)
			p.E246K (3y)	p.R179G (2y)**
				p.G203R (7y)

Results (Y1 vs. Y2)



- AIMS scores were significantly lower in Year 2 than in Year 1 (p = .001).
- All other assessments comparing Year 1 and Year 2 did not yield significance.

Treatments?

- No obvious epilepsy medication works better than others
- Movements generally refractory to meds
- DBS
  - 8/44 DBS
  - All have improved hyperkinetic movements
  - +/- success with dystonia

Conclusions drawn from Years 1 and 2

- Movement versus epilepsy phenotype/genotype
- Breadth of phenotypic variation even within genotype
  - Mild cases
  - Under-testing?
- Additional symptoms not previously recognized

- Need for flexible data collection – motor scales inherently change throughout the course of the day and are often both state and activity dependent
- Need for better objective measures of communication and cognitive functioning

Future Research

- Expand the study team and continue to enroll as many subjects as possible (funding)
- Expand collaborations with basic scientists and other clinical researchers around the world
- Develop and validate a rating scale unique to GNAO1

- Other studies:
  - Role of DBS in GNAO1: Does early implantation before ICU admissions prevent longer term complications and decline?
  - How young is too young?

General lessons in rare disease clinical neuroscience

- Challenges
  - Funding
  - Publishing
  - Statistics
  - Identifying collaborators

- Surprises
  - Pre vs. post genetic testing era differences
  - Phenotypic variability within genotype
  - How gratifying it is to work with families with rare disorders