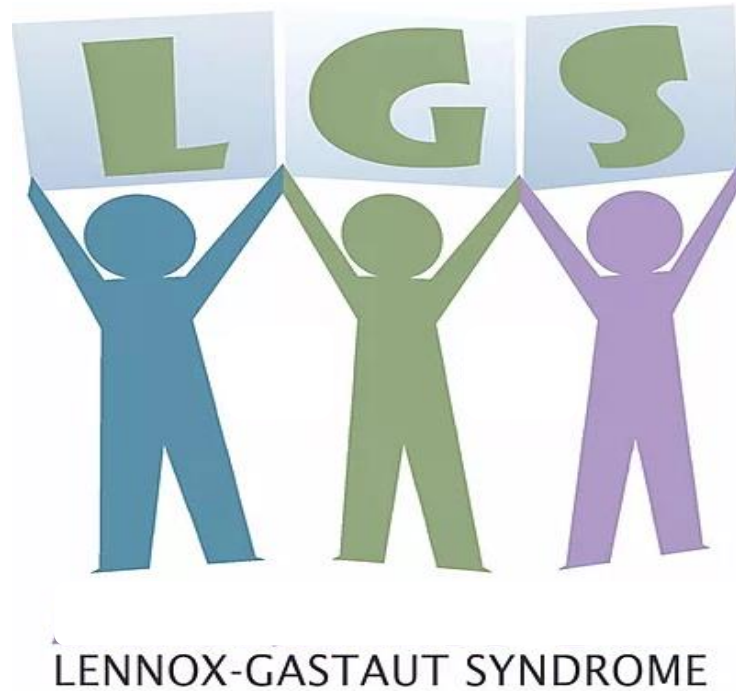


# What is LGS?

## Parent Driven Data from the Natural History Project



Anne T. Berg, PhD  
Lurie Children's Hospital  
Chicago, IL

# Lennox-Gastaut Syndrome Defined?

- Child neurology foundation

- Childhood
- Multiple seizure types; most common: tonic, atypical absence and “drop attacks.”
  - also generalized tonic-clonic and focal seizures as well.
- EEG: high voltage, GSW (<2.5 Hertz), generalized PFA in sleep, waking background slow and disorganized.
- Moderate to severe cognitive disabilities are common
- Multiple different causes, many unknown

- ILAE

- Onset of seizure 1-7 years (peak 3-5 year)
- Tonic seizures ~mandatory, + atonic & atypical absence
- Slow spike&wave
- Cognitive impairment
- Multiple different causes, many unknown

# Lennox-Gastaut Syndrome Defined?

- In the literature (Camfield, Epilepsia 2011)
  - Tonic seizures required for the diagnosis (Arzimanoglou et al., 2009),
  - + myoclonic, atypical absence, nonconvulsive status
  - Slow spike&wave (<2.5 Hz)
  - profound deleterious effects on intellectual and psychosocial function

## **In Major RCTs:**

- Glauser, RUF (Neurology, 2008)
  - atypical absence seizures and drop attacks (i.e., tonic–atonic or astatic seizures) +/- others
  - EEG with slow spike-and-wave complexes (2.5 Hz) within 6 months of study entry
- Devinsky, CBD (NEJM, 2018)
  - Slow spike-and-wave complexes <3 hz
  - ≥two types of generalized seizures, including drop seizures (atonic, tonic, or tonic–clonic) involving the entire body, trunk, or head leading to to fall, injury, or slumping in chair.

# The Natural History Project



[Home Page](#)

Welcome to the Natural History Study !



**For the Participant**

To register for a new study or  
continue with an ongoing  
study, click here.



**For the Medical  
Practitioner &  
Researcher**

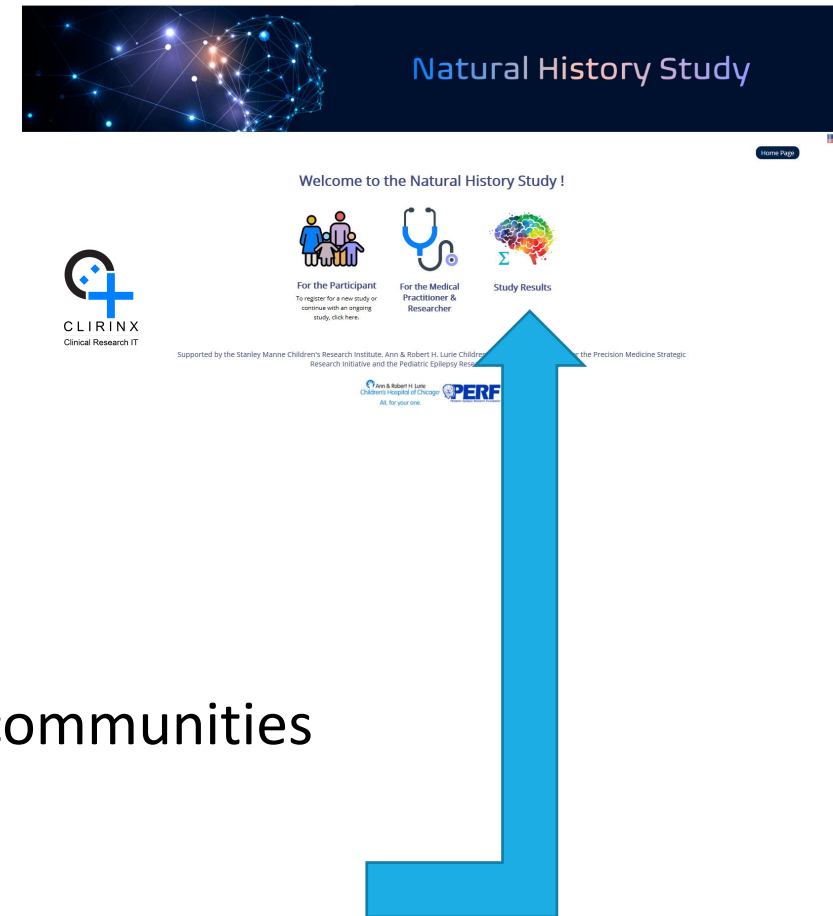


**Study Results**

Supported by the Stanley Manne Children's Research Institute, Ann & Robert H. Lurie Children's Hospital of Chicago under the Precision Medicine Strategic Research Initiative and the Pediatric Epilepsy Research Foundation (PERF).

# How is this different?

- Designed with and by parents and content experts
- More than a check-list
- Intent is to quantify
  - Nature
  - Frequency
  - Severity
  - Variability
- Report results back to the family groups
  - On group website, webinars
  - Dissemination to the family, scientific, and provider communities



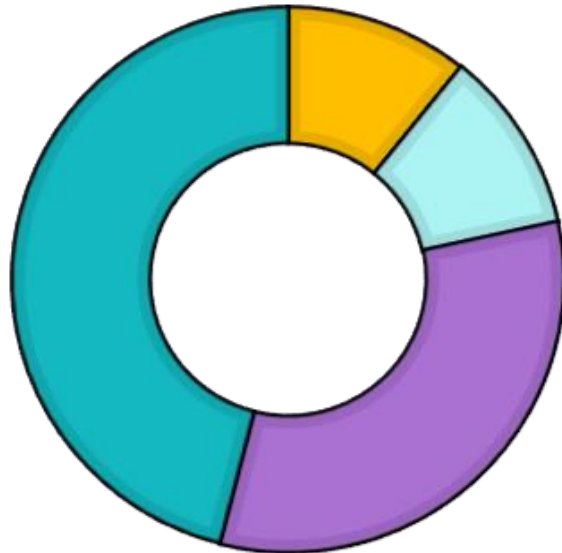
# Lennox Gastaut Syndrome

## *The Natural History Project*

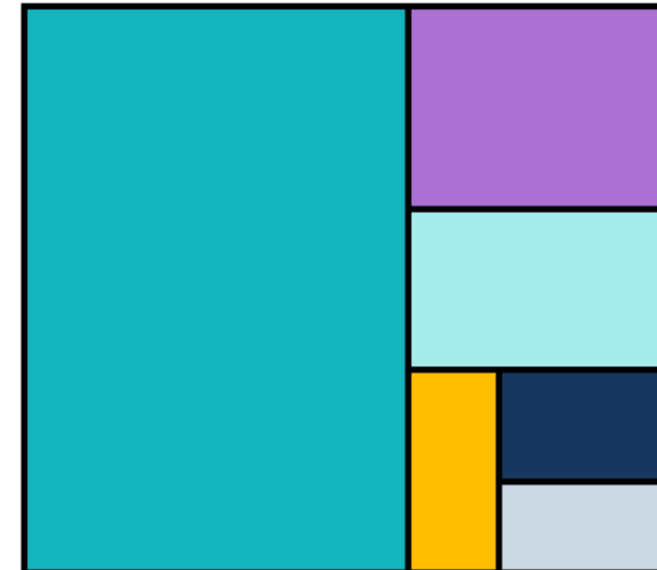
37 parents

43% ♀  
57% ♂

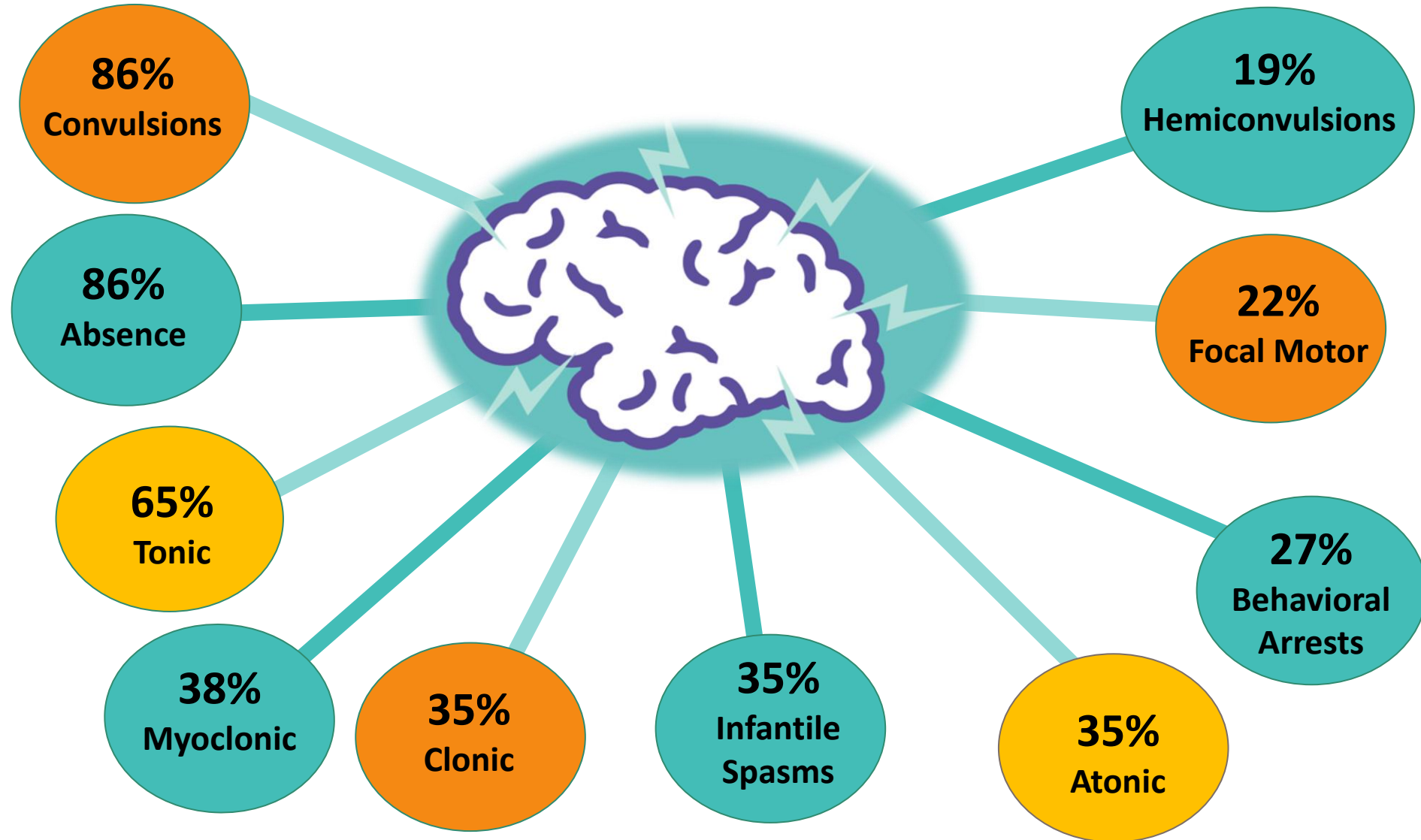
■ 0-4 years (11%)   ■ 5-9 years (11%)  
■ 10-15 years (32%)   ■ 16+ years (46%)



■ Unknown (59%)   ■ Acquired injury (5%)  
■ Brain malformation (14%)   ■ Chromosomal disorder (4%)  
■ Genetic disorder (11%)   ■ Other (5%)



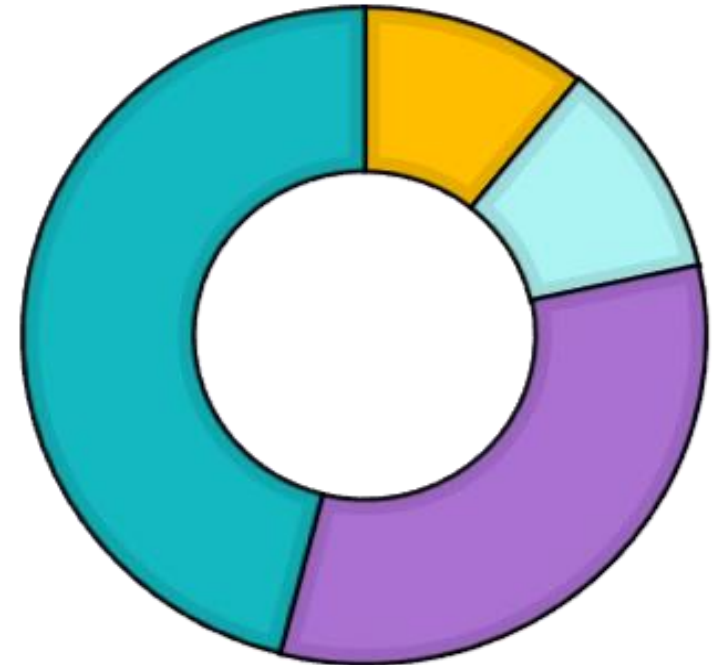
# Seizure types



# Age at onset

- 6 months median
  - As young as day 1
  - Oldest 6 years
  - 90% by ~3 years
- LGS is rarely the initial epilepsy diagnosis!
  - From diagnosis of epilepsy to diagnosis of LGS - ~2 years

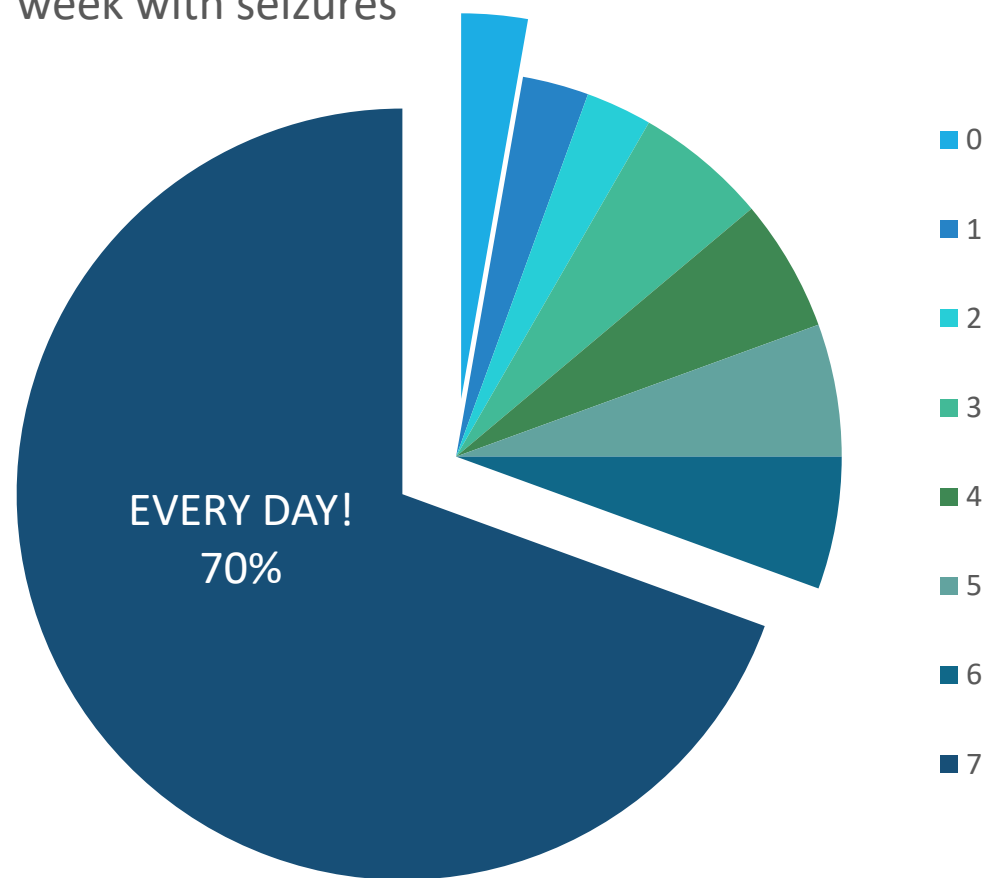
0-4 years (11%)    5-9 years (11%)  
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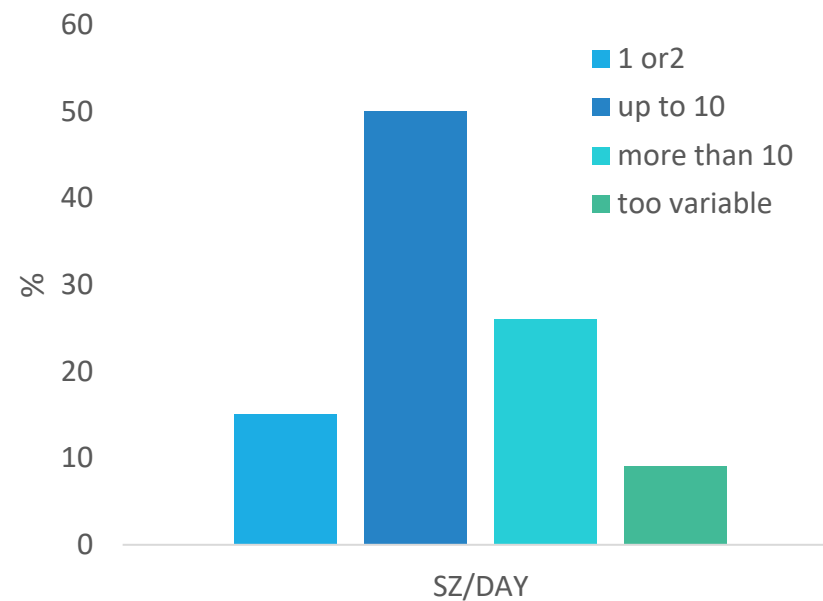


# Seizure Frequency

Days per week with seizures



Seizures per day



# Triggers and predictability

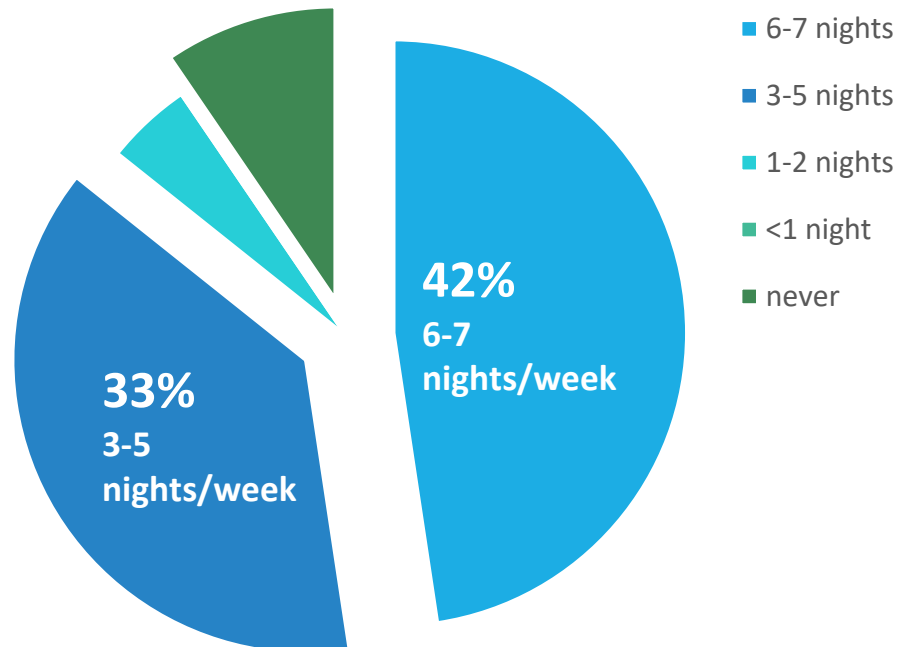
- 58% - have some trigger for seizures
  - 45% with illness or temperature change
  - 26% with visual stimulation
  - 26% emotional excitement
- 51% - moderate to a lot of unpredictability in seizure occurrence



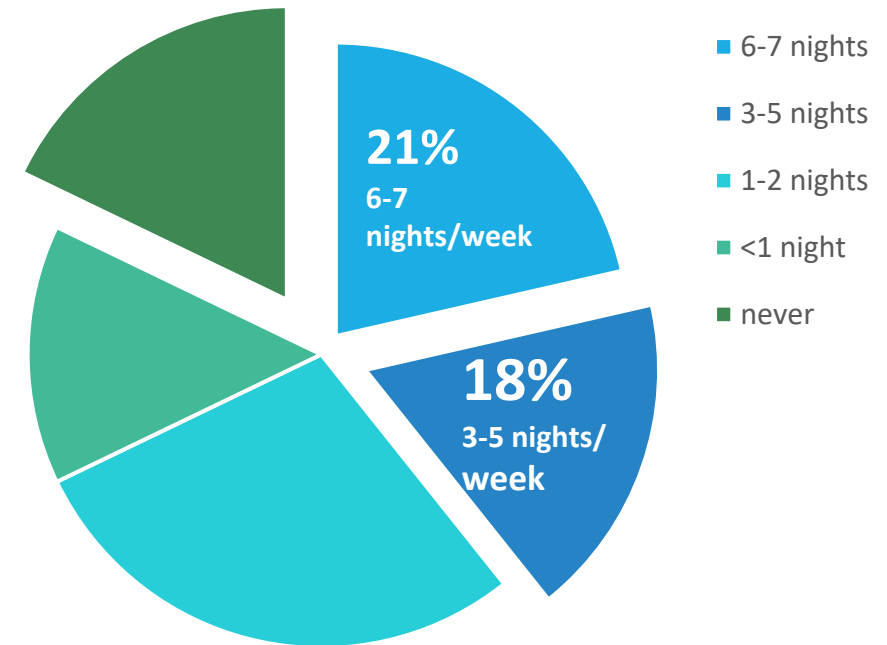
# Seizures and Sleep

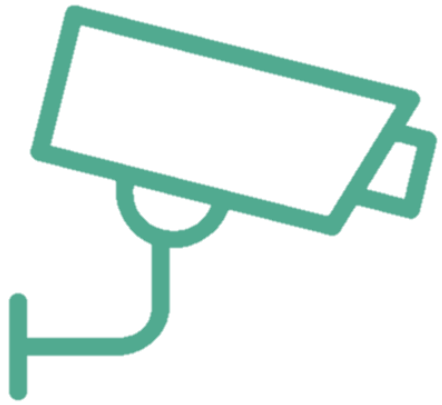


Seizure Nights/week



Nocturnal awakenings/week





# Monitoring sleep

- 81% currently monitor child's sleep
  - 64% video monitoring
  - 32% co-sleeping
  - 27% audio monitoring
  - 23% SAMI movement monitor
  - 18% pulse oximetry
  - 14% Service dog



# Seizure Emergencies



- 82% ever have had a seizure or seizure cluster >10 minutes
- In the previous 6 months
  - 1/3 had prolonged seizures
  - 30% went to the ED at least once\*
  - 15% went multiple times



\*Past 6 months

# Seizure Emergencies



- 51% used any rescue medications\*
  - 27% used rescue meds 1-9 time\*
  - 24% used rescue meds  $\geq 10$  times\*
    - Of those reporting rescue medication use:
      - 30% said a second dose was often needed
      - 25% said a second dose was always needed
- Most common rescue medications: Klonopin and Diastat®
- 45% used bridge medications at least once\*
  - 24% used bridge meds 1-4 times
  - 21% used bridge meds 5 or more time



\*Past 6 months

# Seizure Emergencies

- Currently, 57% have a seizure rescue plan
- Who didn't have a rescue plan?
  - 30% with recent prolonged seizures
  - 38% of those who went to the ED one or more times
  - 50% of those who used bridge meds one or more times
  - 53% of those who used rescue meds one or more times



# Lennox-Gastaut Syndrome Defined?

- Child neurology foundation
  - Childhood
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  - **Moderate to severe cognitive disabilities are common**
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  - **Cognitive impairment**
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  - Tonic seizures required for the diagnosis (Arzimanoglou et al., 2009),
  - + myoclonic, atypical absence, nonconvulsive status
  - Slow spike&wave (<2.5 Hz)
  - **profound deleterious effects on intellectual and psychosocial function**



# Beyond Seizures – Basic Functional Abilities



31% require a mobility device at home or school

25% typically do not manipulate objects with their hands.



50% do not use spoken language



42% cannot feed themselves  
Including 29% with G-tubes

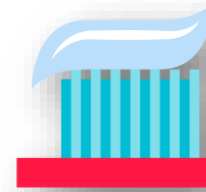


54% inconsistently or rarely communicate even with people they know (e.g. family)

# What can young people with LGS do?



**38%** use spoon and fork



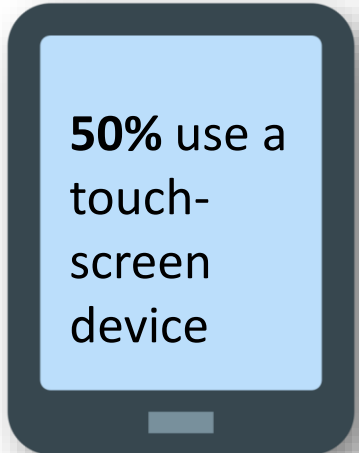
**25%** brush their own teeth



**42%** drink from an open cup



**17%** are completely independent for toilet use



**50%** use a touch-screen device

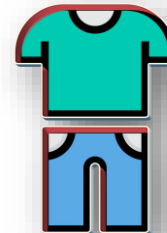


**30%** have simple academic skills



**46%** scribble or draw with a crayon or pencil

**29%** wash and dry their hands



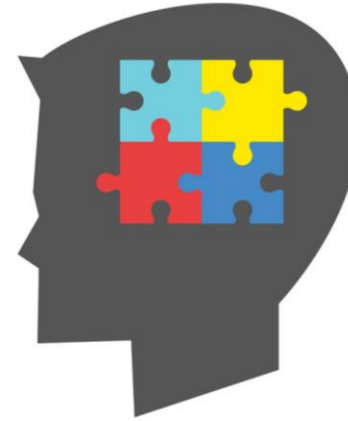
**21%** dress themselves

# Behavior

- Autism

- 35% diagnosed
- 23% features

$>1/2$



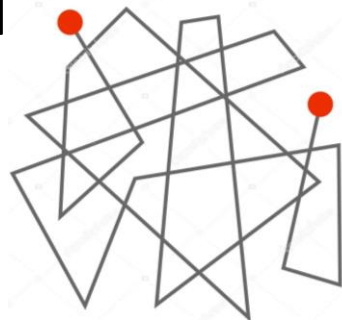
- Anxiety

- 19% diagnosed
- 8% features

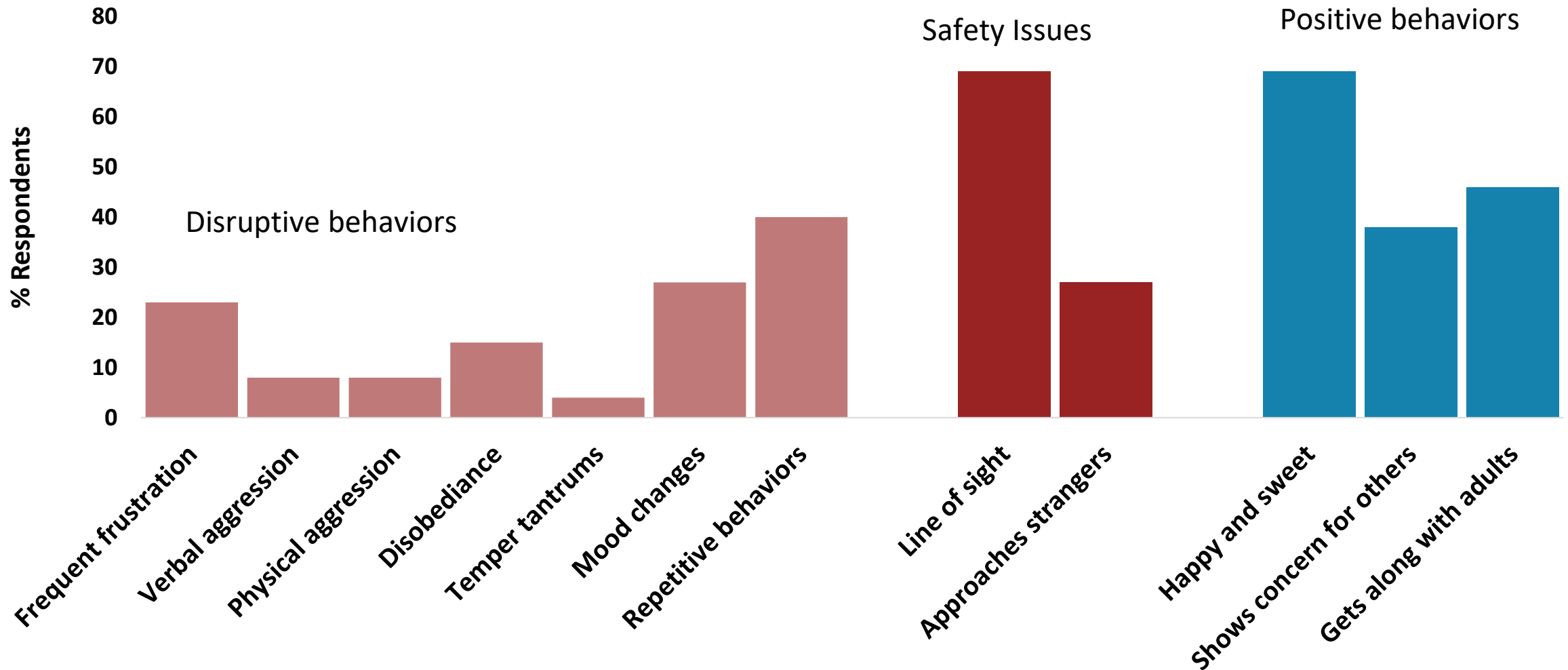


- ADHD

- 27% Diagnosed
- 4% features



# Behavior



# Pastimes

Singing songs  
Listening to music  
Being sung to



Being read to



Playing with water

# Healthcare Team – Currently involved

## Therapists

- **74%** Speech
- **70%** Occupational
- **57%** Physical
- **17%** Behavioral
- **9%** Psychologist
- **9%** Developmental



## Medical Specialists

- **96%** Neurologist
- **43%** Special Needs Dentist
- **43%** Orthopedist
- **30%** Neurosurgeon
- **26%** Ophthalmologist
- **17%** Dermatologist
- **17%** Dietician
- **17%** Gastroenterologist
- **9%** Cardiologist
- **9%** Geneticist

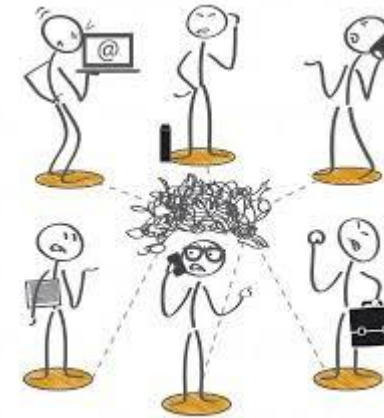


# Healthcare burden

**6** median number of different therapists and medical specialists involved in care



**43%** Of parents feel care is not well coordinated across specialists



**2/3** Of children have 2 or more therapy appointments per week



# Impact on siblings

70% have other children

63% Limited attention  
to other children



69% Other children  
had to grow up faster

Other children  
resented ill sibling?

67% not at all



## About siblings

Adult children still have needs, I can't respond to them. Guilt is overwhelming.

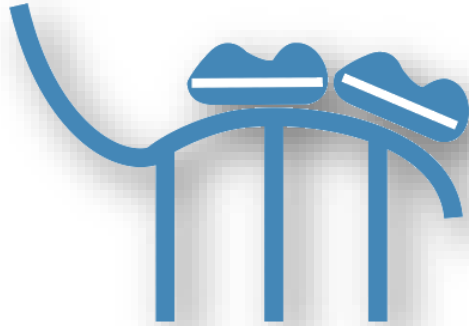
Our daughter is a preschool intervention specialist. The choice was definitely influenced by her sibling.

Our other children's career choices have definitely been affected by their sibling's epilepsy.

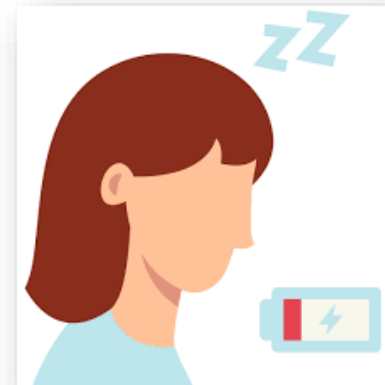


# Impact on parents

**82%** say life feels like a rollercoaster



**78%** report moderate to severe fatigue



# The Natural History Study

- Defined the landscape of Lennox-Gastaut syndrome
  - What is moderate to severe disability?
  - What does that mean?
  - What are the abilities to build on?



# FDA and Natural History

## **Rare Diseases: Common Issues in Drug Development Guidance for Industry**

2012,...2019

Define the disease population, including a description of the **full range of disease manifestations** and identification of important disease subtypes. This may allow selection of patients more likely to progress and develop the endpoints assessed in the context of a clinical trial (prognostic enrichment).



Table S3: Other Secondary Outcomes

Outcome	Placebo	Cannabidiol, 10 mg/kg/d	Cannabidiol, 20 mg/kg/d	Cannabidiol, 10 mg/kg/d vs. Placebo	Cannabidiol, 20 mg/kg/d vs. Placebo
Percentage with ≥ 25%, ≥ 75%, and 100% reduction from baseline in drop-seizure frequency	n/N (%)	n/N (%)	n/N (%)	Odds Ratio (95% CI)	Odds Ratio (95% CI)
≥ 25% reduction	33/76 (43.4)	46/73 (63.0)	47/76 (61.8)	2.22 <sup>†</sup> (1.15 to 4.28)	2.11 <sup>†</sup> (1.10 to 4.04)
≥ 75% reduction	2/76 (2.6)	8/73 (11.0)	19/76 (25.0)	4.55 <sup>†</sup> (0.93 to 22.22)	12.33 <sup>†</sup> (2.76 to 55.13)
100% reduction	0/76 (0)	0/73 (0)	0/76 (0)	N/A	N/A
Percentage experiencing worsening or improvements in drop seizure frequency during the treatment period	n/N (%)	n/N (%)	n/N (%)		
> 25% worsening	7/76 (9.2)	7/73 (9.6)	10/76 (13.2)		
≥ 0% to ≤ 25% worsening	15/76 (19.7)	7/73 (9.6)	8/76 (10.5)		
> 0% to < 25% improvement	21/76 (27.6)	13/73 (17.8)	11/76 (14.5)		
≥ 25% to < 50% improvement	22/76 (28.9)	20/73 (27.4)	17/76 (22.4)		
≥ 50% to < 75% improvement	9/76 (11.8)	18/73 (24.7)	11/76 (14.5)		
≥ 75% improvement	2/76 (2.6)	8/73 (11.0)	19/76 (25.0)		
Percentage reduction from baseline in seizure frequency (average per 28 days) during the treatment period	N	N	N	Estimated Median Difference (95% CI) <sup>a</sup>	Estimated Median Difference (95% CI) <sup>a</sup>
Non-drop seizures	70	55	64	28.31 <sup>†</sup> (10.54 to 43.75)	22.36 <sup>†</sup> (2.22 to 40.10)
Convulsive seizures	76	73	76	22.08 <sup>†</sup> (10.42 to 33.48)	18.58 <sup>†</sup> (5.45 to 31.11)
Nonconvulsive seizures	60	45	59	16.62 <sup>†</sup> (−3.39 to 37.77)	18.87 <sup>†</sup> (0.00 to 40.22)
Tonic seizures	57	56	59	21.78 <sup>†</sup> (7.36 to 35.90)	18.67 <sup>†</sup> (1.62 to 35.02)
Atonic seizures	41	40	50	28.77 <sup>†</sup> (7.08 to 45.55)	16.98 <sup>†</sup> (−8.52 to 37.79)
Tonic-clonic seizures	34	37	41	39.92 <sup>†</sup> (19.66 to 64.55)	27.95 <sup>†</sup> (2.86 to 51.99)
Change from baseline in the patient/caregiver global impression of change in seizure duration <sup>b</sup>	N	N	N	Odds Ratio (95% CI) <sup>c</sup>	Odds Ratio (95% CI) <sup>c</sup>
Tonic seizures	48	49	50	2.75 <sup>†</sup> (1.20 to 6.30)	1.38 <sup>†</sup> (0.62 to 3.09)
Atonic seizures	35	38	43	2.78 <sup>†</sup> (1.11 to 6.96)	1.90 <sup>†</sup> (0.79 to 4.55)
Tonic-clonic seizures	33	34	34	2.74 <sup>†</sup> (1.03 to 7.32)	1.79 <sup>†</sup> (0.67 to 4.74)
Change from baseline in sleep disruption 0–10 numerical rating scale score	N	N	N	Adjusted Mean Difference (95% CI) <sup>d</sup>	Adjusted Mean Difference (95% CI) <sup>d</sup>
Last visit	75	73	74	−0.8 <sup>†</sup> (−1.7 to 0.1)	−0.3 <sup>†</sup> (−1.2 to 0.6)
Change from baseline in Epworth Sleepiness Scale score	N	N	N	Adjusted Mean Difference (95% CI) <sup>d</sup>	Adjusted Mean Difference (95% CI) <sup>d</sup>
Last visit	74	71	72	0.09 (−1.38 to 1.56)	0.01 (−1.46 to 1.47)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Cannabidiol on Drop Seizures  
in the Lennox–Gastaut Syndrome

Orrin Devinsky, M.D., Anup D. Patel, M.D., J. Helen Cross, M.B., Ch.B., Ph.D.,  
Vicente Villanueva, M.D., Ph.D., Elaine C. Wirrell, M.D., Michael Privitera, M.D.,  
Sam M. Greenwood, Ph.D., Claire Roberts, Ph.D., Daniel Checketts, M.Sc.,  
Kevan E. VanLandingham, M.D., Ph.D., and Sameer M. Zuberi, M.B., Ch.B., M.D.,  
for the GWPCARE3 Study Group\*

Outcome	Placebo	Cannabidiol, 10 mg/kg/d	Cannabidiol, 20 mg/kg/d	Cannabidiol, 10 mg/kg/d vs. Placebo	Cannabidiol, 20 mg/kg/d vs. Placebo
Change from baseline in Quality of Life in Childhood Epilepsy overall quality of life score	N	N	N	Adjusted Mean Difference (95% CI) <sup>d</sup>	Adjusted Mean Difference (95% CI) <sup>d</sup>
End of treatment	38	36	33	1.6 <sup>†</sup> (−4.5 to 7.8)	−5.1 (−11.4 to 1.2)
Change from baseline in Vineland Adaptive Behavior Scales (Second Edition) Adaptive Behavior Composite Standard Score	N	N	N	Adjusted Mean Difference (95% CI) <sup>d</sup>	Adjusted Mean Difference (95% CI) <sup>d</sup>
Last visit	45	23	39	0.5 <sup>†</sup> (−1.3 to 2.3)	0.1 <sup>†</sup> (−1.4 to 1.6)

# FDA and Natural History & Trial Readiness

## Rare Diseases: Common Issues in Drug Development Guidance for Industry

2012,...2019

Define the disease population, including a description of the **full range of disease manifestations** and identification of important disease subtypes. This may allow selection of patients more likely to progress and develop the endpoints assessed in the context of a clinical trial (prognostic enrichment).

**Select clinical endpoints** and develop **sensitive and specific outcome measures.**



# The Ability Study

- ~10 days in February, 2020
- 135 parents participated
  - 39 from LGSF!!!

Thank you!!!!

- 42 Dravet syndrome
- 20 KCNB1 Families
- 23 KCNQ2 Cure Alliance
- 10 SCN2A Families
- 1 other

# Mobility

Select clinical endpoints and develop sensitive and specific outcome measures.

TYPICAL



DEE World





# Communication

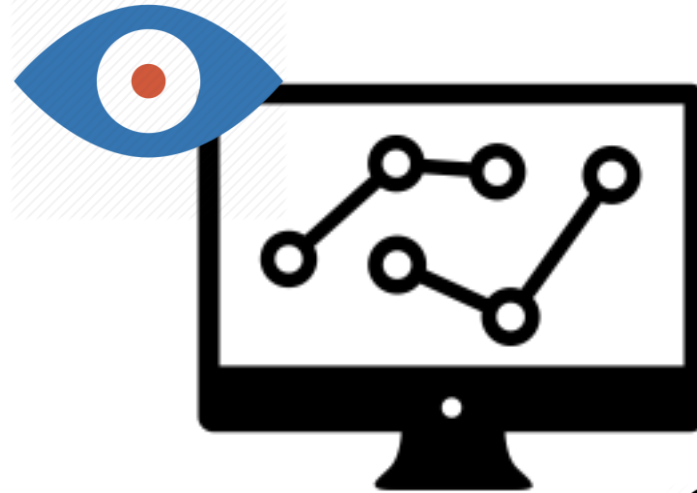
Select clinical endpoints and develop sensitive and specific outcome measures.

TYPICAL

mamama



DEE World





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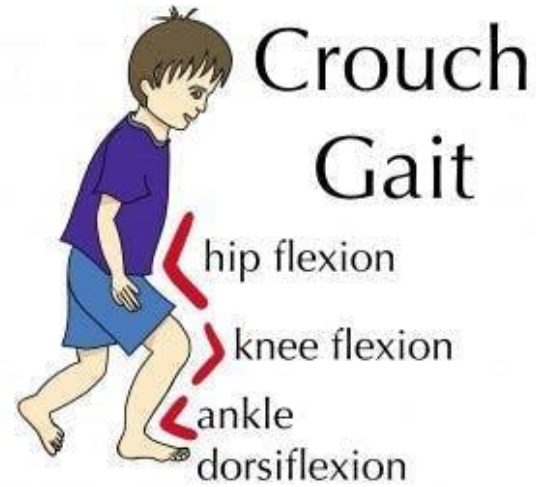
Select clinical endpoints and develop **sensitive and specific outcome measures**.

Conduct a study of sufficient duration to capture clinically meaningful outcomes and variability in the course of the disease.



# On-going projects

- Dravet Syndrome Foundation
  - Longitudinal study of Gait
- FamilieSCN2A
  - Longitudinal study of mobility, communication, and behavior



# What would you like to learn from a Natural History study?

Are there differences between seizure activity and response to medication for kids that have no known cause of LGS as compared to those with an identified cause?

How to prevent other families from having to go through this.

I would like to have an understanding of severity- like a scale or a continuum to help with perspective.

What do we do with children that are obviously so 'broken' and what are we going to do for their family that is carrying such a big burden

The common areas of struggle that we all share but aren't aware of the commonalities would make families feel less alone.

I would like to know that I have been able to help other families that are new to epilepsy

Hoping medical professionals will learn more about what happens from a patient's point of view and be more understanding.

sleep and behavior are hot topics for families.

need to do more work on effect on siblings...for example, how many have anxiety or some other trauma related issue?

Important Persistent incredibly  
remotes,laptops little.Yet proud  
above usually perseveres begun  
next humor ability friends non-verbal  
close Lili fill tools none friendly  
electronics often choices hard Content  
special shows despite approach  
drawn good strong doesn't langue  
challenges activity world rare loves woman  
multiple people loving grown difficult  
random chores gives task things  
time around happy help sweet  
iPad seizures just always PIMO smile  
connected tries work verbal endure  
clean sibling play profound Sometimes allows  
going Most young stimulation amazing mimic lotion  
ithstand awhile extremely signs likes  
completes entertaining describe family  
understand nature