Expressive Communication as a Clinical Trial Outcome for SCN2A-Developmental and Epileptic Encephalopathies

SM Egan[1], L Evans[1], KC Paltell[1], A Kaiser[1], A Nils[1], E Anderson[2], C Chapman[3], K Coffman[4], AJ Kaat[5], G Nesbitt[6], L Schust Meyer[1], AT Berg[7,8]

The FamilieSCN2A Foundation[1], Northwestern-Feinberg School of Medicine, Chicago, IL[2], Ardea Outcomes[3], Children's Mercy Kansas City[4], Northwestern-Feinberg School of Medicine, Dept. Medical Social Sciences, Chicago, IL[5], CLIRINX[6], Northwestern-Feinberg School of Medicine, Dept. Neurology, Chicago, IL[7], COMBINEDBrain, Nashville, TN[8]

1. Background

- SCN2A encodes a neuronal voltage gated sodium channel, NaV1.2 that is primarily found in excitatory neurons throughout the brain.
- SCN2A is one of the genes most commonly associated with early-onset epilepsy, and has been linked to autism spectrum disorder, and developmental delay.
- SCN2A-associated developmental and epileptic encephalopathy (DEE) is a condition with highly variable phenotype and extremely low prevalence (~16k predicted in the United States).
- Outcomes targeting patient-important, core, common features of SCN2A-DEE are needed for future precision medicine trials (e.g., gene-targeted) to ensure eligibility of a maximum number of patients (FDA guidance 2009, 2019, 2022).

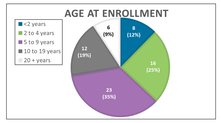
2. Study Design

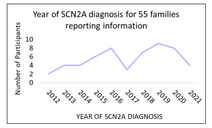
- The SCN2A Clinical Trials Readiness Study (CTRS) is a longitudinal study designed with parents to assess outcomes in their children that are life changing, life limiting, and ultimately important to parents.
- The primary goal of the study is to prepare the SCN2A community with necessary outcome measures for precision medicine clinical trials.
- As part of the Inchstone pilot study, 10 of the families also participated in a Goal Attainment Scaling (GAS) process in which parents identified 3 critically important goals of their choice for their child. Communication was overwhelmingly chosen as a domain of importance by parents and caregivers.

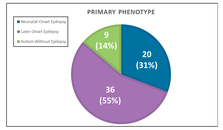
3. Patient Demographics

65 Families came from USA, Canada, UK, Ireland, Israel, Brazil, Columbia, Germany, Spain, Georgia, and India

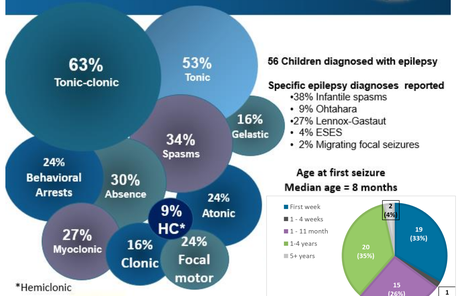
43% ♀ 57% ♂







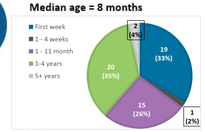
EPILEPSY AND SEIZURES



56 Children diagnosed with epilepsy

Specific epilepsy diagnoses reported
- 38% Infantile spasms
- 9% Ohtahara
- 27% Lennox-Gastaut
- 4% ESES
- 2% Migrating focal seizures

Age at first seizure
Median age = 8 months



91% currently on anti-seizure medications

During past 3 months

33 (59%) had seizures
Of those 33…
21 (64%) –convulsive seizures
21 (64%) – behavioral and myoclonic sz.
14 (42%) – other seizure types

12/33 (36%) of children with recent seizures had 1 or more prolonged seizures

10/33 (30%) children with recent seizures needed rescue medications

BASIC FUNCTION AND ABILITIES

MOTOR

81% Moderate to severe gross motor delay

30% walk outside independently for community distances

40% 2y and older depend on a mobility device for any distance

- Cannot control head
- Cannot sit independently
- Have to be lifted or hoisted

22% cannot grasp objects with their hands

12% pick up raisin with thumb and forefinger

COMMUNICATION

95% Moderate to severe communication impairment

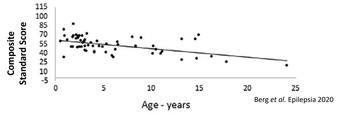
84% inconsistently or rarely communicate even with people they know well (e.g. family)

25% use some spoken language
16% speak as their primary form of communication
25% communicate by sign or device only
48% have no symbolic language (spoken, sign, device)

16% use >100 words/signs/symbols
12% combine 3+ words into sentences
22% understand >100 words/signs/symbols

4. Choosing the Right VABS-3 Scoring for SCN2A
GSV and SS

Standard Scores (SS), which compare an individual to same-aged individuals in the population, are the common approach in using instruments such as the Vineland.
- Composite Vineland scores have a mean of 100, SD=15 and Vineland subdomain SS are standardized to a mean of 15 and standard deviation of 3.SS are notorious for decreasing with age in severely affected groups such as SCN2A-DEE.

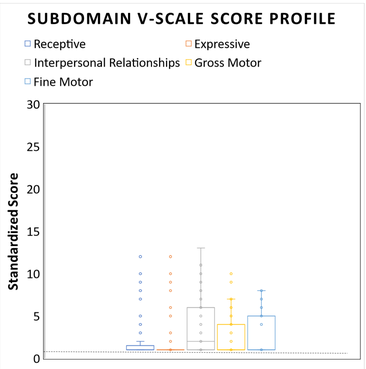


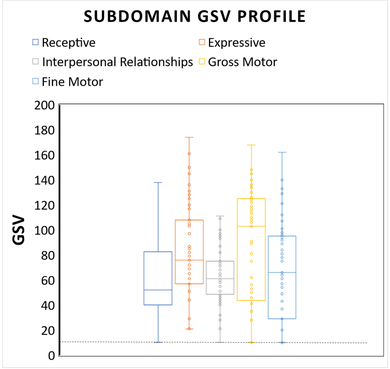
Growth Scale Values (GSV) are person-ability scores derived from the Rasch psychometric model, which provides an interval scale of measurement for each examinee based on their raw score performance."
- For example, changes in 20 points at the bottom or middle or top of the scale are equivalent to each other in GSV terms.
- The minimum value of the GSV is 10.

5. Vineland – 3
GSV Show Better Range and Few Floor Effects Relative to SS

Standardized Scoring
- Floor values of 1 were obtained in 75% for receptive and 83% for expressive communication.
- SS scores are negatively correlated with age.
- Motor SS can only be calculated up to ~7 years of age. All of the other SS can be calculated up to age 90.

Growth Scale Value
- Only 3 (5%) participants received a floor value of 10 for receptive and none for expressive communication.
- Receptive GSV (r_{Sp} =0.36, p=0.004) but not expressive (r_{Sp} =0.07, p=0.57) was positively associated with age.
- GSV scores can be calculated for all participants.





6. Initial Proof of Concept
VABS-3 GSV More Sensitive than SS in SCN2A

GSV show better discrimination across distinct levels of impairment. Cross-sectionally, they discriminate better across levels of important epilepsy-related factors. These findings suggest the GSV may be more sensitive than SS to changes related to these and perhaps other key factors.

Spearman Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations
Vineland - 3 (VABS-3)

GSV	Age at Enrollment	# of antiseizure medications taking currently	Frequency of convulsive seizures [1]	Any episode of prolonged seizure	Frequency of convulsive seizures [2]
Receptive	0.85592 ***0.0036	-0.37 **0.0045	-0.27 *0.05	-0.20 0.15	-0.28 *0.04
Expressive	0.07247 0.5662	-0.45 ***0.0005	-0.32 *0.02	-0.25 0.06	-0.31 *0.02
Interpersonal Relationships	0.21688 0.0827	-0.41 ***0.0019	-0.28 *0.04	-0.13 0.35	-0.27 *0.05
Gross Motor	0.18956 0.1304	-0.51 ***<.0001	-0.18 0.18	-0.35 ***0.0096	-0.18 0.20
Fine Motor	0.2719 *0.0284	-0.51 ***<.0001	-0.28 *0.04	-0.23 0.10	-0.29 *0.04

SS	Age at Enrollment	# of antiseizure medications taking currently	Frequency of convulsive seizures [1]	Any episode of prolonged seizure	Frequency of convulsive seizures [2]
Receptive	-0.15286 0.2241	-0.31 *0.02	-0.23 0.09	0.05 0.74	-0.25 0.07
Expressive	-0.39804 ***0.001	-0.20 0.15	-0.08 0.57	0.01 0.95	-0.11 0.43
Interpersonal Relationships	-0.41 ***0.0005	-0.27 *0.05	-0.30 *0.03	-0.16 0.24	-0.32 *0.02
Gross Motor	-0.12803 0.3912	-0.20 0.21	-0.09 0.57	0.00 1.00	-0.11 0.50
Fine Motor	-0.13866 0.3526	-0.40 **0.01	-0.25 0.13	-0.27 0.10	-0.25 0.13

Legend: # of antiseizure medications taking currently: 0, 1, 2, 3, 4+, **Frequency of convulsive seizure[1]:** 0 = none in past 6 months, 1 = once or twice only, 2 = ~1 – 3 per month, 3 = ~1 per week, 4 = ~2-5 days per week, 6 = 6 – 7 days per week, **Any episodes of prolonged seizure:** 1 = No, 2 = Yes, **Frequency of convulsive seizure[2]:** 0 = None, 1 = < or up to 1/week, 2 = more than 1/week.

Abbreviations

1. **SCN2A –** Sodium Channel 2A, 2. **CTRS -** Clinical Trials Readiness Study, 3. **GAS -** Goal Attainment Scaling, 3. **DEE -** developmental and epileptic encephalopathy, 4. **SS** – Standardize Score, 5. **GSV** – Growth Sale Value

7. CTRS Conclusions

- 9/10 SCN2A parents identified expressive communication as a critically important goal for improvement
- Expressive communication is severely to profoundly impaired in almost all people affected by SCN2A-DEE
- Vineland-3 Standardized Scores (SS) are not an appropriate SCN2A outcomes measure due to severe floor effects
- GSV have good range, no flood effects, and are sensitive to age and key aspects of SCN2A disease seizure severity.

References

1. Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments. JUNE 2022: Docket Number: FDA-2022-D-1385
2. Berg AT et al. SCN2A-Developmental Epilepsies and Encephalopathies: Challenges to trial-readiness for non-seizure outcomes. Epilepsia 2021 62:258-268.
3. AES Poster # 3.452 The Feasibility of Goal Attainment Scaling in SCN2A-associated Neurodevelopmental Disorders. Chapman C. et al. 2022