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FULL-LENGTH ORIGINAL RESEARCH

Epilepsia®

SCN2A-Developmental and Epileptic Encephalopathies: Challenges to trial-readiness for non-seizure outcomes

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Abstract

Objective: *SCN2A*-associated developmental and epileptic encephalopathies (DEEs) present with seizures, developmental impairments, and often both. We sought to characterize the level and pattern of development in children with SCN2A variants, and to address the sensitivity of the Vineland Adaptive Behavior Scales (VABS) in measuring changes over time in children with *SCN2A*-DEEs.

Methods: Clinical histories for participants with pathogenic *SCN2A* variants in the Simons SearchLight project were analyzed for descriptive purposes. VABS scores obtained at study entry and yearly thereafter were analyzed for floor and ceiling effects, change with age, and association with epilepsy through use of regression and longitudinal regression methods.

Results: Sixty-four participants (50 with epilepsy, 30 [47%] female, median age 49 months, interquartile range [IQR] 28 to 101) were included. Histories of birth complications (N = 34, 54%), neonatal neurological signs (N = 45, 74%), and other neurological symptoms (N = 31, 48%) were common and similar in epilepsy and nonepilepsy subgroups. Mean standardized VABS scores (Composite 53.5; Motor, 55.8, Communication, 54.1, Socialization, 59.4, and Daily living skills, 55.1) reflected performance ~3 standard deviations below the normative test average. In longitudinal regression analyses, standardized scores decreased between 1.3 and 2.8 points per year, suggesting regression of abilities. Raw score analyses, however, revealed several subdomains with substantial floor effects (eg, community use); other raw scores increased with increasing age. Participants with epilepsy scored 0.6 to 1 SD lower than those without epilepsy (all P's < .05).

Significance: The VABS, as standardly administered, has shortcomings for addressing growth or regression in individuals with *SCN2A*-DEEs. Some subdomain raw scores reflected substantial floor effects. Raw scores increased so slowly over time that standardized scores declined. Alternative measures sensitive to incremental meaningful change are required if outcomes such as adaptive behavior are to be primary outcomes in short-term clinical trials.

KEYWORDS
phenotype, Simons SearchLight, trial readiness, Vineland Adaptive Behavior Scales

1 | INTRODUCTION

SCN2A encodes the voltage-gated sodium channel $Na_v1.2$, which is primarily expressed in the cortex and several subcortical structures.[1] Its role in neurodevelopmental disorders was first appreciated in the context of benign familial neonatal and infantile seizures[2]; however, it is now recognized to play key roles in more severe neurodevelopmental disorders including autism and severe encephalopathies associated with epilepsy.[3–6]

SCN2A-associated developmental and epileptic encephalopathies (DEEs) are rare.[6] Yet, among children with epilepsy referred for genetic testing, *SCN2A* variants are one of the more common findings,[7,8] especially among neonates.[9]

With the growing potential for true precision medicine in which therapies target the underlying pathophysiology of a specific disease and not merely its symptoms, it is increasingly important to understand the full range of the phenotypes and natural history of rare diseases, and to identify measures that are appropriate to the population and sensitive to meaningful changes in important outcomes. This is essential to the design of clinical trials. Trials of precision therapies must target important clinical outcomes and employ measures that are sufficiently sensitive to discern whether a therapy has produced a meaningful clinical effect, especially over the relatively short term of a typical clinical trial. This goal has been emphasized in recent US Food and Drug Administration (FDA) guidance to industry.[10,11]

In 2015, the Simons Searchlight (previously the Simons Foundation Autism Research Initiative, SFARI) partnered with FamilieSCN2A, a parent-formed nonprofit foundation, to expand their data collection efforts for patients in their registry with *SCN2A* variants. The project involves the systematic collection of data from a large sample of affected probands and the use of the Vineland Adaptive Behavior Scales-II (VABS-II), a clinically valuable, standardized measure of adaptive behavior that often serves as a proxy for development in research and clinical trials.[12–15] The project thus provides a valuable opportunity for evaluating the Vineland's properties in children with *SCN2A*-DEEs before implementing it as a primary or secondary outcome end point in a therapeutic trial.

Key Points

- Neonatal complications, vision disorders, and other medical conditions are common in children with *SCN2A*-DEEs (developmental and epileptic encephalopathies) with or without epilepsy
- Scores on the Vineland Adaptive Behavior Scales (VABS) indicate levels of functioning 2 to 3 standard deviations below population norms
- The poor match of the Vineland to *SCN2A*-DEE levels of function results in significant insensitivity for accurately measuring patients' skills, progress, and treatment response
- Nonseizure domains are being considered as primary or secondary trial outcomes for precision medicine trials in rare DEEs
- Trial readiness needs for *SCN2A*-DEEs are not met by the Vineland; other instruments must be considered

2 | METHODS

2.1 | Data source

Data are from SFARI's SearchLight project, which recruits and studies participants with single gene disorders (https://www.sfari.org/resource/simons-searchlight/). Beginning in early 2015, members of FamlieSCN2A Foundation community began participating. Participants provided variant information, which was verified as pathogenic/likely pathogenic or of uncertain significance (VUS) by the Simons Foundation central genetics core. Data for these analyses were downloaded in August 2019. Only probands whose variant was determined to be pathogenic or likely pathogenic were included. Furthermore, we a priori excluded children with deletions or duplications of the *SCN2A* gene as part of a large copy number variant (CNV), as many other genes were involved, making attribution of the phenotypic findings solely to the *SCN2A* variant uncertain. We also excluded any individuals with inherited variants and a history consistent with benign familial neonatal epilepsy, as this project is focused on *SCN2A*-DEE. Demographic information and detailed medical history were obtained from the family through a structured interview with a genetic counselor. The VABS-II was administered as an interview by a trained genetic counselor. Parents were invited to provide an updated medical history and VABS-II at yearly intervals. In 2019, Searchlight included a separate seizure survey developed with parent input from the Rare Epilepsy Network on-line survey,[16] and which augmented the history obtained in the standard SearchLight form.

Vineland-II: The VABS-II is intended for use over a broad age range from 0 to 60 years. In addition to an overall composite score, four domain scales for motor, communication, socialization, and daily living skills are derived. The composite and domain scores are standardized for age to a mean of 100 and standard deviation (SD) of 15. In addition, subdomain scores are provided for gross motor, fine motor, receptive language, expressive language, written communication, interpersonal relationship, play and leisure time, coping skills, personal, domestic, and community use. The subdomains are standardized to V scores with a mean of 15 and SD of 3.[17] Raw subdomain scores are also provided. Although the VABS-II is used for all ages, items sampling gross motor skills are not part of standard administration after the age of 7 years, and written communication items are only introduced beginning at 3 years.

2.2 | Analyses

2.2.1 | Clinical features

Analyses focused on clinical descriptions of the *SCN2A* cohort and differences in clinical features between those with and without epilepsy. Categorical demographic and clinical characteristics were reported using frequency and percentages and age was reported using median and interquartile ranges.

2.2.2 | Analyses of Vineland scores

Cross-sectional

The cross-sectional analysis included assessments from the initial intake only. Means and SDs were used to describe the distribution of each of the 17 VABS-II domains. The VABS-II standardized and raw scores at the initial intake into the SFARI project were subject to descriptive analyses to determine whether there was evidence of floor or ceiling effects that would limit the effectiveness of the VABS in the *SCN2A* population. Their associations with age at the time of initial evaluation of the child and with the diagnosis of epilepsy were determined as well. Generalized linear regression techniques were employed for multivariable analyses. We also provide the age-equivalent scores to place the performance of the *SCN2A* cohort members in perspective relative to the normative population.

Longitudinal

VABS data from multiple longitudinal assessments per patient were analyzed with repeated-measures mixed-effects models using a first-order autoregressive covariance structure to evaluate the relationship between VABS-II scores and age over time. Least squares means were calculated for the change in VABS-II scores for each year of age. Adjusted analyses included a term for epilepsy. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Estimates for change in each measure for each increasing year of age and corresponding 95% confidence intervals and *P*-values were calculated. *P*-values $< .05$ were considered statistically significant.

Institutional review board approval

Institutional review board (IRB) approval for the SFARI project is maintained by the Columbia University School of Medicine. The data use agreement established between the Simons Foundation and the investigator's institution does not permit release of Simons data to a third party. Interested individuals may request data directly from the Simons Foundation at https://www.sfari.org/.

3 | RESULTS

3.1 | Derivation of sample

Of 77 probands in the SearchLight database, 13 were excluded because their variants were of uncertain significance (N = 9), an inherited mutation with a phenotype of benign familial epilepsy (N = 1), the *SCN2A* gene was part of a large multi-gene deletion or duplication (N = 2), or no clinical information was available (N = 1). Analyses were based on 64 probands; 14 did not have a diagnosis of epilepsy. Medical history files were available for all 64, and at least an initial VABS-II was available for 60 (missing in 3 with and 1 without epilepsy). Parental education (higher of the 2 parents) was missing for 10 children. For the remaining 54, the higher level of education for the 2 parents was a 4-year college degree or higher (N = 44, 81%), an Associate's degree (N = 6, 11%), a high school diploma (N = 3, 6%), and one did not finish high school.

3.2 | Clinical features

Age at enrollment was younger in the epilepsy than nonepilepsy group (Table 1). Sex distribution was comparable in the two groups. In this sample, there were no significant differences between probands with and without epilepsy with respect to birth complications, neonatal neurological signs, vision concerns, and motor/tone disorders, and selected other common concerns raised by parents (eg, constipation, scoliosis).

3.3 | Variants

The *SCN2A* variants of the probands included in these analyses are provided in Table S1.

TABLE 1 Comparison of *SCN2A* probands with and without epilepsy and with neonatal vs postneonatal onset of epilepsy

		Epilepsy	
	Overall (N = 64)	**No (N = 14)**	**Yes (N = 50)**
Age at initial evaluation and sex			
Median age at evaluation (medical history) and Interquartile range (IQR)	49 mo IQR (28-101) Range (7-287 m)	86.5 mo IQR (37-107 m) Range (23-179 m)	43 mo IQR, (26-75 m) Range (7-287 m)
Female	30 (47%)	8 (57%)	22 (44%)
Male	34 (53%)	6 (43%)	28 (56%)
Any birth complication (1)[a]	34 (54%)	7 (50%)	27 (55%)
Heart rate abnl	3 (5%)	1 (7%)	2 (4%)
Temperature	6 (10%)	1 (7%)	5 (10%)
Meconium	28 (13%)	2 (14%)	6 (12%)
Sepsis	1 (2%)	0	1 (2%)
Resp distress	14 (22%)	2 (14%)	12 (24%)
Intensive care unit admission	18 (29%)	2 (14%)	16 (33%)
Neonatal Neurological Signs (3)	45 (74%)	11 (79%)	34 (72%)
Abnormal suck	25 (41%)	6 (43%)	19 (40%)
Stiff	3 (5%)	1 (7%)	2 (4%)
Floppy	23 (38%)	4 (29%)	19 (40%)
Feeding difficulty	27 (44%)	6 (43%)	21 (45%)
Irritable	17 (28%)	2 (14%)	15 (32%)
Lethargic	18 (30%)	4 (29%)	14 (30%)
Vision and neurological symptoms and related disorders			
Developmental eye conditions	31 (48%)	4 (29%)	27 (54%)
Amblyopia	1 (2%)	0	1(2%)
Near sighted	4 (6%)	1 (7%)	3 (6%)
Far sighted	5 (8%)	0	5 (10%)
Nystagmus	6 (9%)	0	6 (12%)
Depth perception	1 (2%)	1 (7%)	0
Strabismus	10 (16%)	1 (7%)	9 (18%)
Astigmatism	5 (8%)	0	5 (10%)
Cortical blindness	17 (27%)	1 (7%)	16 (32%)
Clumsy (17)	17/47 (36%)	6 (60%)	11 (30%)
Hypotonic	50 (78%)	11 (79%)	39 (78%)
Hypertonic	14 (22%)	2 (14%)	12 (24%)
Macrocephaly	4 (6%)	1 (7%)	3 (6%)
Microcephaly	9 (14%)	1 (7%)	8 (16%)
Movement disorder	21 (33%)	3 (21%)	18 (36%)
Tics	4 (6%)	1 (7%)	3 (6%)
Febrile seizures	11 (17%)	1 (7%)	10 (20%)
Other Medical			
Has a Gastrotomy-tube (17)	14/47 (28%)	0/11	14/36 (39%)[*]
Scoliosis (2)	16/62 (26%)	2 (15%)	14 (29%)
Constipation (0)	50 (78%)	6 (43%)	27 (54%)

(Continues)

TABLE 1 (Continued)

	Overall (N = 64)	Epilepsy	
		No (N = 14)	Yes (N = 50)
Evaluations			
MRI	62 (97%)	12 (86%)	50 (100%)**
CT (5)	11/59 (19%)	0	11 (24%)*
PET scan (6)	7/58 (12%)	0	7 (16%)
EEG	60 (94%)	10 (71%)	50 (100%)***

Note: (##) Indicates number with missing data for each factor.

Abbreviations: IQR, interquartile range; MRI, magnetic resonance imaging; CT, computed tomography; PET, positron-emission tomography; EEG, electroencephalogram.

[a]1 missing age at initial evaluation.

*$P < .05$

**$P < .01$

***$P < .001$

TABLE 2 Vineland, standardized, and V scores at initial evaluation for the overall group and by epilepsy

Variable (total N with data)	Overall epilepsy (N = 60) Mean (SD)	Epilepsy		
		No epilepsy (N = 13) Mean (SD)	Epilepsy (N = 47) Mean (SD)	*P*-value
Composite Std[a] (59)	53.5 (13.6)	61.7 (7.5)	51.2 (14.1)	.01
Motor Std[a] (42)	55.8 (14.9)	66.6 (7.5)	53.6 (15.1)	.03
Gross Motor V[b] (42)	7.6 (2.5)	9.4 (1.4)	7.3 (2.6)	.04
Fine Motor V[b] (42)	7.3 (3.2)	9.6 (1.9)	6.8 (3.2)	.04
Communication Std[a] (59)	54.9 (15.9)	63.3 (10.4)	52.5 (16.4)	.03
Receptive V[b] (60)	7.5 (3.6)	10.1 (2.7)	6.7 (3.4)	.002
Expressive V[b] (60)	6.3 (3.2)	7.4 (1.9)	6.0 (3.4)	.15
Written V[b] (38)	7.7 (2.3)	7.4 (2.6)	8.4 (2.0)	.23
Social Std[a] (60)	59.4 (13.9)	64.5 (10.8)	58.0 (14.5)	.14
Interpersonal V[b] (60)	7.1 (2.7)	6.9 (28)	8.1 (2.4)	.15
Play & leisure time V[b] (60)	7.5 (3.0)	7.3 (31)	8.4 (2.8)	.24
Coping skills V[b] (56)	8.6 (2.3)	8.4 (2.4)	9.3 (1.8)	.23
Daily living skills Std[a] (60)	55.1 (15.3)	61.8 (8.2)	53.3 (16.4)	.07
Personal V[b] (60)	6.6 (3.1)	6.3 (3.3)	7.6 (2.2)	.16
Domestic V[b] (56)	8.6 (2.9)	8.2 (3.0)	9.9 (1.8)	.06
Community V[b] (56)	7.1 (3.1)	6.9 (3.4)	7.7 (1.9)	.44

[a]Standardized to mean = 100, SD = 15.

[b]Standardized to a mean = 15, SD = 3.

3.4 | Cross-sectional analysis of VABS-II scores

Mean standardized scores reflected values that were approximately 3 SD below the test normative means (100 for standardized overall composite and domain scores and 15 for subdomain V scores, Table 2). The overall composite standard score was 53.4 (SD = 13.6); the highest recorded score was 88 (low average range). Comparisons of the epilepsy (N = 47) and nonepilepsy (N = 13) groups revealed lower standardized scores in children with epilepsy.

The age equivalents for subdomain scores were in the 11- to 18-month range with the exception of writing (introduced at 3 years), which was 34.7 months (SD = 25.4). Age equivalent and raw scores are provided in Table S2.

The standardized scores decreased with age at evaluation (Figure 1A,B). The raw scores contributing to each of the subdomains tended to increase with age; however, they clustered near the bottom of the possible range of the scores and, for three of the raw score measures, over half of respondents scored 0, the test floor (Figure 1C). These were the subdomains for written communication (67%), which contributes to the communication domain and composite score starting at age 3, and the domestic living (60%) and community (63%) subdomains, which both contribute to the daily living skills domain and to the composite score. Because of this prominent floor effect, the scores for these three subdomains were not further analyzed. For the other subdomains, floor effects (scores of 0) were not as prominent: gross motor (2%), fine motor (12%), receptive communication (3%), expressive communication (0%), interpersonal relations (2%), play and leisure (5%), coping (4%), and personal care (3%). Although standardized scores for motor subdomains are calculated only up through age 6 years, the motor subdomains were administered to some older children, and their raw scores are included in the analyses and graphs.

3.5 | Longitudinal analyses of VABS scores

There was a total of 103 VABS-II administrations for 60 individuals in the *SCN2A* cohort. These represented 60 initial, 27 second, 15 third, and 1 fourth administration. Thirty-three individuals contributed only an initial VABS-II. The average ages at the first, second, and third administrations were 70.4 months (SD = 60.3), 77.5 months (SD = 50.8), and 86.3 months (44.7), respectively, and the fourth administration (N = 1) was at 85 months.

Graphical analysis demonstrated trends similar to those seen in the cross-section data; standardized scores decreased with age while some raw scores clearly increased (Figure 2). On average, in the general population, the standardized scores are expected to remain relatively constant within a limited range over time. Instead, the majority of trajectories fell below the null (0) line (Figure 2: Aii-Composite, Bii-Motor, Eii-Communication). By contrast, raw scores (Figure 2C,D,F,G), of most children who were followed longitudinally experienced an increase in both gross and fine motor scores over time, although there are clusters of children for each domain who were reported not to make gains. Receptive communication raw scores (Figure 2F) tended to increase. By contrast, most children experienced almost no improvement in expressive scores (Figure 2G). Children who initially scored 0 on the writing, community use, and domestic living subdomains did not show any improvement in those domains on subsequent administrations of the VABS.

In a series of multivariable longitudinal models (Table 3), both age and epilepsy diagnosis contributed to standardized

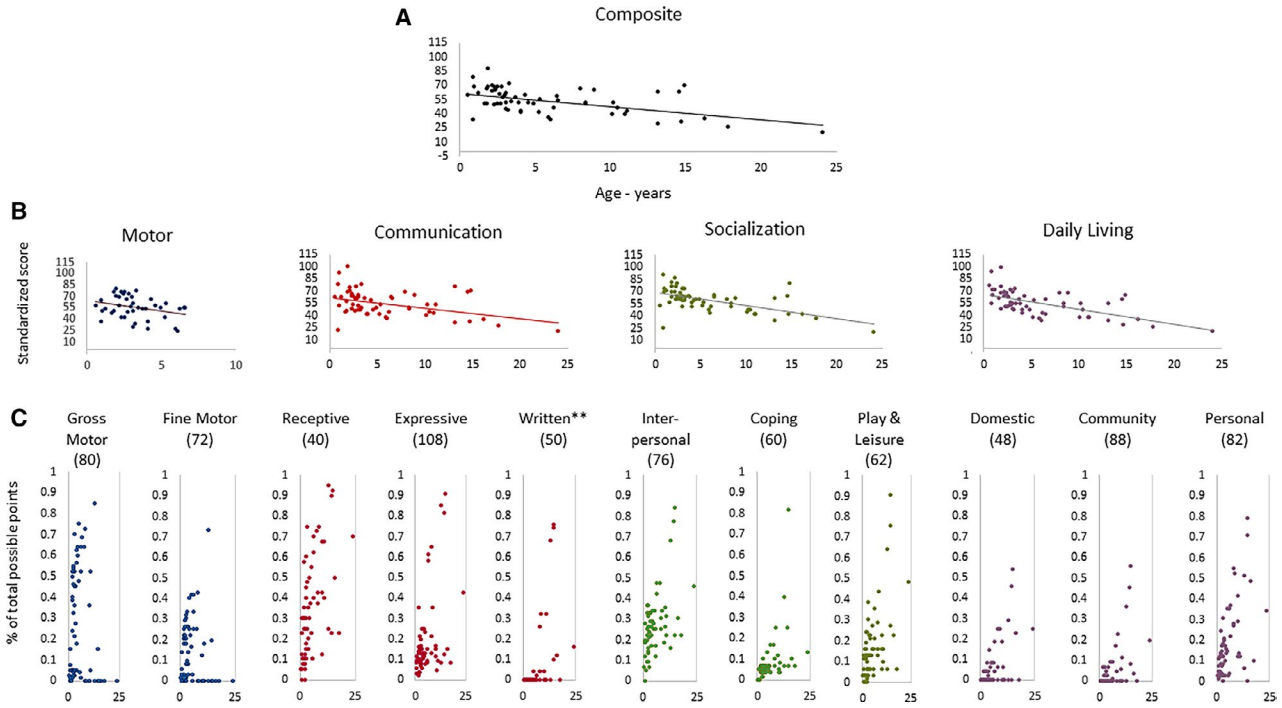

FIGURE 1 Cross-sectional data of the Vineland Adaptive Behavior Scales— standardized and raw scores by age as measured at the time of study entry. A, Composite standard score. B, Standardized domain scores for Motor, Communication, Socialization, and Daily living. C, Raw scores for the 11 subdomains contributing to the 4 domains. *Standardized motor scores are only calculated up until 7 y of age. **Written communication is administered beginning at 3 y of age. The composite and domains scores are standardized to a mean of 100 and standard deviation of 15. Raw scores are expressed as proportion of total possible raw score achieved. The maximum achievable raw score for each subdomain is provided in parentheses

VABS scores. All standardized scores consistently decreased with increasing age of testing. All raw scores, however, increased with age. Furthermore, all scores (standardized and raw) were significantly lower, by up to a full standard deviation, in the group with epilepsy compared to the group without. We examined whether the trajectories were different in children with vs without a diagnosis of epilepsy. The direction of effects suggested a greater decrease in standardized scores for those with epilepsy; however, in this limited sample size, none of the associations was statistically significant.

4 | DISCUSSION

SCN2A-DEE is a severe disorder frequently but not always characterized by epilepsy; *SCN2A* is one of the first genes specifically associated with autism.[4,18] The FDA has emphasized the importance of understanding the natural history of a rare disease prior to engaging in clinical trials,[10,11] and the SearchLight data provide a valuable resource for beginning that process. Our analyses suggest that the clinical phenotypes in children with and without epilepsy, overall, are not markedly different. Statistical power is admittedly limited for these comparisons; however, this is one of the largest, systematically characterized cohorts of *SCN2A*-DEE and provides a valuable reference point for future studies.

Therapeutics for rare diseases such as *SCN2A*-DEE require clinical outcome measures that are relevant and sensitive to meaningful change over the course of a trial-length study. The use of the VABS-II in the SFARI project provides invaluable information about the level and trajectory for development in children with *SCN2A*-DEE and about the performance of this measure in this specific group. Several aspects are notable. First, the average standardized scores in this cohort are about 3 SD below the normalization sample means; only about 1 or 2 of 1000 individuals in the general population score in this range. These scores corresponded to age equivalents that were consistently close to 1 year, although the median age at initial evaluation was 4 years. The Vineland does not sample a large number of skills at this range of function, which limits its sensitivity to distinguish differences in this range among individuals or changes that may occur in a single individual

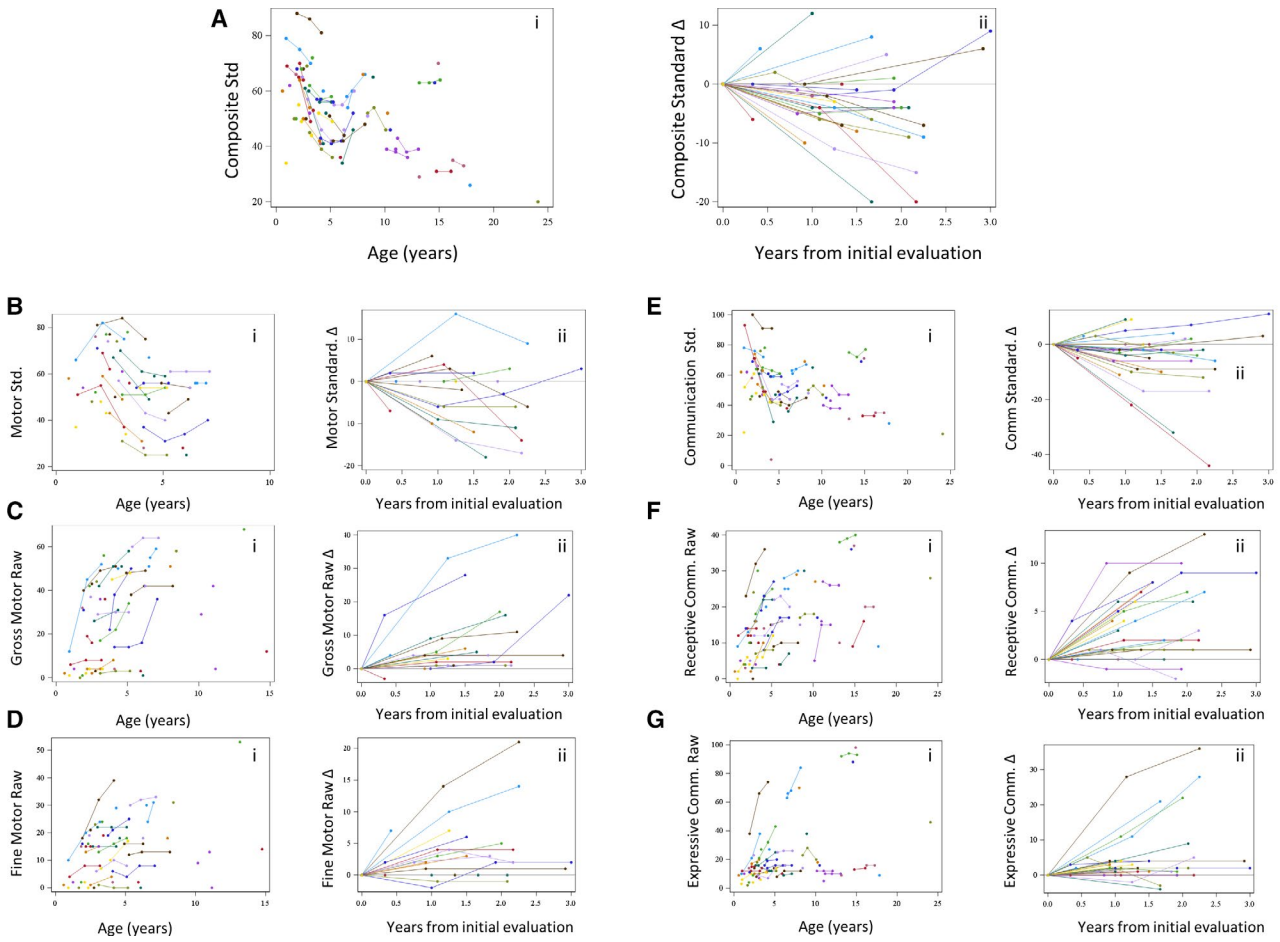

FIGURE 2 Individual subjects scores graphed by ages at evaluation (i) and changes over time from the initial evaluation for each individual (ii). A, Composite standardized score. B, Motor standardized score. C, Gross motor raw score. D, Fine motor raw score. E, Communication standardized score. F, Receptive communication raw score. G, Expressive communication raw score

TABLE 3 Estimated changes in Vineland scores per year of age and effect of epilepsy diagnosis from longitudinal regression analyses

	Estimated difference associated with epilepsy (95% CI)	*P*-value	Estimated change per year of age (95% CI)	*P*-value
Composite Standard	−12.7 (−18.9, −6.4)	.0002	−1.5 (−2.0, −1.0)	<.0001
Motor Standard	−13.9 (−24.7, −3.1)	.02	−2.8 (−4.6, −1.1)	.003
Gross motor V	−2.3 (−4.2, −0.4)	.02	−0.3 (−0.6, 0.0)	.04
Gross Motor Raw	−21.3 (−34.0, −8.5)	.002	2.6 (1.2, 4.0)	.001
Fine Motor V	−3.0 (−5.2, −0.7)	.01	−0.7 (−1.0, −0.4)	.0003
Fine Motor Raw	−12.7 (−19.2. −6.2)	.0004	1.3 (0.6, 2.0)	.0007
Communication Standard	−13.2 (−21.3, −5.0)	.002	−1.4 (−2.0, −0.7)	.0002
Receptive V	−3.6 (−5.5, −1.7)	.0005	−0.2 (−0.3, 0.0)	.02
Receptive Raw	−8.9 (−13.7, −4.2)	.002	1.2 (0.8, 1.6)	<.0001
Expressive V	−1.9 (−3.5, −0.3)	.02	−0.4 (−0.5, −0.2)	<.0001
Expressive Raw	−20.3 (−32.0, −8.5)	.001	2.0 (1.2, 2.9)	<.0001
Social Standard	−9.0 (−15.5, −2.5)	.009	−1.7 (−2.2, −1.2)	<.0001
Interpersonal V	−1.6 (−3.0, −0.2)	.03	−0.3 (−0.4, −0.2)	<.0001
Interpersonal Raw	−8.7 (−14.7, −2.7)	.006	1.4 (0.9, 1.8)	<.0001
Daily Living Skills Standard	−11.4 (−18.2, −4.7)	.0016	−1.9 (−2.4, −1.3)	<.0001
Personal Care V	−2.0 (−3.3, −0.7)	.004	−0.4 (−0.5, −0.3)	<.0001
Personal Care Raw	−14.9 (−21.7, −8.1)	<.0001	1.6 (1.2, 2.1)	<.0001
Play and Leisure Time V	−1.82 (−3.17, −0.47)	.01	−0.39 (−0.50, −0.28)	<.0001
Play and Leisure Time Raw	−9.02 (−14.38, −3.66)	.002	1.24 (−1.66, −0.82)	<.0001

followed over time. At least three of the subdomains (writing, community use, and domestic living) were not appropriate for this severely challenged population for which over half of all children scored 0, and we would not anticipate seeing changes even with effective treatment. In fact, those who scored 0 on these subdomains did not achieve a higher score when reassessed in subsequent years. As calculated for a standard administration of the VABS, this renders scores for the domains to which they contributed (communication and daily living) as well as the composite score, of limited value. Other subdomains (fine and gross motor) had substantial floor effects as well. Although not subject to the same floor effects as writing, community use, and domestic living, the average expressive communication standardized score reflected performance >3 SD below the mean, which is likely a reflection of the large proportion of nonverbal individuals in this group.

The composite Vineland standardized score was used as secondary outcome in two recent randomized trials of cannabidiol for Dravet syndrome[19] and Lennox-Gastaut syndrome.[20] In the first trial, the treated group had a net decline (−2.6 points) on the Vineland (95% CI −6.8 to 1.6) compared to placebo. In the Lennox-Gastaut syndrome trial, relative to placebo control, the 10 mg/kg/d group had a net 0.5-point gain (95% CI −1.3 to 2.3) and the 20 mg/kg/d group had a net 0.1-point gain (95% CI −1.4 to 1.6). Both trials assessed participants over the course of 3 months, a time frame in which few would expect to detect a substantial degree of change, even in the general population. Although direct comparisons concerning the severity of disability in Dravet and Lennox-Gastaut syndrome vs in *SCN2A*-DEE are difficult to make; we expect we would find psychometric properties of the Vineland in the former two similar to those in *SCN2A*-DEE. Of interest, both studies found a significant improvement in the treated vs placebo groups based on the caregiver's global impression of change. Whether this was due to the reduction in seizures or improvement in other aspects of behavior is not possible to determine.

Decreases in developmental, cognitive, or functional measures with increasing age often reflect a progressive disease process such as that documented in natural history studies of mucopolysaccharidosis[21] and neuronal ceroid liopfucinosis.[22] By considering raw scores, however, we have demonstrated that the decline with age in standardized scores was not due to progressive deterioration but to a failure to gain some skills and to a slower than typical progression in others. If there is sufficient granularity to document small increments of improvement, the use of raw scores, rather than standardized score, could be a means for employing components of measures such as the Vineland in severely impaired patient populations such as those with *SCN2A*-DEE. For example, the receptive communication and interpersonal relations subdomains may have adequate spread without floor and ceiling effects and might provide the necessary responsiveness to

change over time required of a clinical outcome assessment. Many other measures are available as well and should be examined carefully to determine their appropriateness for use trials of serious rare diseases such as the DEEs. In this regard, it is also essential to consider the time interval over which clinical outcomes are assessed. Although clinical trials in epilepsy are typically done over a several month period of time, that may be inadequate for measuring clinically meaningful change in behavior and cognition.

Participants with epilepsy consistently had standardized scores that were up to a standard deviation lower than those without epilepsy. Whether this reflects differences due to the variants themselves that are associated with epilepsy, other genomic background factors predisposing to epilepsy, or the effects of epilepsy and medication on behavior and the developing brain cannot be determined from these data.

The results of the longitudinal analyses indicate that standardized composite and domain scores drop an average of 1 to 3 points per year (depending on the specific score). Although the sample does not have sufficient power to provide clear evidence, additional analyses suggested that most of the decline in standardized scores occurred predominantly in the epilepsy group. Admittedly, the small measured differences—secondary in part to the lack of sensitivity of the measures and the limited repertoire of sampled behaviors—would be uninterpretable for a specific child, and are problematic for studies of children with rare diseases.

Potential limitations to our study include the lack of a population base or target population for the sample included in SearchLight. This is true of virtually all studies of rare diseases, especially early in the history of their recognition. The internet has allowed for an unprecedented organizing of rare disease groups, but the denominators for these groups are not knowable. We note that the level of parents' education among participating families was high, with 81% reporting that one or both parents had a 4-year college degree or higher. This suggests some self-selection in participation. Potentially, if the VABS scores are influenced by parental education, our data may reflect an even more optimistic assessment of the Vineland than might be obtained in the more general population. All patients had documented *SCN2A* variants confirmed by qualified geneticists, and all information was collected under a rigorous protocol. A potential bias regarding the findings for age is that older patients who are just now being identified as having *SCN2A*-DEE may have more severe presentations, hence the efforts to find the cause, which has only recently been identified. The findings for the longitudinal analyses, however, demonstrate the decline in standardized scores and the increase or stability in raw scores at the individual level over the course of 2 or 3 years. Hence, this potential bias does not appear to explain the age effects found.

With an increasing focus on natural history, studies for rare diseases such as the DEEs,[10,11] and a greater focus on clinical outcomes other than seizures alone, there is need to identify clinical outcome assessments—both observer-reported and performance measures—that are appropriate for the condition and context of use. Whether parent report is sufficient as a trial outcome is not the issue, as parent report of measures such as the Vineland are strongly correlated with performance measures assessed by a psychologist[21] and are accepted as trial outcomes such as in recent studies of infantile spasms.[15,23] Randomized trials to test the effect of a therapeutic on developmental or adaptive behavioral outcomes will need to identify and demonstrate the validity of those measures for assessing developmental progress and change in the context of the disease targeted by the trial.

The findings from the Simons SearchLight data indicate that standard administration and scoring of the Vineland (as seen in recent trials)[19,20] may not provide the most relevant or sensitive measure for severe DEEs such as *SCN2A*-DEE. Raw instead of standardized scores[24] or limited portions of the Vineland[25] have been used previously in randomized trials of Fragile-X. This may be feasible for a limited number of the subdomains (eg receptive communication and interpersonal relations). Our finding of substantial floor effects (60% scoring 0 on three of the subdomains), and other subdomains where scores were clustered near the bottom of the potential measurement range, suggests that large parts of the Vineland, even the raw scores, may have limited value for identifying small but meaningful changes in abilities over time in the setting of severe disorders such as *SCN2A*-DEE. These are critical considerations in selecting an appropriate measure for a clinical trial outcome. Furthermore, the Vineland is a measure of adaptive behavior. This construct is based on a combination of factors that include physical ability, motivation, cognitive understanding, and opportunity. For example, community use, one of the subdomains with a significant floor, contains items such as "obeys curfews" and "travels alone 5 or more miles to a new place…." These abilities require considerable autonomy before such questions are relevant. Assessments that target unidimensional constructs and that focus on gradations in basic functions such as mobility, eating, communication, and hand use might provide more circumscribed and meaningful outcome measures.

There is much work to do to ensure that the appropriate measures are vetted and ready for use in trials for these rare disorders. The consequence of not carefully considering these issues could lead to situations similar to that seen in the arbaclofen trial for fragile-X syndrome for which the primary outcome measure failed to demonstrate a significant treatment effect, although other measures used in the trial supported the efficacy of the treatment.[24,26] Trials for rare diseases are difficult to perform and require precious resources in the form of parent-patient engagement. Ensuring that the best possible measures—those of relevant outcomes with sufficient granularity to detect meaningful change in the intended context of

use—have been identified and vetted will support the upcoming wave of therapeutic trials of novel treatments targeting specific rare disorders such as *SCN2A*-DEE.

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CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

ETHICAL PUBLICATION STATEMENT

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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