Dear SCN2A-CTRS Families,

Thank you so much for participating in the SCN2A Clinical Trials Readiness study. With your dedicated help, we are moving forward in outcomes assessment for children with SCN2A Related Disorder (SRD). This first report is about the SCN2A-CTRS cohort altogether, and we will tell you toward the end how to find your child's own report should you wish to.

As you know, there is great interest in developing and testing precision therapies for SRD, therapies that do more than suppress seizures and actually improve the condition of affected individuals. There has been little understanding of how to demonstrate in a clinical trial whether the therapies work – do they make your child better?   Do they improve your child's and your family's quality of life? This is for two reasons:

- First, nobody has really known what to consider other than seizures. With your help, we are beginning to focus in on a few critical outcomes that are important and need improvement in just about everyone. These include expressive and receptive communication, gross motor skills, cognition, behavior, and sleep. There are many others, but these are reported to be the most common non-seizure outcomes for most of your children, and they are something that can, in theory, be measured in a randomized trial.

- Second, we don't know how to measure these outcomes for people with SRD, and the instruments that are commonly used don't work well for your children. We realize that all sounds a little esoteric, so here is an example. Suppose you had a baby mouse and you wanted to measure how much weight he was gaining from day to day, so you used your bathroom scale. It would look as though your mouse weighed nothing to begin with and never grew. That is because you had the wrong measurement instrument. And this has been a serious issue for SRD and other severe developmental and epileptic encephalopathies.

In the SCN2A-CTRS, we employed and tested several different measurement instruments and ways of scoring them to find those that could provide meaningful, sensitive assessments of your child's abilities and behaviors. In doing this, we followed guidances from the FDA to help ensure that our findings would be accepted by that agency. We anticipate that these findings you helped create will play a major role in guiding clinical trial design for SRD.

We collected extensive information, thanks to you, and we will be reporting it to the SRD and scientific communities in the upcoming year through webinars, website posts, meeting presentations, and publications. In fact, two presentations from your data were made at the Annual meeting of the American Epilepsy Society in Nashville, TN December, 2022 and can be found on out home page (SCN2A CTRS) by clicking the AES icon.

RESULTS

Who is in the SCN2A-CTRS

65 families participated in the CTRS.

The SRD-affected individuals included 37 boys/men and 28 girls/women. The median age was 6.4 years with 50% being between the ages 4 and 10.5. Six individuals (~10%) were in their 20s.

We will be updating the infographics on our website (SCN2A CTRS). Here we will focus on the results from one of the measures called the *Vineland Adaptive Behavior Scales, Third Edition (Vineland-3), Comprehensive Interview Form*, which you kindly completed on up to <u>four</u> different occasions.

Why did we use the Vineland?

The Vineland is a very well-understood and respected instrument. It is routinely used in clinical trials and clinical research. The FDA is very familiar with it and, there is an impression that the FDA considers it a gold-standard of sorts.

**What is the Vineland, what does it measure, how is it scored?**

The Vineland-3 is a standardized assessment that uses a semi-structured interview to measure the adaptive behavior of individuals from birth to age 90. Adaptive behaviors are daily activities and skills that people use to get along with others, cope with the environment, and take care of themselves. The Vineland-3 is not the same as a developmental or IQ test although there will be strong correlations with developmental and intelligence measures. The *Vineland-3* measures adaptive skills that fall into 4 primary domains, each of which has a further 2 or 3 subdomains as outlined in the table below. The Vineland also provides an overall adaptive behavior composite score.

| Vineland Adaptive Behavior Scales, Third Edition (Vineland-3), Comprehensive Form – Domains, scores and applicable ages			
Domain	**Description**	**How scored Mean (SD)***	**Applicable ages (years)****
Adaptive Behavior Composite	Overall assessment of adaptive behaviors based on communication, daily living skills, and socialization behaviors (motor is not included in the composite for the Vineland).	100 (15)	0-90
Communication	Listening, understanding, and expressing self through sounds, gestures, and speech (including use of adaptive communication devices and/or sign language), and reads/writes in comparison to same age peers.	100 (15)	0-90
Receptive	Understanding communication from others (verbal and nonverbal)	15 (3)	0-90
Expressive	Communicating to others verbally and nonverbally.	15 (3)	0-90
Written	Pre writing & reading and early reading & writing skills	15 (3)	3-90
Daily Living Skills	Completing everyday tasks of living (e.g., feeding, bathing, dressing, toileting) that are appropriate for age.	100 (15)	0-90

Personal	Basic self-care skills (eating, dressing, etc)	15 (3)	0-90
Domestic	Home safety, food preparation, chores, etc	15 (3)	
Community	Getting around the community, shopping, handling money, etc.	15 (3)	
Socialization	Understanding and functioning in social situations and managing stress, etc	100 (15)	0-90
Interpersonal Relationships	Emotions, friendships, interacting with people	15 (3)	0-90
Play & Leisure Time	Playing on own, with others, doing things with others, etc	15 (3)	
Coping Skills	Managing changes, handling frustration and disappointment, etc.	15 (3)	3-90
Motor Skills	use of gross and fine motor skills in daily life.	100 (15)	0-7
Gross Motor Skill	Use of big muscles to control arms legs and trunk	15 (3)	0-7
Fine Motor Skills	Use of wrists and fingers	15 (3)	0-7

*The mean is the average in the population. We usually expect about 95% of the population to fall within the range that is +/- 2 standard deviations (SD) of the Mean. For scores with a mean of 100 (SD 15), that means 95% of the population should scores between 70 and 130 with about 2.5% receiving scores <70. For the subdomain scores with a mean of 15 (SD=3), we would expect 95% of the population to have scores between 9 and 21 with 2.5% receiving scores <70. Be aware that the lowest possible score on the composite and domain scores (that have a mean of 100) is a 20. For the subdomains (with a mean of 15), it is 1.

Standardized scores: *Standardized scores in the table above compare an individual to others in the population who are of the same age. That means your child's scores reflect how he or she is doing relative to others of the same age. The score can be transformed to represent a percentile ranking relative to same-aged peers.* This is exactly what happens at the pediatrician's office when weight, height, and head circumference are measured, and you can see on the charts how your child's measures compare to other children of the <u>same age</u> (and sex).

For young people with SRD, standardized scores tend to be very low and also drop with age. This was demonstrated in the analysis of your data from the Simons project (which used the earlier, 2nd edition of the Vineland). In that study, scores decreased with increasing age (Figure A below). You can see that almost all of the scores are <70, and that scores tend to be lower in older individuals. In the SCN2A-CTRS, we are again seeing that standardized scores are extremely low relative to same-aged peers in the population and decline in older children and over the course of the follow-up period.

Vineland Composite Score (Standardized) in the Simons SCN2A cohort.
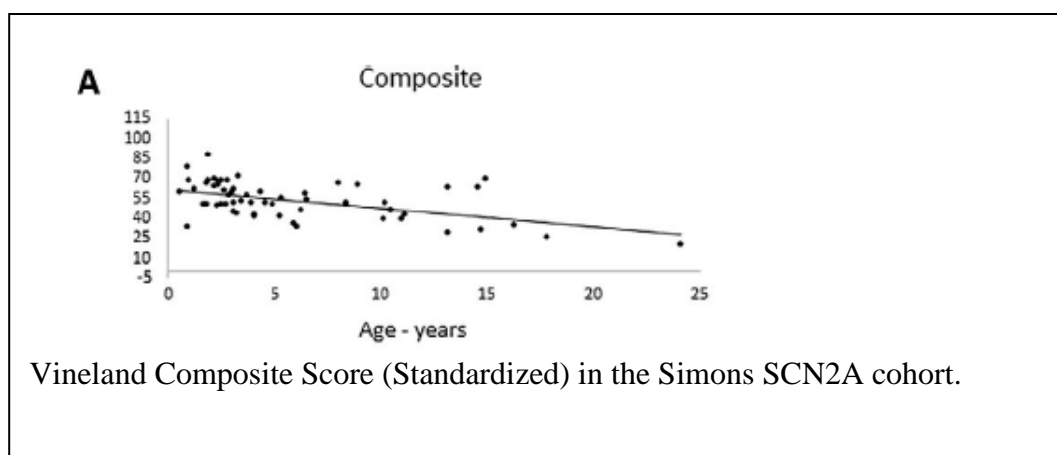
An alternative approach that was explored was to use the raw score, simply the number of points someone achieved in each sub-test of the Vineland-2. The gains are not as great as same-aged peers, but they are gains nonetheless. In the Figure C below, we graphed the raw scores (the number of points each child received regardless of age) against age. With this approach, you can see that some of the subdomains (subtests), especially receptive communication and interpersonal skills showed considerable gains as children got older (what we would hope to see). This means these young people were not regressing in their skills as they got older. They made progress but not as fast as others of the same age.. You can also see that some of the components of the Vineland-2 are *unhelpful* for people with SRD. For example, very few scored above the floor (0) for written communication, coping, domestic skills, and community use.
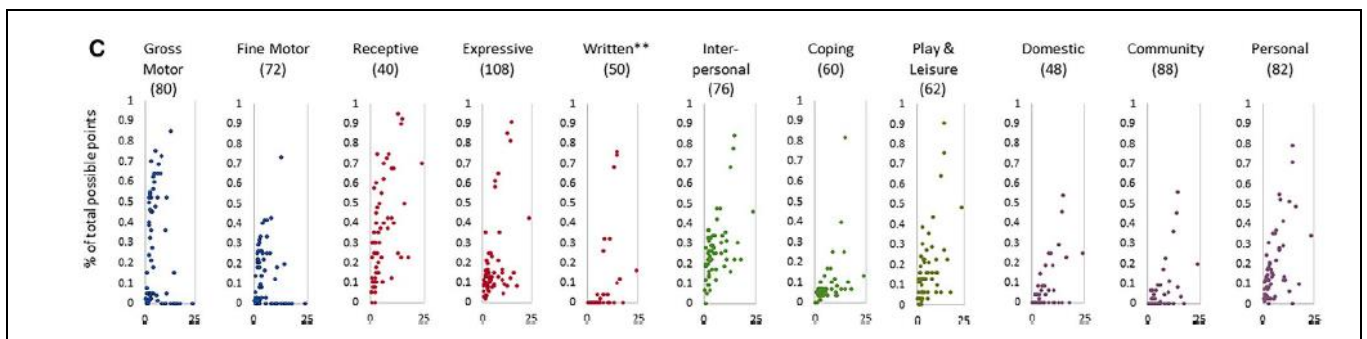
How do standardized scores in the SCN2A-CTRS cohort compare to those in the general population?

In the figure below, the distribution of scores in the general population is shown. In the left-hand bar, you can see that only about 5.5% of the population (~1 in 20) has an adaptive composite score of < ~76, which is the highest score observed in the CTRS; That means 100% of young people in the CTRS scored in roughly the ≤5% range for the population. In fact, more than 10% of the group had an adaptive composite score of 20 (lowest possible), and the median score in the CTRS cohort, 34, indicates that half of the cohort scored in the range that is what we expect to see in only ~0.003% in the general population. That means we would expect <1/10,000 people in the population to have scores this low. The pattern is the same across all of the domain and subdomain scores with few if any of your children reaching scores as high as two standard deviations below the population mean.

Distribution of scores in the general population and in the SCN2A-CTRS
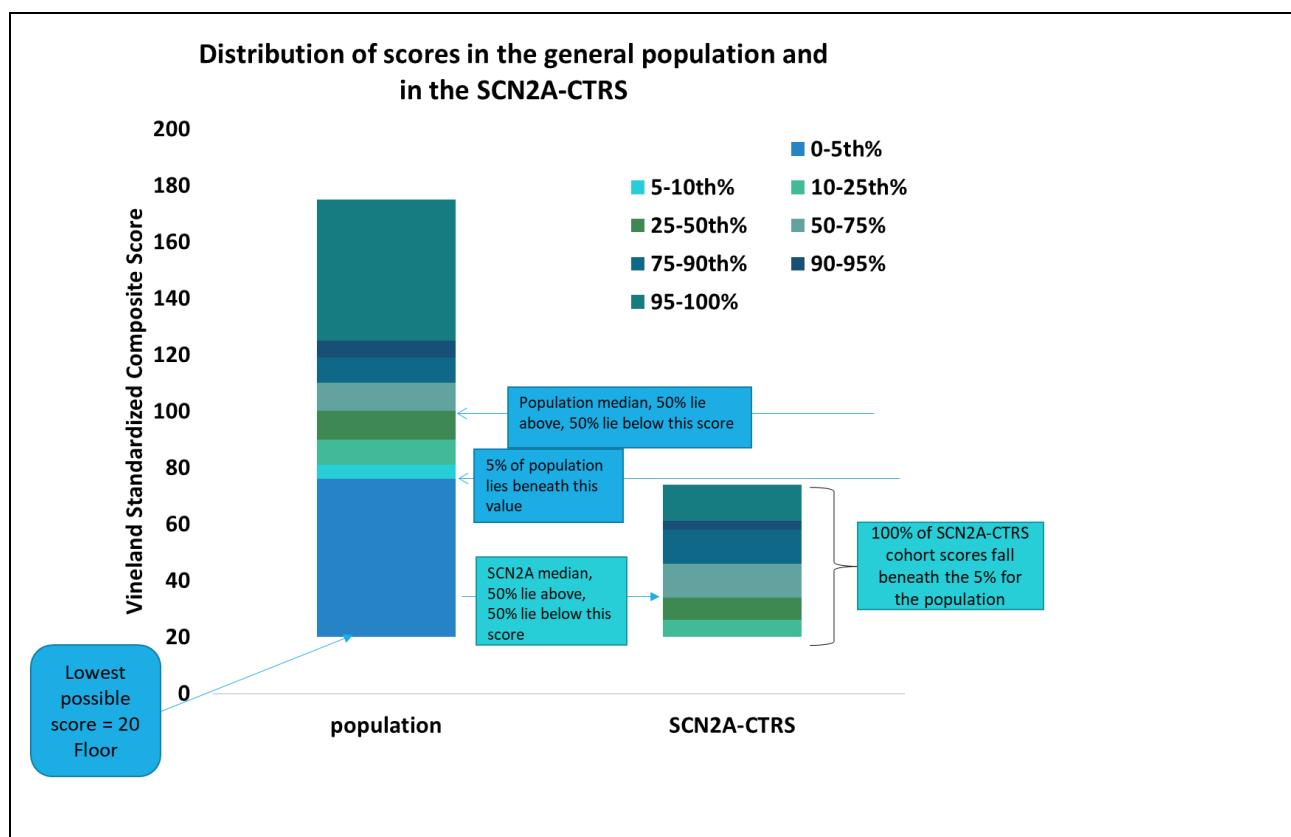
Is the Vineland a good measure for SRD?

From these findings, it seems that the Vineland-3 is completely inappropriate for people with SRD, yet it is often used. But this is with using the standardized scores, which is somewhat akin to using the bathroom scale to weigh the mouse. We need a different way to do this, one that has the necessary granularity and sensitivity to capture those small but important differences. Instead of measuring in kilograms, we need to measure in grams or even milligrams.

Is there an alternative?

Yes! Fortunately, the Vineland-3 has an alternative way of being scored that is not age-dependent and only considers what a person does, not what a person does relative to same-aged peers. That means, when changes occur, they can be more easily captured. This alternative approach is called the Growth Scale Value or GSV.

What are GSVs?

GSVs are ability scores and are not referenced to a population mean and standard deviation or interpreted relative to age. They are closely related to the raw scores (which you already saw above from the Simon's cohort) but have undergone some statistical transformations to make them even more robust indicators of changes in ability. They reflect how much your child has gained in abilities or behaviors. Think about a race in which the goal is to see how far runners can run in 10 minutes (like in the YMCA's indoor triathalon). Everyone starts off at the same point, after a minute, perhaps your

favorite runner is in the middle of the pack, but by the end of ten minutes, that runner finishes last. The runner has not gone backwards or stood still. Your friend just did not cover as much distance as the others. The place in the race is more related to the standard score whereas the absolute distance the runner covers is more like the GSV.

There are a few things to point out about the GSV before we go further.
- First, GSV are only calculated for the 11 subdomains (not the four main domains or the overall composite score).
- Second, the lowest possible score is 10 (the floor), not 0. The maximum possible score varies for each of the subdomains. It is marked in the chart below.
- Third, you cannot make comparisons of GSVs across domains. For example, having (say) a GSV score of 100 in expressive communication and of 90 in fine motor does not mean expressive communication is better than fine motor. They exist on different planes.
- Finally, the GSV are most useful for following someone's progress over time or comparing across individuals for a given domain. For this reason, they have considerable promise for use in trials for SRD.

What do the GSVs look like in the SCN2A-CTRS cohort?
Warning, there will be a lot of data to process in this next section.
In the next graph, each set vertical dots represents one subdomain on the Vineland-3. Each dot represents a percentile of the SCN2A-CTRS Cohort for each subdomain ranging from the absolute minimum score to the absolute maximum score. If you look at the dot's value on the Y-axis, you can get the approximate GSV value for that percentile. The dark blue bars (markers) at the top reflect the maximum possible score anyone could possibly get for each subdomain. While most of the scores in the CTRS are still low, you can appreciate that there is much greater variability and virtually nobody scored at the floor (score of 10) except in some of the areas, like written communication and community use. These may not be top priorities for SRD and definitely are not good measures for SRD. For expressive and receptive communication, gross and fine motor, social and interpersonal, almost everyone registered on the scale and most of these domains have some reasonable variability, which suggests they are measuring differences in adaptive behavior in the cohort even though the standardized scores do not suggest much variability. Going back to our mouse, the GSV scoring is like using a scale that can measure in grams and can distinguish a newborn mouse (~1 gram) from a juvenile (~10-15 grams) from an adult mouse (20-30 grams). These are meaningless weight differences for (say) a cat or a dog, or a human; they would never show up on a bathroom scale. But, they are huge for the mouse. Such seemingly small differences are also huge for SRD-affected individuals, and being able to measure them will be critical to the success of clinical trials.

Growth Scale Values in the CTRS Cohort
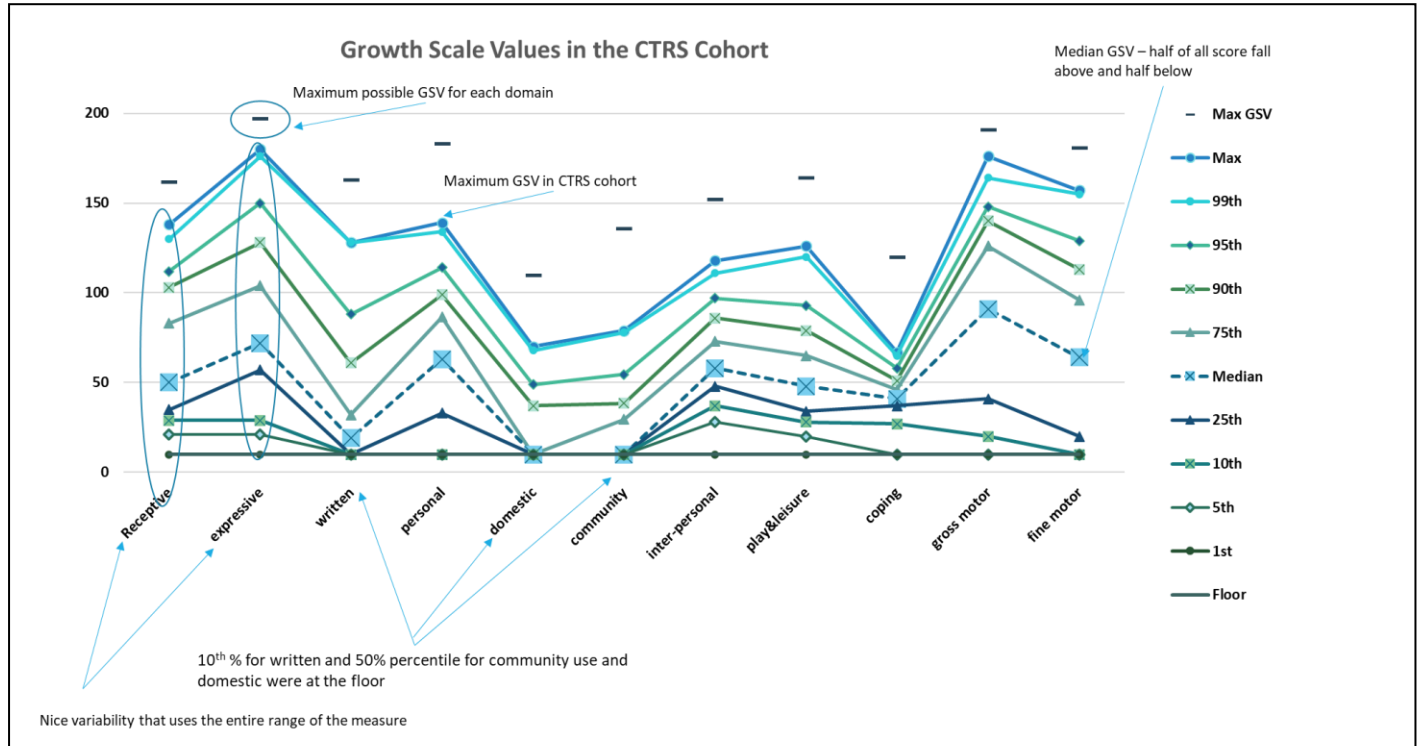
This gives us tremendous hope that the Vineland GSV scoring and perhaps supplemented with some other measures will provide us with an important tool for measuring your children's progress over time and especially in clinical trials of new therapies.

How can I get more detailed information about my child's Vineland?
If you would like a report for your child containing your child's standardized scores as well as the graph above with your child's GSV plotted with the rest of the SRD cohort, please visit the CTRS website and login to your portal **after March 15**. You will find your customized copy there next to you consent form. Just click on the ICON to access it.

If you have any difficulties, please contact us at SCN2ACTRS@SCN2A.org .

Thank you so much for your participation in the CTRS. It has been a pleasure and a privilege to work with you. Please keep an eye out for updates from FamilieSCN2A.

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