



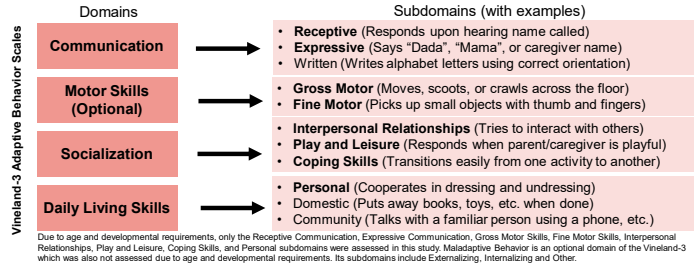
INTRODUCTION

- Dravet syndrome (DS) is a severe developmental and epileptic encephalopathy marked by frequent, recurrent seizures and significant cognitive and behavioral impairments¹
- Establishing treatment benefit for non-seizure outcomes in DS is challenging due to a paucity of DS-specific assessments²
- The Vineland Adaptive Behavior Scales-Third Edition (Vineland-3) is a clinician-administered, standardized assessment that uses a semi-structured interview format with a parent or caregiver to measure an individual's adaptive behavior—the things people do to function in their everyday lives (Figure 1)
- The Vineland-3 is commonly used to assess behavioral outcomes in DS; however, meaningful change thresholds have not yet been established
- In this study, we examined meaningful change on the Vineland-3 and associated impacts on day-to-day life

METHODS

- Design**
- A qualitative, non-interventional study aiming to 1) generate insight into caregiver and clinical expert perspectives of what constitutes meaningful change on the Vineland-3, and 2) generate insight into caregivers' perceptions of the key signs, symptoms, and impacts of DS; the study was conducted in two stages
- Stage 1: Caregivers**
- Eighteen primary caregivers of children and adolescents with DS were recruited from the United States
 - Video-based semi-structured interviews were administered by interviewers trained in the administration of the Vineland-3 (caregiver form)
 - Caregivers reported which items in each subdomain would be meaningful to change after a year of receiving a new treatment and ranked the subdomains from most important (1) to least important (8) to change with treatment
- Stage 2: Clinical experts**
- Seven clinical experts based in the United States, United Kingdom, France, and Australia participated in a video-meeting to discuss the findings from the caregiver interviews. Six of the clinical experts also completed two email-based follow-up activities
 - In the first follow-up activity, clinical experts provided additional information on the signs, symptoms and impacts of DS, the caregiver-reported subdomain rankings, and any cross-cultural differences in DS presentation and meaningful change; in the second follow-up activity, clinical experts reviewed a summary of the previous discussion, confirmed its accuracy, and provided additional feedback as needed
 - Key themes around agreement with caregiver insights, additions to caregiver insights, and additional caveats and considerations were identified through qualitative analysis

Figure 1. Vineland-3 domains and subdomains



RESULTS

Baseline caregiver and child characteristics

- Eighteen caregivers of children and adolescents with DS participated in this study (Table 1)

Table 1. Caregiver and child demographic characteristics

Demographic characteristics	Caregivers (N=18)	Children (N=18)
Mean (range) age, years	39.5 (27–51)	8.2 (2–16)
Sex, n (%)		
Male	3 (16.7)	11 (61.1)
Female	15 (83.3)	7 (38.9)
Race, n (%)		
White	17 (94.4)	14 (77.8)
Asian	1 (5.6)	1 (5.6)
Biracial	0 (0)	2 (11.1)
Not reported	0 (0)	1 (5.6)

- The mean (range) number of current treatments for children with DS was 6.3 (2–15)*

Important signs, symptoms, and impacts of DS

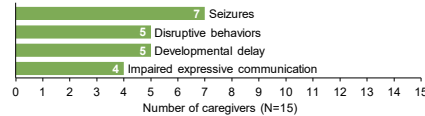
- Seventeen caregivers reported 35 signs and symptoms of DS; seizures (16/17), physical aggression (12/17), and disruptive behavior (12/17) were the most common
- Clinical experts agreed with caregiver-reported signs and symptoms, and noted impacts of DS on caregivers, including fear of Sudden Unexpected Death in Epilepsy, inability to work, sleep disturbances, grief, and spousal conflict
- Clinical experts also noted that across countries, differences in access to new medications, ancillary support services, and medical expertise could impact management of seizures and overall quality of life

*Current treatments included pharmacological treatments, dietary changes or supplements, supportive therapies, and surgery. †The recording failed for one caregiver and transcription was not possible.

Most important signs, symptoms, and impacts of DS to change with treatment

- Caregivers identified seizures, disruptive behaviors, developmental delay, and impaired expressive communication as most important to change with treatment (Figure 2)

Figure 2. Most important signs, symptoms, and impacts to change with treatment as reported by four or more caregivers



“ We have to constantly be on the lookout for anything that's going to trigger a seizure...we have to plan activities around what he's able to handle ”
Caregiver of 16-year-old

- Clinical experts agreed with caregivers on the most important signs, symptoms, and impacts to change with treatment, and noted that they may reflect what caregivers consider to be most disruptive, which could change throughout the child's life

Meaningful change on the Vineland-3

- Caregivers indicated what would represent meaningful change on the eight Vineland-3 subdomains included in the study
- ≥50% of caregivers reported the following changes as meaningful:
 - 2 → A 2-point growth scale value change in Expressive Communication (7/14), Gross Motor Skills (6/12), Interpersonal Relationships (9/14) and Coping Skills (8/13)
 - 3 → A 3-point growth scale value change in Receptive Communication (10/16), Fine Motor Skills (8/11), Play and Leisure (9/15) and Personal (6/11)

KEY FINDINGS

- 1 Small changes in adaptive behavior as measured by the Vineland-3 are considered clinically meaningful for both caregivers of patients with DS and clinical experts
- 2 Changes of 2–3 points in growth scale values across subdomains were considered meaningful to at least 50% of caregivers
- 3 Consistent with other publications, the Expressive Communication and Receptive Communication subdomains of the Vineland-3 were ranked by caregivers as most important to change with treatment
- 4 This study further defines meaningful change thresholds on the Vineland-3 to explore cognitive and behavioral treatment benefits in clinical trials of potential disease-modifying treatments

- Clinical experts agreed that these changes represent clinically meaningful improvement, and that they could vary based on child seizure frequency, age, communication ability, behavior, underlying ability, and caregiver comprehension of the Vineland-3

Ranking of Vineland-3 subdomains

- Caregivers ranked the Expressive and Receptive Communication subdomains as most important to change with treatment; clinical experts generally agreed with caregiver rankings and noted a potential shift in caregiver priorities as the child ages (Table 2)

“ I think number one is 'expressive'...our number one focus right now is helping her to communicate so that she feels heard ”
Caregiver of 2-year-old

Table 2. Caregiver rankings of Vineland-3 subdomains

Child age (years)	Receptive Communication	Expressive Communication	Gross Motor Skills	Fine Motor Skills	Interpersonal Relationships	Play and Leisure	Coping Skills	Personal
2	4	1	6	5	7	2	8	3
3	6	1	8	7	5	6	4	2
4	1	2	5	6	4	8	3	7
5	1	2	4	5	6	7	8	3
5	2	1	7	6	4	8	3	5
6	4	2	6	5	8	7	3	1
6	2	1	7	4	3	5	6	8
8	2	1	4	6	5	8	3	7
8	3	2	8	7	4	6	1	5
8	2	1	5	6	4	7	3	8
8	3	1	7	6	5	8	4	2
11	4	2	6	8	5	7	1	3
12	4	5	7	6	3	8	2	1
12	4	2	3	4	5	7	2	6
14	7	1	8	6	5	4	2	3
15	6	5	7	8	3	4	1	2
16	5	1	8	6	4	7	3	2
Overall (mean) rank	2 (3.3)	1 (2.3)	7 (6.1)	6 (5.7)	5 (4.8)	8 (6.5)	3 (3.4)	4 (3.8)

References: 1. Porter KA et al. J Patient Rep Outcomes 2022; 6 (1): 40. 2. Bachi G et al. Epilepsia 2012; 53 (1): 87–100. Acknowledgements: This study was supported by Stoke Therapeutics. We thank research staff, investigators, and participants. Writing support was provided by Porterhouse Medical US and was funded by Stoke Therapeutics according to Good Publication Practice guidelines.