












RESEARCH ARTICLE

Global modified-Delphi consensus on comorbidities and prognosis of SCN8A-related epilepsy and/or neurodevelopmental disorders

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Abstract

Objectives: We aimed to develop consensus on comorbidities (frequency, severity, and prognosis) and overall outcomes in epilepsy, development, and cognition for the five phenotypes of SCN8A-related disorders.

Methods: A core panel consisting of 13 clinicians, 1 researcher, and 6 caregivers was formed and split into three workgroups. One group focused on comorbidities and prognosis. All groups performed a literature review and developed questions for use in a modified-Delphi process. Twenty-eight clinicians, one researcher, and 13 caregivers from 16 countries participated in three rounds of the modified-Delphi process. Consensus was defined as follows: strong consensus $\geq 80\%$ fully agree; moderate consensus $\geq 80\%$ fully or partially agree, $< 10\%$ disagree; and modest consensus 67%–79% fully or partially agree, $< 10\%$ disagree.

Results: Consensus was reached on the presence of 14 comorbidities in patients with Severe Developmental and Epileptic Encephalopathy (Severe DEE) spanning non-seizure neurological disorders and other organ systems; impacts were mostly severe and unlikely to improve or resolve. Across Mild/Moderate Developmental and Epileptic Encephalopathy (Mild/Moderate DEE), Neurodevelopmental Delay with Generalized Epilepsy (NDDwGE), and NDD without Epilepsy (NDDwoE) phenotypes, cognitive and sleep-related comorbidities as well as fine and gross motor delays may be present but are less severe and more likely to improve

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For affiliations refer to page 12.

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compared to Severe DEE. There was no consensus on comorbidities in the SeL(F) IE phenotype but strong consensus that seizures would largely resolve. Seizure freedom is rare in patients with Severe DEE but may occur in some with Mild/Moderate DEE and NDDwGE.

Significance: Significant comorbidities are present in most phenotypes of *SCN8A*-related disorders but are most severe and pervasive in the Severe DEE phenotype. We hope that this work will improve recognition, early intervention, and long-term management for patients with these comorbidities and provide the basis for future evidence-based studies on optimal treatments of *SCN8A*-related disorders. Identifying the prognosis of patients with *SCN8A*-related disorders will also improve care and quality-of-life for patients and their caregivers.

KEYWORDS

developmental and epileptic encephalopathy, early intervention, multidisciplinary care, phenotypes, severity

1 | INTRODUCTION

SCN8A-related disorders are a set of rare and heterogeneous disorders with five phenotypes, as first described in Gardella, et al.^{1,2}: Severe Developmental and Epileptic Encephalopathy (DEE), Mild/Moderate DEE, Self-Limited (Familial) Infantile Epilepsy (SeL(F)IE), Neurodevelopmental Delay with Generalized Epilepsy (NDDwGE), and NDD without Epilepsy (NDDwoE), which were then further described.¹⁻¹²

In a new global consensus on the diagnosis, phenotypes, treatment, and management of *SCN8A* and Related Disorders,³ consensus about the clinical features of these phenotypes was investigated in-depth, including age at seizure onset and developmental delay, electroencephalography/magnetic resonance imaging (EEG/MRI) findings, seizure types, and predominant symptom(s) at initial presentation. However, little is published about the comorbidities and prognosis of this disorder across the five phenotypes.

Gardella et al.^{1,2} and Johannasen et al.⁶ list comorbidities present in each phenotype based on the Danish *SCN8A* registry. Severe DEE patients notably had intellectual disability, hypotonia, and cortical visual impairment (CVI).^{1,2,5} Across other phenotypes, mild to moderate intellectual disability, speech delay, behavioral disorders, ataxia, and dyskinesia were noted.⁶ Although informative, these data are limited and do not provide the full scope of comorbidities present across the phenotypes, or the severity and prognosis of these comorbidities.

Through a modified-Delphi process involving a global panel of clinicians and caregivers,^{3,13-15} we gained

Key points

- Common comorbidities across *SCN8A* phenotypes impact speech, sleep, intellectual disability, fine and gross motor, and behavior and emotional dysregulation.
- Severe DEE phenotypes experience 14 comorbidities (hypotonia, impaired sleep and speech, and cortical visual impairment); most are likely severe and unlikely to improve.
- Mild/Moderate DEE, NDDwGE, and NDDwoE comorbidities (impaired cognition, motor function, sleep) are less severe and more likely to improve.
- Multidisciplinary care of patients with *SCN8A* is necessary; resources include early referrals, therapies, and complex care.
- Overall prognosis for epilepsy, cognition and development are more likely to deteriorate in Severe DEE and improve in the other phenotypes.

consensus on comorbidities present in each phenotype and their severity and evolution over time; identified key multidisciplinary resources to provide caregivers of individuals with *SCN8A*-related disorders; and assessed the overall prognosis of epilepsy, development, and cognition across phenotypes. We believe that this work will aid in the long-term management of non-seizure symptoms and significantly improve the quality of life of people with *SCN8A*-related disorders.

2 | MATERIALS AND METHODS

2.1 | Modified-Delphi process: leadership team, core panel, review panel

Three rounds of a modified-Delphi process^{3,13-15} involving a global cohort of expert clinicians and caregivers were used to gain consensus on topics including diagnosis, phenotypes, treatments, comorbidities, and prognosis for *SCN8A*-related disorders. The methodology is described in detail in Conecker et al.³, which also provides results from the first published part of this study focused on the diagnosis, phenotypes, and treatments of *SCN8A*-related disorders.

Briefly, a Leadership Team (two pediatric epileptologists), two caregivers, and an independent researcher was created to oversee the process. A core panel (13 expert clinicians, 1 researcher, 6 caregivers) was nominated by the Alliance's *SCN8A* Clinicians Network and families. The core panel divided into three workgroups: (1) diagnosis and phenotypes, (2) treatments, and (3) comorbidities and prognosis; each workgroup conducted a literature review, which was based on an initial literature search. The workgroup vetted and enhanced the preliminary review, adding new sources. Each developed questions for their area of focus and nominated clinicians and caregivers to join

the review panel, who would serve as participants in the modified-Delphi process.

Review panel composition was finalized by the Leadership Team to include most members of the core panel and all additions proposed by the core panel. Representation was limited to one clinician per institution. The final review panel was composed of 28 clinicians, 1 researcher, and 13 caregivers, who participated in the modified-Delphi process (see Conecker et al.³, Figure 1, Table S1). Clinician and researcher responses were combined in reporting of the data, and caregiver data are reported separately (Table S1). Most clinicians cared for at least three patients with *SCN8A*, with less exposure to non-severe phenotypes. Moreover, they had the option to select "don't know/no opinion" if they felt unqualified to answer a question.

The core panel recognized the limitations of assessing comorbidities through a modified-Delphi, specifically the potential narrow exposure of clinicians to the full range and extent of comorbidities. In this instance, this process was still believed to be an appropriate starting point to study these comorbidities. The Delphi process has been applied successfully in other rare diseases where comorbidities are expressed,^{14,15} and the panel participants had significant experience with this rare condition. Although other approaches (chart review, database studies, etc.)

Comorbidities	>50% Frequency Level of Consensus	Severity Level				Level of Consensus	Change Over Time					Level of Consensus
		Severe	Moderate	Mild	No Impairment		Worsen	Stable	Mixed	Improve	Resolve	
Neurological												
1. Fine motor delays	Strong					Moderate						Moderate
2. Gross motor delays	Strong					Moderate						Moderate
3. Movement disorders	Modest					Modest						Moderate
4. Hypotonia	Moderate					Moderate						Modest
5. Cortical blindness/CVI	Moderate					Modest						Modest
6. Autonomic dysfunction	Moderate					Modest						Modest
7. Sleep disturbances	Moderate					Modest						Moderate
8. SUDEP risk	No consensus					Modest						Modest
DD/ID/Cognitive												
9. Speech/Communication delays	Strong					Moderate						Moderate
10. Intellectual Disability (ID)	Strong					Moderate						Modest
11. Behavioral dysregulation	Moderate					Modest						Modest
12. Emotional dysregulation	Modest					Modest						Moderate
13. Autism Spectrum Disorder (ASD)	No consensus					Modest						Moderate
Organ Systems												
14. Orthopedic issues	Moderate					Modest						Modest
15. Gastrointestinal (GI)	Moderate					Moderate						Moderate
16. Feeding	Moderate					Moderate						Moderate
17. Pulmonary	No consensus					Modest						Moderate

FIGURE 1 Severe DEE Comorbidities. Consensus data shown from Clinicians only. Consensus on Estimated Frequency of Comorbidities: Strong: ≥80% Always/almost always; Moderate: ≥80% Always/almost always & Over half of the time; Modest: 67%–79% Always/almost always & Over half of the time. Severity/Change over time Consensus: Strong: ≥80% Always/almost always; Moderate: ≥80% Always/almost always & Frequently; Modest: 67%–79% Always/almost always & Frequently & Around half of the time. C, change over time; F, frequency; S, severity. neurological: 1. F: n=28, 90%; S: n=28, 89%; C: n=28, 100%; 2. F: n=28, 90%; S: n=29, 83%; C: n=28, 96%; 3. F: n=25, 76%; S: n=27, 85%; C: n=28, 93%; 4. F: n=27, 93%; S: n=29, 93%; C: n=29, 69%; 5. F: n=25, 80%; S: n=29, 93%; C: n=29, 79%; 6. F: n=25, 76%; S: n=24, 71%; C: n=24, 92%; 7. F: n=28, 92%; S: n=27, 81%; C: n=27, 81%; 8. F: n=22, 55%; S: n=28, 93%; C: n=27, 93%. DD/ID/Cognitive: 9. F: n=27, 83%; S: n=29, 97%; C: n=28, 93%; 10. F: n=28, 90%; S: n=29, 97%; C: n=29, 69%; 11. F: n=27, 86%; S: n=27, 74%; C: n=27, 74%; 12. F: n=24, 76%; S: n=24, 79%; C: n=24, 92%; 13. F: n=25, 64%; S: n=27, 74%; C: n=27, 85%. Organ Systems: 14. F: n=27, 89%; S: n=23, 96%; C: n=26, 77%; 15. F: n=27, 85%; S: n=28, 89%; C: n=28, 93%; 16. F: n=27, 90%; S: n=29, 90%; C: n=28, 97%; 17. F: n=27, 44%; S: n=26, 81%; C: n=27, 81%.

could yield more comprehensive data on frequency, severity, and prognosis, they concluded that a modified-Delphi process would be the most appropriate study to begin assessing comorbidities in *SCN8A* given the current limitations of the literature focusing on the non-epilepsy/neurology aspects and the small, widely dispersed patient population. The core panel understands the future need for a more systematic approach to include information from databases and more detailed record review. This initial process will drive several research questions and expansion of data collection regarding comorbidities.

2.2 | Developing questions: comorbidities, resources, prognosis

The Comorbidities and Prognosis workgroup, building on the literature and with input from caregivers in the core panel, identified 19 initial possible comorbidities associated with *SCN8A*-related disorders^{1,2,5-12,16-33} (Table S2). In Round 1, the review panel was asked to identify how commonly these 19 comorbidities present across the phenotypes (>50% of the time, around 50% of the time, <50% of the time). Respondents were asked to comment on additional comorbidities that should be queried in subsequent rounds.

Rounds 2 and 3 focused on comorbidities with consensus of high estimated frequency within a phenotype in Round 1 and on refining their characteristics. The threshold for inclusion was agreement of 40% or more respondents that the comorbidity occurred $\geq 50\%$ of the time in at least one of the phenotypes. In addition, comorbidities not included in Round 1, but suggested by respondents, were added to further rounds (Table S2).

Clinicians were posed questions for the comorbidities across all phenotypes. Caregivers were asked to answer the comorbidity questions based on their child's experience only.

In preparation for Round 2, experts, most of whom were not involved in the modified-Delphi process, were consulted (Table S3) to develop clarifying definitions for the comorbidities, as well as scales for severity and change over time (Table S4).

Given the more limited clinician experience with phenotypes outside of Severe DEE (Table S1), severity and change over time measurements were evaluated in reference to Severe DEE for Mild/Moderate DEE, NDDwGE, and NDDwoE phenotypes. For SeL(F)IE, clinicians were asked to select comorbidities that they noted were present in these patients.

To control for potential biases in the data related to the limited exposure of many clinicians to the range of *SCN8A*-related disorders phenotypes, we analyzed the

data based on the experience level of clinicians across phenotypes and compared consensus across the groups.

Questions regarding resources for multidisciplinary care of *SCN8A*-related disorders and prognosis of epilepsy, development, and cognition were posed in Round 1 and followed up in Round 3.

2.3 | Analysis of questionnaires for consensus

Consensus levels were defined as follows³:

- **Strong:** $\geq 80\%$ fully agree
- **Moderate:** $\geq 80\%$ fully or partially agree and $< 10\%$ disagree
- **Modest:** 67%–79% fully or partially agree and $< 10\%$ disagree

The scale varied for some questions to best align with the questions. For example, the scale for estimated frequency level ranged from “always/almost always” to “never/almost never,” whereas the prognosis scale ranged from “worsen” to “improve.” Consensus levels are defined in the figure legends.

“No comment/don't know responses” were excluded from the analysis of responses for each question. However, after excluding these responses, a response rate of $> 50\%$ of all participants in the survey was required to consider consensus. Absolute numbers are included in each figure legend.

3 | RESULTS

In total, 28 of 30 clinicians, 1 researcher, and 13 of 14 caregivers (42/45 panelists) completed Round 1 and two surveys. Twenty-seven clinicians, one researcher, and 13 caregivers responded in Round 3, and 1 clinician did not respond.

3.1 | Comorbidities

From the 19 pre-identified comorbidities queried, 17 had at least 40% agreement of occurrence $> 50\%$ of the time among people with Severe DEE and were explored further. The 17 comorbidities included the addition of orthopedic issues,^{1,16,17} sleep disturbances, and autonomic dysfunction¹⁸ at the suggestion of respondents. Gastrointestinal (GI; encompassing constipation, reflux, vomiting) and feeding (the ability to eat and drink orally without aspiration or penetration) were divided into two separate

comorbidities. Similarly, for clarification, emotional dysregulation (encompassing mood disturbance, depression, irritability, anxiety, and hallucinations) was added to distinguish from behavioral dysregulation (encompassing attention regulation, impulsivity, hyperactivity, aggression, and self-injury) (see [Table S4](#)).

3.1.1 | Severe DEE

Consensus from clinicians suggests that there are 14 of 17 comorbidities with >50% estimated frequency in Severe DEE patients; symptoms are most likely severe and unlikely to improve or resolve ([Figure 1](#) for clinicians; [Figure S1](#) for caregivers).

Neurological

Strong consensus was reached by clinicians and caregivers on the estimated presence of fine and gross motor delays. There was moderate consensus that patients have limited ability to grasp and hold objects and poor head and trunk control, which precludes independent sitting and ambulation. Motor delays were also reported to be unlikely to improve.

There was modest consensus for severe movement disorders.

Severe hypotonia occurs in Severe DEE patients (Moderate), resulting in low muscle tone that precludes voluntary movement and results in an inability to speak/swallow and difficulties with urination and constipation. There was modest consensus from both clinicians and caregivers that hypotonia severity would remain stable.

There was also modest consensus from clinicians on severe cortical blindness/CVI that tends to remain stable over time (Modest).

Symptoms suggestive of autonomic dysfunction are also prevalent with moderate severity (Modest). In contrast, four caregivers indicated symptoms suggestive of severe autonomic dysfunction. Both clinicians and caregivers believed that symptoms are overall unlikely to improve or resolve (Modest).

Clinicians also reported that sleep disturbances are present (Moderate), tend to significantly disrupt sleep on a consistent basis affecting alertness and attention (Moderate), and likely remain stable or fluctuate (Moderate).

Developmental delay/intellectual disability/cognitive

Speech/communication delays and intellectual disability (ID) are highly prevalent in Severe DEE patients (Strong). Patients tend to be non-verbal (Moderate) with severe to profound ID (Moderate). Speech/communication delays

are more likely to remain stable or fluctuate (Moderate). Clinicians believed that ID generally remains stable (Modest), whereas caregivers believed that it is unlikely to improve or resolve.

Although clinicians noted that behavioral and emotional dysregulation is frequent (Moderate to Modest) and often severe (Modest), four and three caregivers, respectively, indicated that they did not observe behavioral or emotional dysregulation in their children.

Organ systems

There was moderate consensus on the estimated presence of orthopedic issues in the majority of cases, and modest consensus that therapies improve mobility and comfort.

Unique to the Severe DEE phenotype, severe GI and feeding issues are prevalent (Moderate). These challenges result in frequent challenges with constipation, “nothing by mouth” (NPO) status, and full tube or other dependencies for feeding (Moderate). These issues are also unlikely to improve/resolve (Moderate).

Although there was no consensus on a >50% estimated frequency of pulmonary issues among clinicians, five of six Severe DEE caregivers reported pulmonary issues (Mild/Moderate severity).

3.1.2 | Mild/moderate DEE

There was consensus from clinicians on the estimated presence of 7 of 17 comorbidities (Neurological, DD/ID/Cognitive) with ≥50% estimated frequency in Mild/Moderate DEE patients. Symptoms are overall less severe and more likely to improve compared to Severe DEE ([Figure 2A](#) for clinicians; [Figure S1](#) for caregivers).

Neurological

Both clinicians and caregivers reported fine motor delays and gross motor delays present in patients with Mild/Moderate DEE (Modest), which tend to be less severe (Moderate) and more likely to improve (Moderate).

Sleep disturbances are present in Mild/Moderate DEE (Modest); are less severe (Modest); and may remain stable, mixed, or improve (Modest).

Clinicians did not find consensus on the estimated presence of hypotonia, but four caregivers indicated Mild/Moderate issues, which mostly improved.

DD/ID/cognitive

Speech/communication delays, ID, and behavioral and emotional dysregulation are all present in the majority of patients with Mild/Moderate DEE (Modest). Speech delays are less severe (Moderate) and more likely to improve (Moderate). ID is less severe (Moderate) and is more likely to

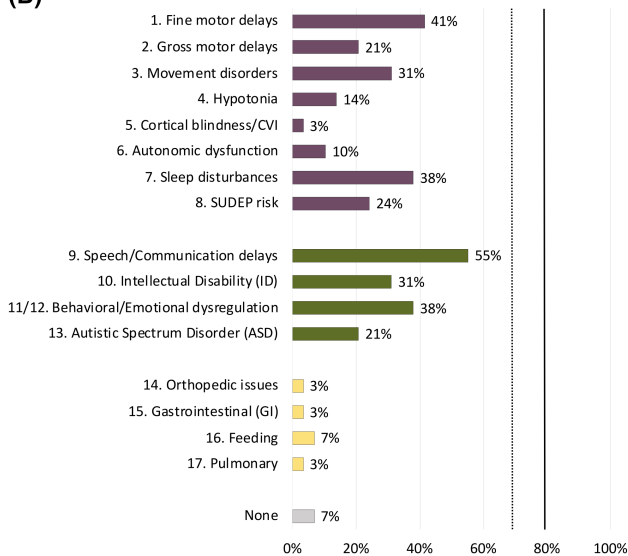
(A)	A. Mild/Mod DEE					B. NDD with Generalized Epilepsy					C. NDD without Epilepsy				
	Consensus on $\geq 50\%$ Frequency	Severity	Level of Consensus	Change Over Time	Level of Consensus	Consensus on $\geq 50\%$ Frequency	Severity	Level of Consensus	Change Over Time	Level of Consensus	Consensus on $\geq 50\%$ Frequency	Severity	Level of Consensus	Change Over Time	Level of Consensus
Neurological															
1. Fine motor delays	Modest		Moderate		Moderate	No Consensus		Moderate		Moderate	Modest		Moderate		Moderate
2. Gross motor delays	Modest		Moderate		Moderate	No Consensus		Moderate		Moderate	Modest		Moderate		Moderate
3. Movement disorders	No consensus		Moderate		Modest	No Consensus		Strong		Modest	No Consensus		Modest		Moderate
4. Hypotonia	No Consensus		Moderate		Moderate	No Consensus		Moderate		Moderate	No Consensus		Moderate		Moderate
5. Cortical blindness/CVI	No Consensus		Modest		No Consensus	No Consensus		Modest		No Consensus	No Consensus		Modest		No Consensus
6. Autonomic dysfunction	No Consensus		Moderate		Moderate	No Consensus		Moderate		Moderate	No Consensus		Moderate		Moderate
7. Sleep disturbances	Modest		Modest		Modest	Modest		Modest		Modest	Modest		Modest		Moderate
8. SUDEP risk	No Consensus		Moderate		Modest	No Consensus		Moderate		Modest	No Consensus		Modest		No Consensus
DD/ID/Cognitive															
9. Speech/Communication delays	Modest		Moderate		Moderate	Modest		Moderate		Moderate	Modest		Moderate		Moderate
10. Intellectual Disability (ID)	Modest		Moderate		Moderate	Modest		Moderate		Modest	Moderate		Moderate		Moderate
11. Behavioral dysregulation	Modest		Moderate		Moderate	No Consensus		Moderate		Modest	Modest		Moderate		Moderate
12. Emotional dysregulation	Modest		Moderate		Moderate	No Consensus		Moderate		Modest	Modest		Moderate		Moderate
13. Autism Spectrum Disorder (ASD)	No Consensus		Modest		Modest	No Consensus		Modest		Modest	Modest		No Consensus		Modest
Organ Systems															
14. Orthopedic issues	No consensus		Modest		Modest	No Consensus		Modest		Modest	No Consensus		Modest		Moderate
15. Gastrointestinal (GI)	No Consensus		Moderate		Moderate	No Consensus		Moderate		Moderate	No Consensus		Moderate		Modest
16. Feeding	No Consensus		Moderate		Moderate	No Consensus		Moderate		Moderate	No Consensus		Moderate		Moderate
17. Pulmonary	No Consensus		Moderate		Modest	No Consensus		Modest		Modest	No Consensus		Modest		Modest

Legend:

Severity	More Severe	Same as Severe DEE	Less Severe
Change over time	Worsening	Same as Severe DEE	Improvement

(B)

SeL(F)IE Comorbidities



remain stable or improve (Moderate). Behavioral and emotional dysregulation both tend to be less severe (Moderate) and more likely to remain stable or mixed (Moderate).

Finally, there was no consensus on the estimated presence of autism spectrum disorder (ASD), although three caregivers reported ASD in their children.

Organ systems

There was no consensus from clinicians on the estimated presence of any comorbidities relating to various organ systems (orthopedic issues, GI, feeding, and pulmonary issues).

3.1.3 | NDDwGE

Clinicians had more limited consensus on comorbidities present in the NDDwGE phenotype; they found 3 of 17 comorbidities (speech, ID, sleep), with a $\geq 50\%$ estimated frequency. Symptoms are also overall less severe and more likely to improve compared to Severe DEE (Figure 2B for clinicians; Figure S1 for caregivers).

Sleep disturbances are likely to occur in NDDwGE patients (Modest) but are more likely less severe (Modest) and are unlikely to worsen (Modest).

FIGURE 2 Mild/Moderate developmental epileptic encephalopathy (DEE), neurodevelopmental delay with generalized epilepsy (NDDwGE), neurodevelopmental delay without epilepsy (NDDwoE) comorbidities. Consensus data shown from Clinicians only. C, change over time; F, frequency; S, severity. A. Mild/Mod DEE: Neurological: 1. F: $n=28$, 86%; S: $n=28$, 93%; C: $n=24$, 83%; 2. F: $n=28$, 82%; S: $n=27$, 89%; C: $n=24$, 88%; 3. F: $n=25$, 44%; S: $n=25$, 88%; C: $n=21$, 67%; 4. F: $n=27$, 52%; S: $n=28$, 96%; C: $n=24$, 88%; 5. F: $n=27$, 19%; S: $n=27$, 70%; C: $n=22$, 59%; 6. F: $n=20$, 30%; S: $n=20$, 85%; C: $n=26$, 85%; 7. F: $n=26$, 73%; S: $n=25$, 76%; C: $n=27$, 78%; 8. F: $n=25$, 60%; S: $n=23$, 83%; C: $n=22$, 68%. DD/ID/Cognitive: 9. F: $n=27$, 96%; S: $n=27$, 89%; C: $n=25$, 84%; 10. F: $n=27$, 100%; S: $n=26$, 92%; C: $n=27$, 89%; 11. F: $n=24$, 88%; S: $n=22$, 95%; C: $n=23$, 91%; 12. F: $n=23$, 83%; S: $n=22$, 100%; C: $n=22$, 95%; 13. F: $n=25$, 60%; S: $n=24$, 71%; C: $n=24$, 79%. Organ Systems: 14. F: $n=24$, 25%; S: $n=24$, 79%; C: $n=20$, 70%; 15. F: $n=28$, 50%; S: $n=28$, 93%; C: $n=24$, 83%; 16. F: $n=27$, 44%; S: $n=27$, 85%; C: $n=24$, 92%; 17. F: $n=24$, 38%; S: $n=23$, 83%; C: $n=20$, 75%. B. NDDwGE: Neurological: 1. F: $n=28$, 64%; S: $n=28$, 93%; C: $n=24$, 83%; 2. F: $n=28$, 46%; S: $n=29$, 93%; C: $n=24$, 91%; 3. F: $n=26$, 19%; S: $n=25$, 80%; C: $n=21$, 67%; 4. F: $n=25$, 40%; S: $n=27$, 96%; C: $n=23$, 91%; 5. F: $n=27$, 4%; S: $n=27$, 67%; C: $n=21$, 57%; 6. F: $n=21$, 29%; S: $n=21$, 86%; C: $n=26$, 85%; 7. F: $n=24$, 67%; S: $n=25$, 76%; C: $n=22$, 73%; 8. F: $n=24$, 54%; S: $n=23$, 87%; C: $n=22$, 73%. DD/ID/Cognitive: 9. F: $n=27$, 67%; S: $n=26$, 88%; C: $n=24$, 88%; 10. F: $n=27$, 69%; S: $n=25$, 92%; C: $n=24$, 75%; 11. F: $n=24$, 50%; S: $n=24$, 100%; C: $n=23$, 78%; 12. F: $n=24$, 54%; S: $n=22$, 95%; C: $n=22$, 77%; 13. F: $n=26$, 35%; S: $n=24$, 67%; C: $n=24$, 67%. Organ Systems: 14. F: $n=23$, 13%; S: $n=23$, 78%; C: $n=20$, 70%; 15. F: $n=28$, 21%; S: $n=28$, 86%; C: $n=24$, 83%; 16. F: $n=28$, 21%; S: $n=27$, 81%; C: $n=24$, 83%; 17. F: $n=24$, 13%; S: $n=23$, 74%; C: $n=20$, 70%. C. NDDwoE: Neurological: 1. F: $n=28$, 86%; S: $n=28$, 93%; C: $n=25$, 84%; 2. F: $n=29$, 69%; S: $n=29$, 90%; C: $n=26$, 85%; 3. F: $n=26$, 46%; S: $n=26$, 77%; C: $n=26$, 81%; 4. F: $n=27$, 63%; S: $n=28$, 93%; C: $n=24$, 88%; 5. F: $n=27$, 15%; S: $n=27$, 67%; C: $n=21$, 62%; 6. F: $n=20$, 25%; S: $n=26$, 85%; C: $n=25$, 88%; 7. F: $n=26$, 69%; S: $n=25$, 68%; C: $n=27$, 78%; 8. F: $n=25$, 12%; S: $n=23$, 70%; C: $n=22$, 50%. DD/ID/Cognitive: 9. F: $n=28$, 96%; S: $n=27$, 89%; C: $n=25$, 88%; 10. F: $n=28$, 82%; S: $n=27$, 85%; C: $n=28$, 93%; 11. F: $n=25$, 92%; S: $n=24$, 83%; C: $n=24$, 88%; 12. F: $n=24$, 88%; S: $n=22$, 77%; C: $n=22$, 86%; 13. F: $n=25$, 84%; S: $n=24$, 63%; C: $n=24$, 75%. Organ Systems: 14. F: $n=23$, 30%; S: $n=23$, 74%; C: $n=27$, 81%; 15. F: $n=26$, 58%; S: $n=27$, 85%; C: $n=23$, 78%; 16. F: $n=25$, 44%; S: $n=26$, 85%; C: $n=23$, 83%; 17. F: $n=23$, 22%; S: $n=22$, 73%; C: $n=19$, 68%. D. Self-limited (familial) infantile epilepsy (SeL(F)IE): Percentage of clinicians who believe that each comorbidity occurs in SeL(F)IE; Shown from Clinicians only, $n=29$. CVI, cortical visual impairment; SUDEP, sudden unexpected death in epilepsy patients.

There was consensus on the estimated presence of speech/communication delays and ID in NDDwGE patients (Modest) (Figure 2).

3.1.4 | NDDwoE

Eight of 17 comorbidities were found to have a $\geq 50\%$ estimated frequency for NDDwoE; symptoms are overall less severe and more likely to improve compared to Severe DEE (Figure 2C for clinicians; Figure S1 for caregivers).

Clinicians reached consensus on the estimated presence of fine and gross motor delays in NDDwoE patients (Modest), both of which are less severe and more likely to improve (Moderate).

Sleep disturbances likely occur (Modest), with a possibility of similar severity and prognosis as Severe DEE or less severity/improvement (Moderate to Modest).

Speech/communication delays (Modest) and ID (Moderate) are present in NDDwoE patients but tend to be less severe and improve over time compared to patients with Severe DEE (Moderate). Behavioral and emotional dysregulation (Modest) also occur, and they are likely to remain stable or fluctuate over time (Moderate).

Finally, ASD is present in this phenotype and was the only phenotype with consensus among clinicians on $\geq 50\%$ estimated frequency of ASD (Modest).

3.1.5 | SeL(F)IE

There was no consensus on comorbidities with $\geq 50\%$ estimated frequency in SeL(F)IE patients (Figure 2D for clinicians).

3.2 | Resources: complex care of comorbidities, transition of care

Given the multitude of complex and severe comorbidities present in the Severe DEE phenotype, multidisciplinary care is needed (Table 1: Clinicians & Caregivers: Strong). Resources that should be offered to all SCN8A families at the earliest applicable time include early intervention services; occupational, physical, and speech therapy, consultation with social workers who have expertise in neurodisabilities; and early referrals to complex care pediatric clinics and palliative care as appropriate (Clinicians & Caregivers: Strong). Clinicians should provide patients with access to other specialists as needed (Clinicians: Moderate; Caregivers: Strong).

Engagement by caregivers in research is also important—clinicians should discuss with caregivers the value of enrolling their child in diverse research opportunities (Clinicians: Moderate; Caregivers: Strong). Clinicians should also encourage engagement with family advocacy groups for community and advancing knowledge (Clinicians: Moderate; Caregivers: Strong).

TABLE 1 Resources.

Findings	Clinician		Caregiver	
	responses	Level of consensus	responses	Level of consensus
Multidisciplinary Care				
Multidisciplinary care is needed for children with more severe forms of SCN8A.	n = 28, 100%	Strong	n = 12, 92%	Strong
Resources to be Offered to Families at Earliest Applicable Time				
Early intervention services	n = 29, 100%	Strong	n = 13, 92%	Strong
OT/PT/Speech	n = 29, 93%	Strong	n = 13, 85%	Strong
Access to social workers with expertise in children with neurodisabilities	n = 28, 93%	Strong	n = 13, 85%	Strong
Access to other specialists as needed including GI, Respiratory, Neuropsych/Dev Peds, Sleep medicine, Orthopedics, Physical Medicine & Rehabilitation	n = 29, 100%	Moderate	n = 13, 85%	Strong
Access to complex care pediatric clinic, as applicable	n = 29, 86%	Strong	n = 13, 85%	Strong
Access to hospice, as applicable	n = 27, 81%	Moderate	n = 13, 85%	Strong
Provide early referrals to complex care & palliative care as appropriate	n = 28, 86%	Strong	n = 13, 100%	Strong
Research and Family Advocacy Groups				
Discuss value of enrolling child in diverse research opportunities (surveys, dedicated SCN8A registry, clinical trials, brain tissue donation, etc.)	n = 28, 96%	Moderate	n = 13, 100%	Strong
Encourage engagement with family advocacy groups for community & advancing knowledge	n = 28, 96%	Moderate	n = 13, 92%	Strong
Transition of Care				
Providing a transition document (brief summary) is very important prior to transition of care.	n = 29, 93%	Strong	n = 12, 83%	Strong

Note: Areas with Strong Consensus (green): % responding 'Fully Agree' shown. Areas with Moderate (blue), Modest, or No Consensus: % responding 'Fully Agree' or 'Somewhat Agree' shown.

Abbreviations: Dev Peds, developmental pediatrics; GI, gastrointestinal; Neuropsych, neuropsychology; OT, occupational therapy; PT, physical therapy.

Finally, during the transition of care from pediatric to adult providers, providing a transition document is very important (Clinicians & Caregivers: Strong). In an open-ended question, clinicians noted several factors critical to transition of care: finding the right provider with knowledge of DEEs, and SCN8A-related disorders more specifically; good communication between the pediatric and adult neurologist; and providing proper support for families. The most significant barrier to transition, noted by 18 clinicians, was that many adult providers are not comfortable or familiar with DEEs and SCN8A-related disorders.

3.3 | Prognosis: epilepsy, cognition, and development by phenotype

Overall prognosis for epilepsy, cognition, and development was assessed. All are more likely to deteriorate in Severe DEE and improve in the other phenotypes.

There was Moderate consensus among clinicians that Severe DEE patients are unlikely to achieve seizure freedom (Figure 3 for clinicians; Figure S1 for caregivers). There was consensus that both cognition and development are more likely to have limited change or deteriorate (Moderate). This is consistent with the lack of improvement/resolution of various comorbidities.

Patients with Mild/Moderate DEE are more likely to achieve some periods of seizure freedom, experience a range of cognition outcomes from modest deterioration to modest improvement (Moderate), and experience a range of developmental outcomes from limited change to modest improvement (Moderate).

There was no consensus on cognition and development outcomes for NDDwGE due to a level of disagreement (15%) from clinicians that did not meet the threshold for consensus (<10% disagreement).

Finally, patients with NDDwoE are more likely to experience limited change or modest improvement in

	Prognosis					
	Significant Deterioration	Modest Deterioration	Limited Change	Moderate Improvement	Significant Improvement	Level of Consensus
Severe DEE						
Epilepsy						No consensus
Cognition						Moderate
Development						Moderate
Mild/Moderate DEE						
Epilepsy						Modest
Cognition						Moderate
Development						Moderate
SeL(F)IE						
Epilepsy						Strong
NDD with Generalized Epilepsy						
Epilepsy						Modest
Cognition						No consensus
Development						No consensus
NDD without Epilepsy						
Cognition						Moderate
Development						Moderate
	Seizure Freedom					
	Never	Rarely	Some of the Time	Most of the Time	All of the Time	Level of Consensus
Severe DEE						Moderate
Mild/Moderate DEE						Moderate
NDD with Generalized Epilepsy						Moderate

FIGURE 3 Prognosis. Consensus data shown from Clinicians only. Prognosis: Strong: ≥80% Strongly agree; Moderate: ≥80% Strongly agree & Somewhat agree, <10% disagree; Modest: 67%–79% Strongly agree & Somewhat agree, <10% disagree. C, Cognition; D, Development; E, Epilepsy. Severe DEE: E: n = 27, 74% agree, 14% disagree; C: n = 28, 93%; D: n = 28, 89%; Mild/Mod DEE: E: n = 27, 70%; C: n = 26, 81%; D: n = 28, 82%; SeL(F)IE: E: n = 18, 94%; NDDwGE: E: n = 26, 69%; C: n = 27, 74% agree, 15% disagree; D: n = 27, 74% agree, 15% disagree; NDDwoE: C: n = 28, 86%; D: n = 27, 93%. Seizure Freedom: Strong: ≥80% One category; Moderate: ≥80% Two categories OR 67%–79% One category. Severe DEE: n = 28, 93%; Mild/Mod DEE: n = 27, 67%; NDDwGE: n = 26, 88%.

cognition and development (Moderate), consistent with comorbidity data, suggesting that these areas are more likely to see improvement over time.

4 | DISCUSSION

4.1 | Comorbidities

Through the modified-Delphi process we reached strongest consensus on the estimated presence, severity, and prognosis of comorbidities in the most severe phenotype of *SCN8A*-related disorders and less consensus in other phenotypes.

Patients with Severe DEE experience the most comorbidities spanning the nervous system and various other organ systems, with the greatest severity and lower likelihood of improving. Although clinicians noted that behavioral and emotional dysregulation^{19,20} is frequent and often severe (Modest) in patients with

Severe DEE, most of their caregivers indicated that they did not observe behavioral or emotional dysregulation in their children. This may be attributed to challenges associated with confirming these symptoms (e.g., depression or poor attention) in children with profound and pervasive disabilities.

Mild/Moderate DEE, NDDwGE, and NDDwoE phenotypes were estimated to have fewer comorbidities—mainly cognitive, speech, and sleep—with some fine and gross motor delays. They are less severe and more likely to improve than in Severe DEE. Initial data from clinicians suggest that SeL(F)IE patients may experience other comorbidities in addition to movement disorders, which have yet to be reported in the literature.

Seven comorbidities were identified as occurring frequently across the phenotypes of *SCN8A*-related disorders. Speech and sleep issues and intellectual disability occur most of the time in four phenotypes: Severe DEE, Mild/Mod DEE, NDDwGE, and NDDwoE (limited consensus was reached on comorbidities in SeL(F)IE). Fine

and gross motor skills impairment and behavioral and emotional dysregulation were estimated to occur frequently in three phenotypes: Severe DEE, Mild/Moderate DEE, and NDDwoE.

Although we reached consensus on comorbidities across phenotypes, clinicians had comparatively limited experience working with SeL(F)IE, Mild/Moderate DEE, NDDwGE, and NDDwoE phenotypes, likely due to significantly more Severe DEE patients being sent to and requiring treatment from tertiary health care centers. In addition, given the small number of caregivers across the phenotypes (no SeL(F)IE and one participant for NDDwGE and NDDwoE each), it was challenging to compare clinician and caregiver responses. Although respondents were always given the “Don’t know/no opinion” option if they did not feel comfortable responding, some participating clinicians expressed concerns about bias toward guessing and avoiding the “don’t know” option. To evaluate for possible biases, we analyzed the data based on the experience level of clinicians across phenotypes and found limited variance in the responses of those with less vs more extensive experience with the phenotypes other than Severe DEE.

4.2 | Engagement in community and research

Despite limitations of this methodology in a rare and highly heterogeneous disorder, the results provide important baseline information on the estimated frequency, severity, and prognosis for the many comorbidities across the five phenotypes. Improved understanding of the multiple non-seizure comorbidities occurring across all *SCN8A* phenotypes is needed to inform clinicians, families, and researchers alike, recognizing that these conditions often require early intervention, have a dominant impact on overall quality of life, and may even be life-threatening.

There was strong consensus across both clinicians and caregivers that clinicians should review emerging research on *SCN8A*-related disorders. This is underscored by the consensus on the estimated frequency, diversity, and impact of many comorbidities across the five phenotypes. There was also consensus that clinicians should be open to education and findings shared by families, fostering a collaboration between clinicians and caregivers to learn more about *SCN8A* research. Many caregivers in the *SCN8A* community gain insights through research and community efforts. Through these fora, caregivers both become informed about recent and emerging research and contribute to the understanding of the course of the disease and types of comorbidities not yet discussed in the literature.

Clinicians can also play an important role in advancing further knowledge on *SCN8A*-related disorders by staying informed of diverse research opportunities (e.g., patient registries, clinical trials, and brain tissue donation). There was also consensus that clinicians play an important role in helping caregivers recognize their pivotal role in research expanding both understanding and improved treatments of this rare disorder. Clinicians can further support families by working with and encouraging families to engage with family advocacy groups across the globe for both community and advancing knowledge.

4.3 | Research gaps

The following specific comorbidity areas requiring additional research were identified based on the opinions of the authors and supported by caregiver-reported estimated frequency and impact on quality of life, and/or some discussion in the literature, but limited consensus through this modified-Delphi strategy.

- Research the frequency, impact, and treatments for the presence of specific movement disorders¹ and sleep disturbances across phenotypes—the latter has been noted in a preclinical model of *SCN8A*²² but has not been reported in published clinical reports.
- Increased research is needed to more accurately document issues related to autonomic dysfunction, GI issues, and CVI—often reported by families but not reflected in the literature-across the phenotypes.
- Investigate high-risk and causes of sudden unexpected death in epilepsy (SUDEP)^{7,23–29} as well as potential strategies to reduce the high rate of premature deaths in the *SCN8A* population.²⁶ Both clinicians and caregivers agreed that severe risk for SUDEP is present in Severe DEE, as defined by the estimated presence of multiple risk factors including uncontrolled/frequent seizures and frequent generalized convulsive seizures. Clinicians and caregivers believed that SUDEP risks were unlikely to improve or resolve, highlighting the need for better understanding of SUDEP across all phenotypes and strategies to reduce the risk.
- Study and document the incidence and management of pulmonary risks. Although there was no consensus on a >50% estimated frequency of pulmonary issues among clinicians, most caregivers of Severe DEE reported pulmonary issues. There have also been published reports of respiratory tract infection as the cause of death in several patients with *SCN8A*-related disorders.^{1,26}

- Reassess the SeL(F)IE phenotype in *SCN8A*-related disorders; although seizures might be self-limited, evidence from this study suggests that a number of other comorbidities might be associated with this phenotype.
- Expand study of comorbidities in phenotypes other than Severe-DEE; document the occurrence and impact of a wide range of comorbidities across all phenotypes.

We did not reach consensus on optimal treatments for *SCN8A*-related comorbidities. Although consensus on treatment protocols for *SCN8A*-related disorders comorbidities may be limited, early diagnosis of the disorder is still important, as early intervention could improve overall development.³ Additional research is needed to find optimal treatments for these various comorbidities, with treatments possibly differing by phenotype given the wide variation in severity.

4.4 | Resources and referrals

Consensus was reached on key resources relating to the multidisciplinary care of patients with *SCN8A*-related disorders needed to manage the many comorbidities present, although community resources may vary from location to location. Early referrals to relevant specialists and early interventions for known potential comorbidities—notably occupational, speech, and physical therapies—across all phenotypes are suggested. The best possible outcomes will occur when specialists work together to provide holistic, coordinated care to patients. There was consensus that referral to complex care and hospice may also be necessary, as appropriate (Table 1). Recommendations for specific resources and referrals may differ based on phenotype. For Mild/Moderate DEE, NDDwGE, and NDDwoE patients, follow-up care for behavioral and emotional challenges may be necessary, as indicated by consensus on these comorbidities.⁶ Transition of care to adult neurologists may be challenging given that they may have less familiarity with many of the early genetic DEEs. Moreover, adult neurologists may often have more limited access to multidisciplinary teams to address comorbidities. As more people with *SCN8A*-related disorders reach adulthood, establishing a network of adult neurologists familiar with *SCN8A*-related disorders (and a wide range of other DEEs) will be critical for maintaining quality of care.

Caregivers noted that families who have children with *SCN8A*-related disorders require referrals and access to counseling or mental health resources given the significant emotional, physical, and financial challenges associated with this disorder.

4.5 | Overall prognosis of epilepsy, development, and cognition

We sought and reached consensus on the overall prognosis for *SCN8A*-related disorders phenotypes in three broad categories: epilepsy, development, and cognition. Cognition and development are more likely to deteriorate in Severe DEE and improve in the other phenotypes. Seizure freedom (for a 6-month period) is rarely or never achieved in Severe DEE, whereas it is achieved some or most of the time for Mild/Moderate DEE and NDDwGE. This is consistent with data from a large cohort studying 177 patients with Severe DEE, with only 20% experiencing seizure freedom.⁶ Cognition and development are most likely to deteriorate in Severe DEE, whereas likely to experience modest improvement or limited change in Mild/Moderate DEE and NDDwoE.

Although this process of collaboration by leading *SCN8A*-related disorders practitioners and caregivers from across the globe has yielded important areas of consensus regarding the five *SCN8A*-related disorder phenotypes—including new information about the estimated frequency, severity, and prognosis of comorbidities for each—major gaps in understanding have been identified. Continued partnerships among leading *SCN8A* clinicians and caregivers along with basic researchers, and industry, offer major opportunities for advancing scientific understanding and more evidentiary-based treatment of all individuals with *SCN8A*-related disorders. Collaboration will be key to improving outcomes and quality of life for all those currently and yet to be affected by the many forms of *SCN8A*-related disorders.

5 | CONCLUSION

The global modified-Delphi process yielded consensus regarding novel information on the estimated frequency, severity, and prognosis of comorbidities in the *SCN8A*-related disorder phenotypes, resources to manage these comorbidities, and overall prognosis for *SCN8A*-related disorders across the five phenotypes. We identified 14 comorbidities commonly present in Severe DEE and fewer comorbidities commonly present in other phenotypes. These results hold promise to result in better management and improved long-term outcomes for symptoms beyond seizures for all patients with *SCN8A*-related disorders.

AUTHOR CONTRIBUTIONS

Gabrielle Conecker: Conceptualization (equal), Data curation (supporting), Funding Acquisition (lead), Investigation (equal), Methodology (supporting), Project

Administration (equal), Resources (lead), Software (equal), Supervision (lead), Writing – Original Draft Preparation (equal), Writing – Review & Editing (equal). **Maya Y Xia:** Data Curation (lead), Data Curation (equal), Investigation (supporting), Methodology (supporting), Software (equal), Validation (lead), Visualization (lead), Writing – Original Draft Preparation (equal). **JayEtta Hecker:** Conceptualization (equal), Data Curation (equal), Funding Acquisition (supporting), Investigation, (equal), Methodology (supporting), Project Administration (equal), Visualization (lead), Supervision (supporting), Writing – Original Draft Preparation (equal), Writing – Review & Editing (supporting). **Christelle Achkar:** Investigation (supporting), Writing – Review & Editing (supporting). **Cristine Cukiert:** Investigation (supporting), Writing – Review & Editing (supporting). **Seth Devries:** Investigation (supporting), Writing – Review & Editing (supporting). **Elizabeth Donner:** Investigation (supporting), Writing – Review & Editing (supporting). **Mark Fitzgerald:** Investigation (supporting), Writing – Review & Editing (supporting). **Elena Gardella:** Investigation (supporting), Writing – Review & Editing (supporting). **Michael Hammer:** Investigation (supporting), Writing – Review & Editing (supporting). **Anaita Hegde:** Investigation (supporting), Writing – Review & Editing (supporting). **Chunhui Hu:** Investigation (supporting), Writing – Review & Editing (supporting). **Mitsuhiro Kato:** Investigation (supporting), Writing – Review & Editing (supporting). **Tian Luo:** Investigation (supporting), Writing – Review & Editing (supporting). **John Schreiber:** Investigation (supporting), Writing – Review & Editing (supporting). **Yi Wang:** Investigation (supporting), Writing – Review & Editing (supporting). **Tammy Kooistra:** Investigation (supporting), Writing – Review & Editing (supporting). **Madeleine Oudin:** Investigation (supporting), Writing – Review & Editing (supporting). **Kayla Waldrop:** Investigation (supporting), Writing – Review & Editing (supporting). **Tyler Youngquist:** Investigation (supporting), Writing – Review & Editing (supporting). **Dennis Zhang:** Investigation (supporting), Writing – Review & Editing (supporting). **Elaine Wirrell:** Conceptualization (supporting), Data Curation (supporting), Methodology (lead), Writing – Review & Editing (equal). **M. Scott Perry:** Conceptualization (supporting), Data Curation (supporting), Methodology (supporting), Writing – Review & Editing (equal).

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CONFLICT OF INTEREST STATEMENT

M.S.P. has received honoraria for consulting from Zogenix/UCB, Jazz Pharmaceuticals, Pyros, Azurity, Neurelis, Eisai, Marinus, Stoke Therapeutics, and Biocodex. E.C.W. has received honoraria for consulting from Acadia, Amicus, Longboard, Neurocrine, and Encoded Therapeutics. J.M.S. has received honoraria for consulting and/or speaking for Zogenix/UCB, Neurocrine Biosciences, and Marinus Pharmaceuticals. E.J.D. has received honoraria from UCB and Jazz Pharma. The remaining authors have no conflicts of interest.

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.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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