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Epilepsia

RESEARCH ARTICLE

Global modified Delphi consensus on diagnosis, phenotypes, and treatment of *SCN8A*-related epilepsy and/or neurodevelopmental disorders

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Abstract

Objective: We aimed to develop consensus for diagnosis/management of *SCN8A*-related disorders. Utilizing a modified Delphi process, a global cohort of experienced clinicians and caregivers provided input on diagnosis, phenotypes, treatment, and management of *SCN8A*-related disorders.

Methods: A Core Panel (13 clinicians, one researcher, six caregivers), divided into three subgroups (diagnosis/phenotypes, treatment, comorbidities/prognosis), performed a literature review and developed questions for the modified Delphi process. Twenty-eight expert clinicians, one researcher, and 13 caregivers from 16 countries participated in the subsequent three survey rounds. We defined consensus as follows: strong consensus, ≥80% fully agree; moderate consensus, ≥80% fully/partially agree, <10% disagree; and modest consensus, 67%–79% fully/partially agree, <10% disagree.

Results: Early diagnosis is important for long-term clinical outcomes in *SCN8A*-related disorders. There are five phenotypes: three with early seizure onset (severe developmental and epileptic encephalopathy [DEE], mild/moderate DEE, self-limited (familial) infantile epilepsy [SeL(F)IE]) and two with later/no seizure onset (neurodevelopmental delay with generalized epilepsy [NDDwGE], NDD without epilepsy [NDDwoE]). Caregivers represented six patients with severe DEE, five mild/moderate DEE, one NDDwGE, and one NDDwoE. Phenotypes vary by age at seizures/developmental delay onset, seizure type, electroencephalographic/

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magnetic resonance imaging findings, and first-line treatment. Gain of function (GOF) versus loss of function (LOF) is valuable for informing treatment. Sodium channel blockers are optimal first-line treatment for GOF, severe DEE, mild/moderate DEE, and SeL(F)IE; levetiracetam is relatively contraindicated in GOF patients. First-line treatment for NDDwGE is valproate, ethosuximide, or lamotrigine; sodium channel blockers are relatively contraindicated in LOF patients.

Significance: This is the first-ever global consensus for the diagnosis and treatment of *SCN8A*-related disorders. This consensus will reduce knowledge gaps in disease recognition and inform preferred treatment across this heterogeneous disorder. Consensus of this type allows more clinicians to provide evidence-based care and empowers *SCN8A* families to advocate for their children.

KEYWORDS

developmental and epileptic encephalopathy, function of variant, heterogeneity, phenotypes, sodium channel blockers

1 | INTRODUCTION

First identified as a pediatric epilepsy in 2012,[1] *SCN8A*-related epilepsy and/or neurodevelopmental disorders (*SCN8A*-related disorders) are heterogeneous conditions with varying clinical presentations, ranging from severe developmental and epileptic encephalopathy (DEE) to neurodevelopmental delay (NDD) without epilepsy (NDDwoE).[2–11] Caused by variants in the *SCN8A* gene, which encodes the Nav1.6 channel, *SCN8A*-related disorders have an estimated incidence of 1 in 56 000[9] based on a study done in the Danish population and a predicted incidence of 7.37 per 100 000 births.[12] More than 500 cases worldwide have been published.[13] Early recognition and appropriate treatment of these conditions has the potential to impact outcomes but is likely hampered by the lack of established diagnosis and treatment guidelines.

Diagnosis of *SCN8A*-related disorders is made via genetic testing using gene panels or whole exome sequencing.[14–17] Despite increased use of genetic testing, there are currently no published clinical indications to aid in timely genetic testing and improved diagnosis rates of *SCN8A*-related disorders.

Recent studies have identified distinct phenotypes of *SCN8A*-related disorders, with potential correlations between phenotypes and functional consequences of *SCN8A* variants.[7,9] Additional studies explored potential correlations between the phenotypes and functional consequences of *SCN8A* variants and the impact on choice of therapy.[10,11] Sodium channel blockers (SCBs; e.g., oxcarbazepine and carbamazepine) have been reported as efficacious antiseizure medications (ASMs) for patients with focal seizures and gain-of-function (GOF) variants,[3,18,19] whereas levetiracetam may worsen seizures and contribute to developmental regression.[6,20] In-depth characterization of the severe DEE[6] and self-limited (familial) infantile epilepsy (SeL[F]IE)[21] have been reported, and characterization of the intermediate phenotypes of *SCN8A*-related disorders have also been published.[8,9] However, consensus from a global community of experts on the clinical presentation on these phenotypes, treatment, and evolution of these phenotypes has not been published, but could improve diagnosis, treatment, and management of this complex disorder.

Given the absence of clear consensus on the diagnosis and treatment of *SCN8A*-related disorders, we established an international panel of clinicians and caregivers with expertise in *SCN8A* to develop the first global consensus

Key points

- There is consensus on five *SCN8A* phenotypes that vary by age at onset, EEG and MRI findings, seizure type, and preferred first-line treatment.
- Early diagnosis improves seizure outcomes.
- Severe DEE, mild/moderate DEE, and SeL(F)IE have early seizure onset, with oxcarbazepine or carbamazepine as preferred first-line treatment.
- NDDwGE and NDDwoE have later or no seizure onset, dominated by NDD; NDDwGE first-line treatment is valproate, ethosuximide, or lamotrigine.
- Variant function (gain vs. loss of function) is important for assessing proper treatment and anticipating phenotypes and outcomes.

on *SCN8A*-related disorders using a modified Delphi process. In this paper, we discuss results related to phenotypes, diagnosis, and treatment of *SCN8A*-related disorders, with comorbidities and prognosis included in a companion paper.[22]

2 | MATERIALS AND METHODS

2.1 | Leadership Team and Core Panel

A Leadership Team, consisting of two project cochairs (a clinician and a caregiver), an experienced process guide (clinician), and two analysts (a caregiver and an independent researcher) provided project oversight, construction and analysis of surveys, and synthesis of results (Figure 1; Table S1 outlines the affiliation, roles, and experience of the entire team).

A Core Panel, nominated by an existing *SCN8A* Clinicians Network and caregivers of people with *SCN8A*, was selected to complete a literature review and draft initial survey content. Selections for the Core Panel were finalized by the Leadership Team based on the nominees' knowledge and experience in *SCN8A* and geographic diversity. The panel, led by the cochairs, consisted of 13 clinicians, one researcher, and six caregivers, spanning seven countries. The researcher included is the geneticist who first identified *SCN8A* as a pediatric epilepsy in his own daughter[1]; he developed and maintains a global international longitudinal *SCN8A* registry[23] and collaborates with families across the globe on a continuous basis to improve understanding of the disease.[11,24–26]

The Core Panel divided itself by self-selection into three workgroups: (1) diagnosis and phenotypes, (2) treatments, and (3) comorbidities and prognosis. Each workgroup completed an assessment of the published literature, developed questions relating to their focus area, and nominated clinicians and caregivers for the Review Panel. The Core Panel reviewed and finalized the manuscript and are the principal authors of the results.

2.2 | Literature review

An initial thorough literature review on *SCN8A*-related disorders was conducted focusing on diagnosis and genetic testing, clinical presentation across phenotypes (age at onset, seizure types, comorbidities), optimal treatments for seizures, and long-term prognosis. The Core Panel used this initial review as a resource to independently summarize the literature on *SCN8A* through July 2022, refining search terms and assessing the scope and reliability of various studies. An annotated summary of the literature was distributed to all members of the Review Panel for reference during completion of the surveys.

2.3 | Review Panel

A Review Panel was established to participate in three survey rounds on which consensus findings would be based. Review Panel selection was based on nominations by the Core Panel, with a focus on broadening the representation of clinicians from around the world with experience in the management of *SCN8A*-related disorders; additional caregivers with extensive personal knowledge of diverse *SCN8A* experiences were also nominated. Composition of the Review Panel was finalized by the Leadership Team to include members of the Core Panel (excluding the Leadership Team) and additional members proposed by Core Panelists. Representation was limited to one clinician per institution. The final Review Panel was composed of 28 clinicians, one researcher, and 13 caregivers who participated in the modified Delphi process (Figure 1; Table S1 outlines the affiliation, roles, and experience of the entire team). Most clinicians cared for three or more patients with severe DEE, whereas most had less exposure to other phenotypes. However, the survey instrument allowed respondents to answer "do not know/no opinion" when they felt unqualified to offer a response. Clinician and researcher data were combined in reporting of the data, and caregiver data are reported separately.

To establish experience in *SCN8A*-related disorders, clinicians provided years of experience and total number of *SCN8A* patients they have treated, whereas caregivers provided the age of their child with an *SCN8A*-related disorder, as well as the number of cases of *SCN8A*-related disorders with which they were personally familiar.

2.4 | Modified Delphi process and questionnaires

Three survey rounds were used in the modified Delphi process.[27–29] The first round was created by the Core Panel based on the literature review and consolidated by the Leadership Team. The questionnaire was subsequently distributed to the Review Panel via a SurveyMonkey link. Core Panel members were not involved in the creation of questionnaires for subsequent rounds, to reduce any potential bias in responses.

Most questions were posed to clinicians and caregivers; for phenotype-specific questions, caregivers answered

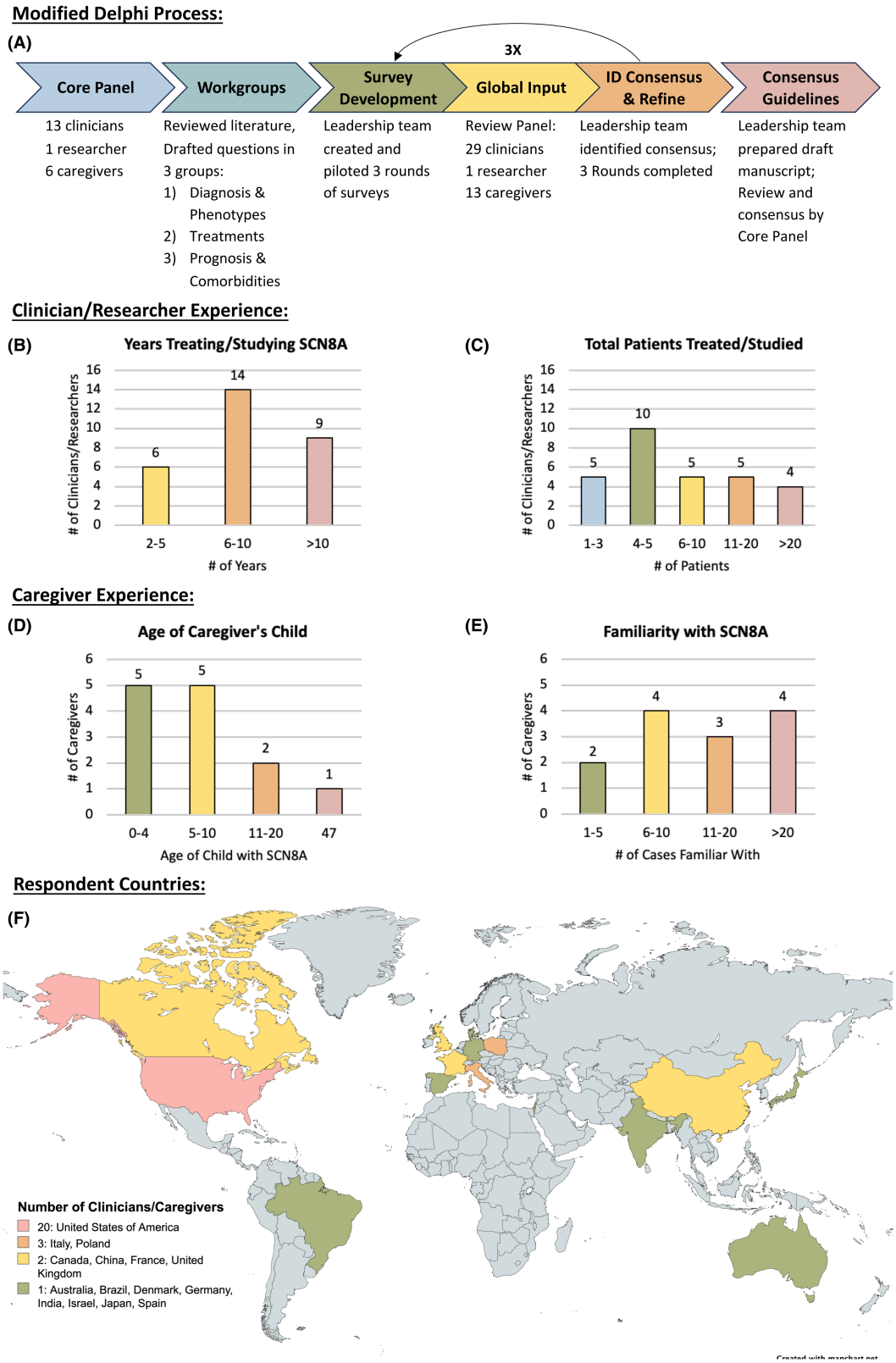


FIGURE 1 Modified Delphi process and clinician/caregiver experience levels. (A) Modified Delphi process involved developing a Core Panel, which split into three workgroups to review the literature and draft questions. The Leadership Team created three rounds of surveys and sent them out to the Review Panel to complete. The Leadership Team also identified consensus and prepared a draft manuscript for the Core Panel to review. (B, C) Clinician/researcher experience shown via years treating/studying *SCN8A* and total patients treated/seen. (D, E) Caregiver experience shown via age of caregiver's child in years and familiarity with *SCN8A*-related disorders. (F) Respondents on the Review Panel spanned 16 countries and five continents.

only for their child's phenotype. Although each caregiver provides some leadership in the community and is familiar with experiences of different families, they were most confident answering questions based on their own child's phenotype and experiences.

The first round covered the following areas:

1. Diagnosis: scenarios for obtaining genetic testing, importance of early diagnosis, importance of determining function of variant.
2. Phenotypes: establishing consensus about the existence of five phenotypes, characteristics of phenotypes (age at onset, seizure types, comorbidities, electroencephalographic (EEG)/magnetic resonance imaging (MRI) findings, prognosis).[7,9]
3. Treatments: optimal treatments based on phenotype and function of variant, adding/weaning medications, contraindicated medications, alternative treatments (ketogenic diet [KD], vagus nerve stimulator, cannabidiol (CBD), resective surgery, deep brain stimulation/responsive neurostimulation), rescue medications, transition of care, vaccinations.
4. Counseling: areas to be counseled on after diagnosis, resources and referrals to provide families.

Round 2 primarily focused on identifying consensus on estimated levels of severity and prognosis for comorbidities across the five phenotypes[22] and clarified consensus on EEG/MRI findings, importance of early diagnosis, and treatments based on function of variants.

Round 3 consisted of clarifying questions pertaining to comorbidities,[22] overall prognosis (epilepsy, development, and cognition),[22] and optimal first-line treatments based on phenotypes.

A Likert scale was used for most questions (fully disagree, partially disagree, neutral, partially agree, fully agree, do not know/no opinion). Free response questions were used for specific questions (e.g., age at onset, EEG and MRI descriptions, optimal first-line treatments, maximum number of ASMs, transition to adult care).

Consensus levels were defined as follows:

- Strong: ≥80% fully agree.
- Moderate: ≥80% fully or partially agree and <10% disagree.
- Modest: 67%–79% fully or partially agree and <10% disagree.

For each independent question, no comment/do not know responses were excluded from analysis of responses. A total responder rate of >50% after excluding no comment/do not know responses was required to calculate consensus.

3 | RESULTS

Forty-two of 45 panelists (28/30 clinicians, one researcher, 13/14 caregivers) completed survey round 1, and all 42 respondents completed round 2. In round 3, 27 clinicians, one researcher, and 13 caregivers completed the survey, with one clinician not responding.

3.1 | Diagnosis: Genetic testing and counseling

Table 1 shows consensus related to use of genetic testing, importance of early *SCN8A* diagnosis and function of variants, and areas for counseling of families after diagnosis.

Clinicians agreed that broad genetic testing should occur in:

1. All cases of drug-resistant epilepsy <3 years without clear structural cause (strong).
2. Any neurodevelopmental disorder of unknown cause without epilepsy (moderate).
3. All cases of epilepsy <3 years without clear acquired structural cause (moderate).

There was consensus that genetic testing should include an epilepsy gene panel and/or exome sequencing and/or whole genome sequencing (clinicians and caregivers: strong), although there was no consensus on an optimal tool. Additionally, all cases with new *SCN8A* variants should have parental testing conducted to determine whether the variant is inherited (clinicians: moderate), and families should be counseled by a geneticist on areas such as mosaicism (clinicians and caregivers: strong).

Clinicians and caregivers both agreed that early diagnosis of *SCN8A* DEE improves seizure outcomes (clinicians: moderate; caregivers: strong) and early use of SCBs in *SCN8A* DEE improves long-term seizure outcomes (clinicians and caregivers: moderate). However, there was no consensus among physicians and only moderate consensus among caregivers that early genetic diagnosis improves developmental outcomes.

Understanding the functional consequences of *SCN8A* variants on Nav1.6 channel activity is important in informing treatment and anticipating phenotype (clinicians and caregivers: moderate). There was moderate consensus from clinicians on the importance of determining the function of the variant when receiving an *SCN8A* genetic report and methods for doing so.

Features more likely to be seen in patients with loss-of-function (LOF) variants include:

TABLE 1 Diagnosis and counseling.

	Clinician		Caregiver	
Findings	**Responses**	**Level of consensus**	**Responses**	**Level of consensus**
Cases for genetic testing				
All cases of drug resistant epilepsy <3 years without clear structural cause	$n=29$, 97%	Strong		
Any neurodevelopmental disorder of unknown cause without epilepsy	$n=29$, 93%	Moderate		
All cases of epilepsy <3 years old without clear acquired structural cause	$n=29$, 93%	Moderate		
Tools for genetic testing				
Genetic testing should include an epilepsy gene panel and/or exome sequencing and/or whole genome sequencing	$n=29$, 97%	Strong	$n=13$, 100%	Strong
Parental testing/Mosaicism				
All cases with new *SCN8A* variants should have parental testing conducted to determine whether the variant is inherited	$n=29$, 90%	Moderate		
Families with newly diagnosed *SCN8A*-related disease should see a geneticist for a number of reasons including counseling on mosaicism	$n=29$, 90%	Strong	$n=13$, 85%	Strong
Importance of early diagnosis				
Early diagnosis of *SCN8A* DEE improves clinical outcomes for both seizure control and development	$n=29$, 93%	Moderate	$n=13$, 92%	Strong
Early diagnosis of *SCN8A* DEE improves seizure outcomes	$n=28$, 92%	Moderate	$n=13$, 85%	Strong
Early diagnosis of *SCN8A* DEE improves developmental outcomes	$n=28$, 68%	No consensus; 18% disagree	$n=13$, 100%	Moderate
In *SCN8A* DEE, early use of sodium channel blockers for seizure control improves long-term seizure outcomes	$n=27$, 96%	Moderate	$n=12$, 83%	Moderate
In *SCN8A* DEE, early use of sodium channel blockers for seizure control improves long-term developmental outcomes	$n=27$, 67%	No consensus; 11% disagree	$n=12$, 92%	Moderate
Importance of function of variant				
Determining the function of the variant (i.e., LOF or GOF) is important to inform treatment and to anticipate phenotype	$n=29$, 90%	Moderate	$n=13$, 100%	Moderate
Knowing that a patient has an *SCN8A* variant is not enough, and it is necessary to know functional implications of the variant when deciding on first line treatments	$n=29$, 86%	No consensus; 14% disagree	$n=13$, 85%	Strong
It is important to determine GOF/LOF when you receive an *SCN8A* genetic report; this can be done by reviewing the report, literature, and/or reviewing established associations of key aspects of symptom presentation (i.e. age at onset, types of seizures, adverse response to sodium channel blockers, etc.) with function	$n=29$, 97%	Moderate		

TABLE 1 (Continued)

Findings	Clinician		Caregiver	
	Responses	Level of consensus	Responses	Level of consensus
Features relating to loss of function (LOF) variants				
Autism without epilepsy	$n=29$, 92%[a]	Strong	$n=13$, 100%[a]	Strong
Developmental delays or movement disorders without epilepsy	$n=29$, 85%[a]	Strong	$n=13$, 100%[a]	Strong
Lack of positive response to sodium-channel blockers except lamotrigine	$n=29$, 84%[a]	Strong	$n=13$, 71%[a]	Moderate
Later age at seizure onset (>2 years old)	$n=29$, 65%[a]	No consensus	$n=13$, 86%[a]	Strong
Areas for counseling at or soon after diagnosis				
Wide spectrum of severity	$n=29$, 93%	Strong	$n=13$, 92%	Strong
Review potential prognosis within and across phenotypes	$n=28$, 100%	Moderate	$n=13$, 85%	Strong
Expected presence and evolution of comorbid conditions including movement disorders, gastrointestinal issues, behavioral challenges, etc	$n=29$, 83%	Strong	$n=12$, 92%	Strong
Likelihood of drug-resistant epilepsy and importance of balancing quality of life with seizure control	$n=29$, 97%	Moderate	$n=13$, 92%	Strong
Need for seizure emergency plan and rescue medications	$n=29$, 90%	Strong	$n=13$, 100%	Strong
Risk of sudden unexpected death in epilepsy (SUDEP)	$n=29$, 86%	Strong	$n=13$, 92%	Strong
Understanding seizure types and possible triggers			$n=12$, 92%	Strong
Risks and benefits of recommended treatments including non-antiseizure medication options			$n=12$, 92%	Strong
Prognosis, as requested			$n=11$, 82%	Strong

Note: Areas with strong consensus (green): percentage responding "fully agree" is shown. Areas with moderate (blue), modest, or no consensus: percentage responding "fully agree" or "somewhat agree" is shown. Question not asked (gray).

Abbreviations: DEE, developmental and epileptic encephalopathy; GOF, gain of function; LOF, loss of function; SUDEP, sudden unexpected death in epilepsy.

[a]Percentage responding "somewhat more suggestive of LOF" or "much more suggestive of LOF".

1. Autism without epilepsy (clinicians and caregivers: strong).
2. Developmental delays or movement disorders without epilepsy (clinicians and caregivers: strong).
3. Lack of positive response to SCBs except lamotrigine (clinicians: strong; caregivers: moderate).

Finally, clinicians and caregivers reached strong consensus on several areas relating to family education and counseling following diagnosis of *SCN8A*-related disorders, including provision of information on the wide spectrum of severity, comorbid conditions, and seizure control (e.g., collaboration on a seizure emergency plan, use of rescue medications, sudden unexpected death in epilepsy risk, and potential seizure types).

3.2 | Characterization and clinical presentation of phenotypes

Figure 2 shows the defining characteristics of the phenotypes, including age at seizure and developmental delay onset, seizure types, EEG and MRI findings, and function of variants based on clinician consensus. Supplemental Figure S1 includes data from caregivers.

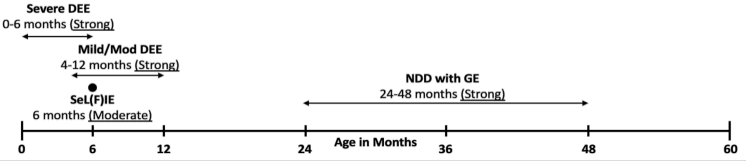
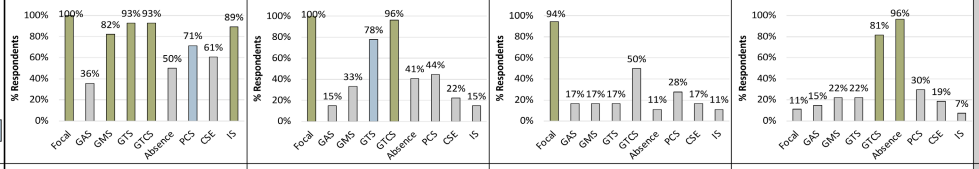
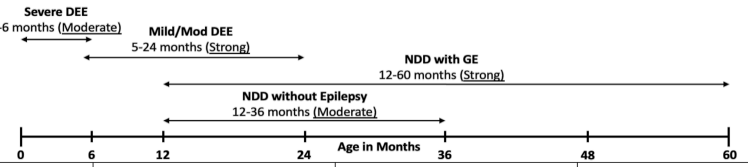
Phenotypes	Severe DEE	Mild/Moderate DEE	SeL(F)IE	NDD with Generalized Epilepsy	NDD without Epilepsy
Description (Clinician & Caregiver)	**Early onset seizures** (infantile spasms, tonic-clonic/tonic/focal/myoclonic seizures); **Severe Intellectual Disability/Developmental Delay**; **Comorbidities** include gastrointestinal/feeding, hypotonia, gross/fine motor delays, cortical visual impairment, behavioral challenges (Strong)	**Early onset** of predominantly **focal and motor seizures**, seizures are often refractory; **Multiple but less severe comorbidities** than Severe DEE (Moderate)	**Age-limited seizures** during infancy with often **no other health or developmental problems**, overall **improvement in seizures**; **Movement disorders (paroxysmal dyskinesia)** have been associated (Moderate)	**Later onset** after typical development of predominantly **absence seizures**; **Multiple comorbidities**, although consistently less severe and more likely to improve relative to Severe DEE (Moderate)	**Neurodevelopmental disorders and/or intellectual disability** without epilepsy (Strong)
First Symptom	Seizures/Seizures and Developmental Delays occur about the same time (Strong)	Seizures (Strong)		Most often seizures, but in some cases preceded by developmental delays (Moderate)	Developmental delay (Strong)
Age of Seizure Onset					
Seizure Types (Strong: ≥80%; Moderate: 67-79%)					
EEG	Although initial EEG may be normal, it typically becomes abnormal after epilepsy onset and remains so through the course of epilepsy. (Moderate)	1. A normal initial EEG does NOT exclude a diagnosis of Mild/Moderate DEE. (Moderate) 2. Although the initial EEG may be normal, it typically becomes abnormal after epilepsy onset and remains so through the course of the epilepsy. (Moderate)	A normal initial EEG does NOT exclude a diagnosis of SeL(F)IE. (Moderate)	Although the initial EEG may be normal, it typically becomes abnormal after epilepsy onset and remains so through the course of the epilepsy. (No consensus)	
MRI	The initial MRI is frequently normal, but may become abnormal over time (often demonstrating atrophy). (Moderate)	The initial MRI is normal and most frequently remains normal throughout the course. (Moderate)		The initial MRI is normal and most frequently remains normal throughout the course. (Moderate)	The initial MRI is normal and most frequently remains normal throughout the course. (Strong)
Age of Developmental Delay Onset					
Likely Function of Variant	GOF (Moderate)	GOF[9,11] (No consensus)	GOF[9,11] (No consensus)	LOF[9,11] (No consensus)	LOF (Strong)

FIGURE 2 Characterizing five phenotypes of *SCN8A*-related disorders. Consensus data are shown from clinicians only, except for phenotype description (clinicians and caregivers). Gray boxes indicate that the question was not asked/did not apply to specific phenotype. Unless otherwise noted: areas with strong consensus: percentage responding "fully agree" is shown; areas with moderate, modest, or no consensus: percentage responding "fully agree" or "somewhat agree" is shown; age at onset consensus: strong, ≥80%; moderate, 67%–79%. Description: severe developmental epileptic encephalopathy (DEE): $n=42$, 88%; mild/moderate DEE: $n=37$, 97%; self-limited (familial) infantile epilepsy (SeL(F)IE): $n=33$, 91%; neurodevelopmental delay (NDD) with generalized epilepsy (NDDwGE): $n=37$, 95%; NDD without epilepsy (NDDwoE): $n=37$, 81%. First Symptom: severe DEE: $n=29$, 97%; mild/moderate DEE: $n=26$, 88%; NDDwGE: $n=28$, 93%; NDDwoE: $n=26$, 88%. Age at seizure onset: severe DEE: $n=28$, 96%; mild/moderate DEE: $n=26$, 92%; SeL(F)IE: $n=18$, 67%; NDDwGE: $n=27$, 93%. Seizure types: severe DEE: $n=28$; mild/moderate DEE: $n=27$; SeL(F)IE: $n=18$; NDDwGE: $n=27$. Electroencephalography (EEG): severe DEE: $n=28$, 93%; mild/moderate DEE: (1) $n=23$, 87%; (2) $n=25$, 88%; SeL(F)IE: $n=24$, 92%; NDDwGE: $n=28$, 86% agree, 14% disagree. Magnetic resonance imaging (MRI): severe DEE: $n=29$, 96%; mild/moderate DEE: $n=26$, 96%; NDDwGE: $n=28$, 100%; NDDwoE: $n=26$, 81%. Age at developmental delay onset: severe DEE: $n=25$, 76%; mild/moderate DEE: $n=23$, 96%; NDDwGE: $n=25$, 100%; NDDwoE: $n=20$, 70%. Likely function of variant: severe DEE: $n=25$, 76%; mild/moderate DEE: $n=26$, 58%; SeL(F)IE: $n=19$, 58%; NDDwGE: $n=23$, 52%; NDDwoE: $n=26$, 96%. "Absence" indicates absence/atypical absence seizures. "Focal" indicates focal motor/nonmotor seizures. CSE, convulsive status epilepticus (>30 min); GAS, generalized atonic seizures; GE, generalized epilepsy; GMS, generalized myoclonic seizures; GOF, gain of function; GTCS, bilateral/generalized tonic–clonic seizures; GTS, generalized tonic seizures; IS, infantile spasms; LOF, loss of function; PCS, prolonged convulsive (motor) seizures (5–29 min).

Consensus from both clinicians and caregivers was gained on the general clinical presentation and age at seizure onset of five phenotypes:

Three with early seizure onset often within the first 6 months of life:

1. Severe DEE (strong)
2. Mild/moderate DEE (moderate)
3. SeL(F)IE (moderate)

Two with later or no seizure onset dominated by NDD:

4. NDD with generalized epilepsy (NDDwGE; moderate)
5. NDDwoE (strong)

Importantly, the phenotypes are also characterized by differences in seizure types.

In severe and mild/moderate DEE, initial EEG may be normal, but typically becomes abnormal throughout the

course of epilepsy (moderate); some noted EEGs oftentimes show multifocal spikes and background slowing.

Initial MRIs are also frequently normal across all phenotypes; however, MRIs may become abnormal (often demonstrating atrophy) in severe DEE patients (strong), whereas MRIs frequently remain normal in other phenotypes (strong to moderate).

Severe DEE is more likely to be associated with GOF variants (moderate) and NDDwoE with LOF variants (strong), consistent with previous published findings.[7,9–11] Consensus related to the typical function of variants with other phenotypes was not achieved.

3.3 | Treatments: ASMs, seizure action plans, vaccine schedule

Optimal first-line treatments for severe DEE, mild/moderate DEE, and SeL(F)IE phenotypes are oxcarbazepine and carbamazepine (Table 2; clinicians: moderate). Optimal first-line treatments for NDDwGE are valproate, ethosuximide, and lamotrigine (clinicians: moderate).

When treating *SCN8A* patients with GOF variants, sodium channel-blocking mechanisms are preferred first-line therapies (clinicians: strong; caregivers: moderate) and may be used at doses above the recommended maximum range if tolerated (clinicians and caregivers: moderate), which 58% of caregivers ($n=12$) reported doing. *SCN8A* GOF patients should be cautious of levetiracetam (clinicians: strong), whereas *SCN8A* LOF patients should be cautious of SCBs (clinicians: strong).

There was also moderate consensus from clinicians that the maximum number of ASMs used concurrently in *SCN8A* patients should be 3–4. Although caregivers reported 0–4 ASMs currently in use, 83% ($n=12$) still had concerns that their child was on too many ASMs. There was also modest consensus from clinicians that seizure type has a high impact on treatment choice.

Clinicians also agreed on various scenarios for adding and weaning medications, with strongest consensus for adding medications when prolonged seizures/status epilepticus or frequent convulsive seizures occur, and weaning medications based on efficacy and side effects of current medications.

Based on clinician experience, the KD is somewhat effective for *SCN8A* patients (moderate), and five caregivers reported effectiveness. Notably, there was strong consensus from clinicians that there is not a role for resective surgery in *SCN8A* patients. Although there was limited consensus on the use of these non-ASM treatments, clinicians and caregivers both still agreed that the full range of treatment options (KD, CBD, surgery, etc.) should be explored as appropriate (strong).

Clinicians agreed that phenytoin and fosphenytoin are preferred intravenous therapies for status epilepticus after failure of first-line benzodiazepines (modest), and both clinicians and caregivers felt that levetiracetam is not a proper next-line treatment for status epilepticus (moderate).

There was moderate consensus from clinicians that all routine vaccinations should be given either per usual schedule or with an amended schedule.

Clinicians and caregivers both agreed that all patients who are at risk for seizures should have a seizure action plan (SAP; strong).

4 | DISCUSSION

SCN8A-related disorders are highly heterogeneous, contributing to complexities in diagnosis and treatment. This rigorous modified Delphi process yielded international consensus from clinicians and caregivers on the presence of five distinct phenotypes proposed in the past few years,[7,9] with variations in the clinical presentation and optimal first-line treatments across these phenotypes. The many areas of consensus from this process will hopefully lead to earlier diagnosis, more evidence-based treatment, and improved outcomes for patients with *SCN8A* (Figure 3).

Early diagnosis of *SCN8A* is important for long-term seizure outcomes and potentially developmental outcomes. Consensus on genetic testing indications[15] as well as phenotypic characteristics from this study will aid in earlier diagnosis, and specific biomarkers of *SCN8A* across phenotypes will need to be identified to aid in earlier diagnosis, prevent misdiagnosis, and reduce missed opportunities for diagnosis. Additionally, although our study only asked about genetic testing in patients with epilepsy <3 years old due to the early onset and time course of *SCN8A*, clinicians should follow the latest guidance on genetic testing. The latest guidelines from the National Society of Genetic Counselors recommend genetic testing for all people with unexplained epilepsy regardless of age as well as all neurodevelopmental disorders of unknown cause without epilepsy.[30]

Beyond agreeing on the presence of five distinct phenotypes, this consensus further defined their clinical presentations, including age at onset for seizures and developmental delay, seizure types, and findings on EEG and MRI. Diagnosing and treating patients based on phenotypes should help clinicians provide more tailored and reliable treatment, counseling, and prognosis information for each individual, which in turn may contribute to improved long-term outcomes and quality of life.

Initial naming of the phenotypes for this study was built on the phenotype names established in Gardella and

TABLE 2 Treatments.

Findings	Clinician Responses	Clinician Level of consensus	Caregiver Responses	Caregiver Level of consensus
Optimal first-line treatments by phenotype				
In patients with Severe DEE, the optimal first line treatments are either oxcarbazepine or carbamazepine	$n = 28$, 93%	Moderate	$n = 5$, 80%	Moderate
In patients with Mild/Mod DEE, the optimal first line treatments are either oxcarbazepine or carbamazepine	$n = 28$, 86%	Moderate	$n = 3$, 67%	Modest
In patients with SeL(F)IE, the optimal first line treatments are either oxcarbazepine or carbamazepine	$n = 28$, 100%	Moderate		
In patients with NDD with Generalized Epilepsy, the optimal first line treatments are either valproate, ethosuximide, or lamotrigine	$n = 28$, 93%	Moderate	$n = 1$, 0%	No consensus Somewhat disagree
GOF vs. LOF treatments				
Medications with sodium channel blocking mechanisms of action are preferred first-line therapies for people with GOF variants in *SCN8A*	$n = 29$, 97%	Strong	$n = 12$, 100%	Moderate
If a person with *SCN8A* GOF is demonstrating benefit from increasing dose of sodium channel drugs, it is appropriate to increase the dose over the recommended maximum range if the medication is otherwise tolerated	$n = 28$, 89%	Moderate	$n = 12$, 92%	Moderate
Seizure freedom is more likely in persons with *SCN8A* loss-of-function	$n = 21$, 71%	Modest	$n = 8$, 100%	Strong
Poorly tolerated medications				
SCN8A GOF patients should be cautious of Levetiracetam	$n = 24$, 83%	Strong		
SCN8A LOF patients should be cautious of Sodium Channel Blockers	$n = 24$, 92%	Strong		
Adding/weaning medications				
3-4 is the maximum number of anti-seizure medications that should be used concurrently for *SCN8A* patients	$n = 29$, 76%	Moderate		
For persons who are not seizure-free, I would likely add another medication if the following occurs				
1. Prolonged seizures or Status epilepticus	$n = 28$, 89%	Strong		
2. Frequent convulsive seizures	$n = 29$, 83%	Strong		
3. Frequent non-convulsive seizures	$n = 29$, 90%	Moderate		
4. New therapy recently approved for *SCN8A* specifically	$n = 29$, 93%	Moderate		
Factors to consider when determining which medications to remove when modifying therapies				
1. Efficacy of current medications	$n = 29$, 90%	Strong		
2. Side effects of current medications	$n = 29$, 90%	Strong		
3. Duplicative mechanism of action	$n = 29$, 79%	Moderate		
4. Impact of current medication on developmental progress	$n = 29$, 79%	Moderate		

TABLE 2 (Continued)

Findings	Clinician		Caregiver	
	Responses	Level of consensus	Responses	Level of consensus
5. Caregiver concerns	$n=29$, 76%	Moderate		
Seizure type has a high impact on treatment choice	$n=29$, 79%	Modest		
Non-ASM treatments				
Ketogenic diet is somewhat effective in *SCN8A* patients	$n=23$, 70%	Moderate		
There is not a role for resective surgery in *SCN8A* patients	$n=20$, 90%	Strong		
Clinicians should explore the full range of treatment options, including diet, CBD, surgical options, etc. as appropriate	$n=28$, 82%	Strong	$n=13$, 92%	Strong
Emergency medications				
Phenytoin and fosphenytoin are preferred IV therapies for status epilepticus after failing first line benzodiazepines	$n=29$, 72%	Modest		
Levetiracetam is not a proper next-line treatment for status epilepticus	$n=26$, 85%	Moderate	$n=13$, 92%	Moderate
Vaccinations				
All routine vaccinations should be given either per usual schedule or with an amended schedule	$n=29$, 97%	Moderate		
Seizure action plan (SAP)				
All *SCN8A* patients with seizures should have a Seizure Action Plan	$n=28$, 100%	Strong		
All *SCN8A* patients who are at risk for seizures should have a Seizure Action Plan	$n=29$, 100%	Strong	$n=13$, 92%	Strong
Clinician quality of care				
Neurologists are encouraged to be open to education/review research and findings that can often be brought up by families	$n=29$, 90%	Strong	$n=13$, 85%	Strong
Neurologists should consider family experience and preferences when looking to balance seizure control in order to optimize quality of life	$n=29$, 100%	Strong	$n=13$, 85%	Strong

Note: Areas with strong consensus (green): percentage responding "fully agree" is shown. Areas with moderate (blue), modest (red), or no consensus: percentage responding "fully agree" or "somewhat agree" shown. Question not asked (gray).

Abbreviations: CBD, cannabidiol; DEE, developmental epileptic encephalopathy; GOF, gain of function; IV, intravenous; LOF, loss of function; NDD, neurodevelopmental delay; SeL(F)IE, self-limited (familial) infantile epilepsy.

Moller[7] in 2019, which were further refined in Johannasen et al.[9] in 2022; however, some survey respondents expressed confusion. There was concern that mild/moderate DEE and severe DEE were not distinct phenotypes and should be one phenotype on a spectrum, and others voiced concerns about the mild/moderate DEE and NDDwGE phenotypes as one phenotype on a spectrum.[8] With consensus on defining clinical characteristics, including differences in age at seizure and developmental delay onset, seizure types, and MRI and EEG features, we were able to refine the names and definitions of the phenotypes to reach a high level of consensus. However, further study is needed to refine the phenotypes building on data from large cohorts of *SCN8A* patients exploring genotype–phenotype and variations within phenotypes.[9,11,24] This work will also be important for identifying potentially significant correlations of specific variants with phenotypes[3,6,8,15,16,20,31–36] as well as possible heterogeneity.[3,8,34–37]

Improved understanding of *SCN8A* phenotypes will expand as new unique cases continue to be diagnosed or

Diagnosis

If…
- **All people** with unexplained epilepsy regardless of age[30]
- **Neurodevelopmental disorder** of unknown cause without epilepsy

→ **Then,**
- **Genetic testing** using epilepsy gene panel, exome sequencing and/or WGS

↓ **SCN8A Diagnosis**

Counseling

- **Parental testing**, counseling on mosaicism
- **Wide spectrum** of severity
- **Prognosis** within & across phenotypes
- **Comorbid** conditions
- Seizure emergency plan, rescue meds
- Risk of **SUDEP**
- **Ensure families receive access to other resources**, as needed

5 Phenotypes

Early Onset

Severe DEE
- **Sz Onset:** 0-6 mo
- **DD Onset:** 0-6 mo
- **Sz Types:** Focal, Generalized, IS
- **GOF**
- **Comorbidities[22]:** Limited mobility, cognitive function, functional vision; Non-verbal; NPO
- **Seizure Freedom[22]:** Rarely/Never
- **Prognosis[22]:** Limited change to deterioration

Mild/Moderate DEE
- **Sz Onset:** 4-12 mo
- **DD Onset:** 5-24 mo
- **Sz Types:** Focal, Generalized
- **GOF[9,11]**
- **Comorbidities[22]:** Delayed motor abilities, language; Some cognitive understanding
- **Seizure Freedom[22]:** Some of the time
- **Prognosis[22]:** Limited change to improvement

SeL(F)IE
- **Sz Onset:** 6 mo
- **Sz Types:** Focal
- **GOF[7,9]**
- **Comorbidities[22]:** Paroxysmal dyskinesia
- **Prognosis[22]:** Significant improvement

First-Line Epilepsy Treatments

Oxcarbazepine & Carbamazepine

Later Onset

NDD with Generalized Epilepsy
- **Sz Onset:** 24-48 mo
- **DD Onset:** 12-60 mo
- **Sz Types:** Absence, GTCS
- **LOF[9,11]**
- **Comorbidities[22]:** Delayed language; Some cognitive understanding
- **Seizure Freedom[22]:** Some/Most of the time
- **Prognosis[22]:** Limited change to improvement

NDD without Epilepsy
- **DD Onset:** 12-36 mo
- **LOF**
- **Comorbidities[22]:** Delayed motor abilities, language; Some cognitive understanding; ASD
- **Prognosis[22]:** Limited change/moderate improvement

First-Line Epilepsy Treatments

Valproate, Ethosuximide, or Lamotrigine

Management of SCN8A

- **Max ASMs:** 3-4
- **GOF**: ↑ dose of SCBs as needed, cautious of Levetiracetam;
- **LOF**: Cautious of SCBs
- **Seizure Action Plan** for all patients at risk for seizures
- **Routine vaccinations:** Usual or amended schedule
- Consider **family experience and preferences** when balancing seizure control to optimize quality of life
- Remain **open to education/review research** and findings, especially those brought up by families

Resources[22]

- **Multidisciplinary care** for severe SCN8A
- Early intervention services
- OT/PT/Speech
- **Social workers** with expertise in NDDs
- **Specialists**: GI, Respiratory, Sleep, Ortho, etc.
- **Complex care** pediatric clinic, palliative care
- **Full range** of treatment options (CBD, KD, surgery)
- **Family advocacy groups**, research opportunities
- Transition of care document

documented that may not align with current definitions of the phenotypes (e.g., one family reported seizure onset in teen years with severe impacts after years of typical development and another reported nonsevere outcomes of an individual with a highly recurrent variant that typically has a severe presentation [unpublished cases shared

FIGURE 3 Overview of diagnosis, phenotypes, treatment, and management of *SCN8A*-related disorders. Summary of diagnosis, phenotypes, treatment, and management workflow based on consensus from modified Delphi process. Areas where consensus was not gained relating to loss of function (LOF)/gain of function (GOF) have relevant citations. Consensus on comorbidities and prognosis from Conecker[22]are included. ASD, autism spectrum disorder; ASM, antiseizure medication; CBD, cannabidiol; DD, developmental delay; DEE, developmental epileptic encephalopathy; GI, gastrointestinal; GTCS, bilateral/generalized tonic–clonic seizures; IS, infantile spasms; KD, ketogenic diet; NDD, neurodevelopmental delay; NPO, nothing by mouth; OT, occupational therapy; PT, physical therapy; SCB, sodium channel blocker; SeL(F)IE, self-limited (familial) infantile epilepsy; SUDEP, sudden unexpected death in epilepsy; Sz, seizure; WGS, whole genome sequencing.

during International SCN8A Alliance family meetings]). Better understanding of the diverse *SCN8A* phenotypes holds promise to support earlier diagnosis, better targeted treatments, anticipation and early treatment of comorbidities, and evidence-based information on long-term prognosis.

This effort also led to consensus for optimal first-line treatments for *SCN8A* by phenotypes. However, it is important to note that the literature suggests that SCBs may be effective in milder phenotypes of *SCN8A*, with the majority of severe DEE patients (80%) being resistant to any ASMs, including SCBs.[6,9] We were not able to identify second- or third-line treatment options or optimal drug combinations, which may be necessary in more complex cases. Additionally, clinicians should follow recommended protocols for treating infantile spasms, which are commonly seen in the severe DEE phenotype.[38,39]

We also reached consensus on treatments relating to GOF versus LOF. Whereas GOF patients should be cautious of levetiracetam and LOF patients cautious of SCBs, it is important to note that there are exceptions reported in the literature,[20] and treatment of *SCN8A* will require personalized approaches. In the future, models, such as that reported in Hack et al.,[11] who developed and validated a predictive model of the likely function of an individual's variant based on observed clinical features, could be helpful in providing an early and more reliable indication of the function of the variant in individual cases to improve tailored treatments and outcomes.

As the efficacy of existing medications for some *SCN8A* phenotypes (such as fenfluramine[40]) is better understood and new treatments targeting *SCN8A*[41,42] in ongoing clinical trials or possible emerging disease-modifying therapies get approved, optimal first-line treatments may be refined. More complex cases, including potential cases of mixed GOF and LOF or severe LOF, will also require more personalized treatment options. Given concerns with polypharmacy, developing evidence-based protocols for adding and weaning medications will also be important.[26] Collaboration between clinicians and caregivers will be essential in this process.

Additional research is required to better understand the efficacy of non-ASM treatments.

This study suggests that the KD may be effective for some patients, which is consistent with the literature[6,43]; however, there have also been reports of limited effectiveness[44] as well. Whereas clinicians reached strong consensus that there is no role for resective surgery in *SCN8A*, there was a recent report of a resective surgery in an *SCN8A* patient that decreased seizure frequency.[45] Additionally, although there was no consensus on the efficacy of CBD, there are mixed reviews on CBD in the literature,[6,9,20] suggesting that some patients may benefit from CBD.

Finally, counseling regarding the wide spectrum of severity, potential prognosis, comorbidities, and seizure emergency plans should be provided to caregivers, as needed. Of note, we reached consensus from both caregivers and clinicians that SAPs are important for all *SCN8A* patients at risk for seizures, but only 58% of participating caregivers have an SAP for their child. Clinicians need to work closely with caregivers to develop and maintain SAPs.[46–49] Similarly, although clinicians agreed that routine vaccinations should be given either per usual schedule or with an amended schedule, only 54% of participating caregivers said their child followed this scheduling, highlighting the need for updating current practices under these recommendations.

There was strong consensus across both clinicians and families that clinicians review research and be open to education and findings shared by families and that families' preferences be considered in balancing seizure control and quality of life. Many *SCN8A* caregivers are active partners in ongoing research and are often well informed about recent and emerging research. Caregivers should be included as full partners with their child's care team; because every aspect of treatment involves choices in an environment of substantial uncertainty, caregivers' values and priorities need to be clear and considered in treatment plans. Clinicians can also play an important role in advancing further knowledge of *SCN8A* by staying informed about advances in research. Clinicians can also help families recognize their pivotal role in diverse research opportunities (e.g., SCN8A registry, clinical trials, brain tissue donation) and encourage their participation.

Our use of the modified Delphi approach yielded significant consensus on the diagnosis, clinical presentation, and

treatment of *SCN8A*. However, there were some limitations to this study, attributed largely to the rare and highly heterogeneous nature of *SCN8A*, which limits the exposure of many clinicians to the full spectrum of the disorder. Clinicians had limited experience outside of the severe DEE phenotype (see Table S3 in Conecker[22]), possibly due to less severe cases of *SCN8A* not requiring the higher level of care provided at tertiary centers and potential underdiagnosis. Limitations were also present in the caregiver group, where we had a limited number of respondents for each phenotype due to the heterogeneity of the disorder. This made it difficult to compare consensus between caregivers and clinicians for phenotype-specific questions. Furthermore, an inherent limitation present in the modified Delphi approach is that consensus may be based on current practices but not necessarily the most recent findings, due to adoption of novel insights requiring time to enter clinical practice.

5 | CONCLUSIONS

Through this international modified Delphi approach, we successfully identified many areas of consensus to aid in the diagnosis, treatment, and management of *SCN8A*-related disorders. We hope that these results will lead to earlier diagnosis, more targeted and effective treatments, and proper management across phenotypes to improve clinical outcomes and quality of life for *SCN8A* patients. Gaps in knowledge and areas that lacked consensus will inform future research priorities and collaboration.

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); 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 P. 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). **J. 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, Neurelis, Pyros, Azurity, Eisai, Marinus, Stoke Therapeutics, and Biocodex. E.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.D. has received honoraria from UCB and Jazz Pharmaceuticals. 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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