A Research Roadmap for SCN8A-Related Disorders: Identifying Knowledge Gaps and Aligning Research Priorities Across Stakeholders

The SCN8A Research Consortium*

Knowledge Gaps and Barriers to Progress

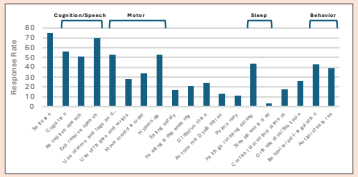
Despite significant scientific advancements since the publication of the index patient in 2012, there remains an incomplete understanding of disease mechanisms and best practices for management of SCN8A-related disorders (SCN8A-RD).

Gaps in Understanding and Management of SCN8A-RD

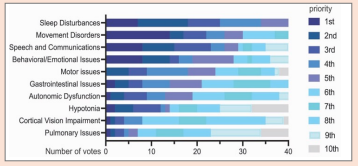
- Disease mechanisms not fully understood
- ASMs inadequate, non-selective
- Polypharmacy not well studied, hit-or-miss
- Treatments for comorbidities lacking
- Mechanisms of non-seizure outcomes not understood
- No strategies to deal with the high premature death rate
- Incomplete understanding of natural history
- Lack of biomarkers to track disease progression, treatment response

Stakeholder Survey Results

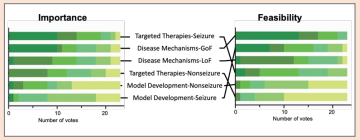
Caregivers: Rankings of the top five challenges affecting quality of life (QoL)



Clinicians: Ranking importance of research on 10 comorbidities to improve QoL



Scientists: Importance & feasibility of research to accelerate therapeutic approaches



Biotech/Pharma

Therapeutic approaches
- GoF: knockdown expression, promote inhibitory activity
- LoF: block "poison exons", target microRNAs with ASOs CRISPR activation.

Challenges
- Rarity of disease
- Risk of excessive knockdown
- Delivery to relevant brain regions
- Classify patients based on clinical features (GoF versus LoF)

Integration of Survey Results

Table 2. Points of agreement among stakeholders and responsiveness to caregiver priorities

Priority Area (Alignment)	Points of Agreement	Clinician Responsiveness	Scientist Responsiveness
Seizure vs Non Seizure Outcomes (Partial)	All recognize importance of both; caregivers prioritize non-seizure outcomes (61%), clinicians and scientists focus more on seizure control	Recognize importance of comorbidities, but seizures remain top priority	Primary focus on seizure therapies
Comorbidities (High)	All recognize importance	Prioritize sleep, movement, and behavioral issues	Recognize importance, but not primary focus
Gene Therapies vs. Conventional ASMs (Partial)	Caregivers strongly prefer research into gene therapies (73%), clinicians prioritize ASMs, scientists focus on both	Prioritize traditional ASM approaches over gene therapies	More focus on gene therapies then on other targeted treatments
Novel ASMs (High)	All see importance, but different emphasis	Top priority, first line and adjunctive top priority	Focus on novel small molecules repurposed drugs
Research Models (Partial)	Agreement on natural history studies, but different emphases; Caregivers interested in participating in studies, scientists focus on lab models	Align well with caregiver interest in participation; Emphasize registries and digital health technology involving patients	Focus on transgenic mouse models (do not directly involve patients), less on patient-involved studies

Table 3. Points of Agreement on Research Priorities of Clinicians and Scientists.

Research Area	Clinician Priority	Scientist Priority	Agreement Level
Disease Mechanisms	Recognized as important research area	Top research priority	High
Non-Seizure Outcomes	Comorbidities recognized as important research area (patients)	Non-seizure phenotypes recognized as Important research area (models)	Partial
Treatment & Therapeutics	Top research priority (mostly ASMs)	Top priority (targeted therapies for seizures)	High
Gene Therapies	Recognized as Important research area	Top research priority	High
Cell Types and Brain Regions	Implicit support through emphasis on disease mechanisms	Ranked as important for understanding epileptogenesis	Moderate
Biomarkers	High priority for research tools and methods	Important for disease mechanisms and therapeutics	High
Registries & Natural History Studies	SCN8A registry as top priority for research tools	Recognized value of registry data to guide lab research	High
Electrophysiology & Neurophysiology	Recognized as crucial	Listed as key areas of expertise	High
Pharmacology & Drug Development	Prioritized research on first line and adjunctive ASMs	Focused on selective Nav1.6 therapies and repurposed drugs	Moderate
Research Tools	Electrophysiology, neurophysiology, predictive models, biomarkers	Transgenic mouse for testing therapeutics, Registry, Lab-Clinic collaboration, biomarkers	n/a
Seizure Research	1st line ASMs & adjunctive, polypharmacy, off-label ASMs, repurposed drugs	Disease mechanism, ASO gene therapy/Goldilocks,	Low
Non-seizure Research	Sleep, Movement, Speech, Behavior	Cognitive, behavioral, movement, SUDEP, hypotonia	Moderate
Interdisciplinary Collaboration	interclinic partnerships and multidisciplinary collaboration	Highlighted importance of lab clinic collaborations	High

WG1. Advancing Transforming Therapeutics: Development & Delivery

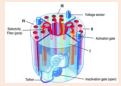
Gap: Current ASMs are limited in their ability to control seizures without significant side effects, and are ineffective in mitigating a wide range of comorbidities commonly experienced by patients
Goal: Develop transformative therapeutics that are effective in reducing seizure burden and with fewer adverse side effects.
Priority: Utilize existing (and develop new) animal models to design, test and deliver 1) small molecules that directly target $Na_V1.6$, and 2) genetic therapies that directly correct or alter the DNA or mRNA to restore protein function

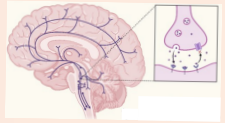
WG2: Non-Seizure Outcomes: Mechanisms, Management, and Therapies

Gap: Limited understanding of multiple non-seizure morbidities that are of significant concern to caregivers
Goal: Better understand the physiology of non-seizure outcome and advance best practices for treatment and management
Priority: Create catalog of comorbidities, their prevalence, and their impact on QoL, establish appropriate outcome measures for the full spectrum of phenotypes, and work with scientists to develop preclinical models that are feasible for laboratory studies

WG3: Improving Current Therapeutics: First line, Adjunctive, Combination, and Alternative Approaches

Gap: Despite availability of >30 ASMs, there are high rates of refractory seizures and is little known about optimal treatment regimens.
Goal: Improve therapeutics on a short time scale by implementing existing procedures and methods that could be efficiently standardized.
Priority: Implement strategy to 1) collect daily seizure frequency data in a prospective, accurate manner, 2) collect data in a standardized format from clinics, EMR, and Registry, and 3) design computational pipeline to integrate and model data using machine learning to improve diagnosis, prognosis and clinical management





WG4: Biomarkers: Tracking Disease Progression and Treatment Response

Gap: There are currently no known biomarkers to monitor the course of the disease or to aid in validation of transformational therapeutics
Goal: Develop biomarker panels to facilitate development of interventions to prevent epilepsy and reverse progression after it is established
Priority: Perform molecular analyses of blood samples and gather neuroimaging and EEG data from patients across the disease spectrum to identify potential biomarkers linked to seizure activity and disease progression. Validate biomarkers through longitudinal studies to establish prognostic value and associations with clinical outcomes

WG5: Whole Brain/Body: Brain Regions, Cell Types, Circuitry, Neuromodulation & Epileptic Body

Gap: Limited understanding genotype-phenotype relationships at the level of circuit biology and pathophysiology in different cell types and body regions.
Goals: Elucidate mechanisms by which pathogenic variants alter network and organ system dynamics leading to the development of seizure and non-seizure outcomes.
Priorities: Perform electrophysiological, molecular and neuroimaging studies of the changes caused by GoF and LoF variants in different cell types, brain circuits, and organs in various mouse models, human tissues, and and brain organoids derived from human iPSCs..

Discussion

- To accelerate progress, the *International SCN8A Alliance* sponsored a conference in Boston MA in August of 2024 with the goals to stimulate collaborative interdisciplinary efforts toward improving quality of life (QoL) for patients presenting with a range of SCN8A-RD phenotypes.
- Surveys were crafted before the meeting to identify common concerns among stakeholders and to assess responsiveness to caregiver priorities. The survey data were analyzed to ascertain core gaps and put forward research strategies to fill these gaps.
- Researchers with expertise representing five core areas that emerged from integrated analysis of the survey data formed teams that broke out in five Working Groups (after a unanimous participant vote) at the meeting.
- The Working Groups developed research strategies to address knowledge gaps that including both short- and long-term priorities to improve understanding of disease and its management for the spectrum of SCN8A-RD phenotypes.
- Importantly, the four stakeholder groups worked together in this effort, incorporating the priorities of the caregiver community.
- Challenges included identification of funding mechanisms and the need to recruit additional methodologies and research personnel to the field.
- While the ultimate goal is to cure the disease it was recognized that a realistic series of intervening benchmarks will help to temper expectations of the community of families and patients.
- The comprehensive framework established by the Roadmap effort serves to guide the research community to efficiently reach these critical goals.

*The SCN8A Research Consortium

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