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RESEARCH ARTICLE

Selecting effective antiseizure medications for early treatment of SCN8A-related epilepsy using a machine learning approach incorporating clinician and caregiver assessments

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Abstract

Objective: Despite rapid advances in understanding the disease spectrum and its progression, little is known about which antiseizure medications (ASMs) are likely to be beneficial or detrimental as first-line therapies for patients with SCN8A-related epilepsy (SCN8A-RE). This is a critical issue given low rates of seizure freedom and treatment resistance rates that exceed 75%. In this study, we test the hypothesis that machine learning (ML) algorithms can improve selection of ASMs that are likely to benefit patients with SCN8A-RE.

Methods: We leverage comprehensive medical data in the International SCN8A Patient Registry to construct a neural network that recommends ASMs based on a caregiver-centered composite measure incorporating improvements in seizure control, alertness, and side effects. We directly compare the recommendations of the algorithm to preferences of clinician experts through a follow-up survey and evaluate how ASM selection is influenced when informed by the ML algorithm.

Results: Despite challenges resulting from the prevalent use of polypharmacy and frequent suboptimal treatment responses, the algorithm identified ASMs likely to be beneficial in $76\% \pm 3\%$ of cases while never recommending a detrimental ASM in 1100 trials. Clinician experts independently recommended beneficial ASMs in 22% (16/72) of cases, a rate that increased to 46% (11/24) when choices were given based on algorithm recommendations.

Significance: The results indicate that ML algorithms can improve selection of ASMs that are likely to be beneficial in the early treatment of SCN8A-RE patients, with little risk of recommending ASMs with detrimental effects—a particular hazard for patient populations requiring long-term maintenance on polypharmacy. The results also expand the number of recommended ASMs from two sodium channel blockers (SCBs) identified in a recent consensus process to five SCBs and a γ -aminobutyric acidergic drug. The algorithm lays the groundwork for incorporating composite measures that include both seizure control and quality of life metrics.

KEYWORDS

machine learning, pediatric epilepsy, rare diseases

1 | INTRODUCTION

Pathogenic variants in the voltage-gated sodium channel gene, *SCN8A* (encoding Na_v1.6), underlie a wide spectrum of clinical phenotypes, ranging from neurodevelopmental delays with or without seizures to severe developmental and epileptic encephalopathy (DEE).¹ Shortly after discovery of the index patient in 2012 and the inclusion of the *SCN8A* gene on commercial epilepsy panels, an online registry was established,² and many case reports and cohort studies followed, describing the spectrum of the disorder.³ More recently, machine learning (ML) methods were developed to classify patients into clinically meaningful subgroups.^{1,3,4} Despite these gains, there is limited consensus on optimal treatment regimens for individuals with *SCN8A*-related epilepsy (*SCN8A*-RE).⁴ Whereas refractory rates for pediatric epilepsy are typically approximately 30%,^{5,6} more than 75% of *SCN8A*-RE patients continue to experience seizures after trial of two or more ASMs.^{1,2,7}

Selecting among the large number of available ASMs for early treatment is complicated by the paucity of evidence-based data on the effective management of *SCN8A*-RE. Clinicians have been challenged to prescribe ASMs or adjust their doses by a “trial and error” process, often leading to suboptimal seizure control and various adverse effects.^{8–10} In addition, approximately 85% of patients are taking multiple ASMs, which further hinders efforts to determine best first-line therapies.⁷ A modified Delphi process involving 30 international clinicians with expertise in treating patients with *SCN8A*-RE found low levels of consensus for best first-line ASMs, with only two ASMs (oxcarbazepine and carbamazepine) identified as optimal treatments for patients with a range of seizure severities.⁴

In this study, we test the hypothesis that ML algorithms can improve selection of ASMs that are likely to benefit patients in the early treatment phase. ASMs under consideration include those that were prescribed just before and after initial diagnosis of *SCN8A*-RE. Building on our previous ML studies,^{11,12} we construct an algorithm to predict which ASMs are most likely to be beneficial based on caregiver scores for those medications that improved (or worsened) seizure control (frequency and duration), side effects, and alertness. Our first task was to describe the current medication landscape. Then, we leveraged clinical data and previously constructed ML algorithms to evaluate the 17 ASMs that were most frequently prescribed for *SCN8A*-RE. Following algorithm construction, clinicians

Key points

- To advance procedures to select optimal treatment regimens for patients with *SCN8A*-related epilepsy, we construct an ML algorithm to recommend ASMs based on caregiver assessments.
- The algorithm recommends beneficial ASMs in approximately 76% of cases while nearly always avoiding those with detrimental effects.
- Further assessment of the algorithm by clinical experts supported recommendation of a set of six ASMs that are likely to be beneficial in the early treatment of *SCN8A*-related epilepsy.

with experience treating *SCN8A*-RE were recruited to evaluate the extent to which (1) ASMs selected by clinicians aligned with recommendations by the algorithm and (2) ASM selections were modified when clinicians were informed by the algorithm.

2 | MATERIALS AND METHODS

2.1 | Data collection and inclusion criteria

Data for 301 individuals were collected using the International *SCN8A* Patient Registry (Registry)² during the period from January 2017 through December 2023. Individuals providing informed consent were included in this study. Selected features included those that are routinely assessed in a clinical setting at early stages of disease presentation. Inclusion criteria were possession of a pathogenic or likely pathogenic *SCN8A* variant validated in a commercial testing lab or by following guidelines of the American College of Medical Genetics.¹³ A more complete description of the population and genetic variants can be found in Tables 1 and 2 and in Figures S1 and S2.

Individuals were classified into clinical subgroups according to previously described methods.^{11,12,14} Briefly, we used the unsupervised ML approach of Hack et al.¹² to classify patients into one of three phenotypic subgroups: developmental encephalopathy (DE), epileptic encephalopathy (EE), and DEE. See Hack et al.¹⁴ for more details on the clinical characteristics of these phenotypic subgroups.

TABLE 1 Patient study features classified by subgroup.

Features	Overall, <i>n</i> = 220	Clinical subgroups			
		DE, <i>n</i> = 46	EE, <i>n</i> = 45	DEE, <i>n</i> = 76	LOF+, <i>n</i> = 53
Female, <i>n</i> (%)	108 (49.1)	17 (37.0)	25 (55.6)	38 (50.0)	28 (52.8)
Male, <i>n</i> (%)	112 (50.9)	29 (63.0)	20 (44.4)	38 (50.0)	25 (47.2)
GOF, <i>n</i> (%) ^a	167 (75.9)	46 (100.0)	45 (100.0)	76 (100.0)	0 (.0)
LOF, <i>n</i> (%)	53 (24.1)	0 (.0)	0 (.0)	0 (.0)	53 (100.0)
Prolonged SZ freedom, <i>n</i> (%)	108 (49.1)	33 (71.7)	24 (53.3)	29 (38.2)	22 (41.5)
Severe ID/DD, <i>n</i> (%) ^a	119 (54.1)	29 (63.0)	0 (.0)	72 (94.7)	18 (34.0)
Developmental delay, <i>n</i> (%) ^a	152 (69.1)	46 (100.0)	1 (.02)	75 (98.7)	29 (54.7)
Seizure first, <i>n</i> (%) ^a	157 (71.4)	31 (67.4)	45 (100.0)	43 (56.6)	38 (71.7)
Probability of LOF, median (IQR) ^a	.088 (.01 to .527)	.02 (.002 to .111)	.052 (.01 to .116)	.03 (.005 to .102)	.726 (.558 to .758)
Age at seizure onset, median (IQR), months	4 (2 to 9)	5 (3 to 7)	5 (2 to 8)	3 (.75 to 4)	16 (3 to 36)
Age at DD onset, median (IQR), months ^a	8 (3 to 60)	5 (3 to 12)	120 (48 to 180)	2 (1 to 3)	42 (15 to 156)
SZ-DD onset gap, median (IQR), months ^a	-2 (-51.75 to .5)	-1.75 (-5.56 to .88)	-117 (-172 to -44.7)	0 (-1 to 1)	-18 (-121 to 1)
Longest period SZ-free, median (IQR), months ^a	6 (1.5 to 16.5)	12 (9 to 24)	10 (4 to 36)	1 (.5 to 2)	6 (2.7 to 20.5)
Developmental quotient, median (IQR) ^a	35.2 (8.3 to 100)	34.6 (13.3 to 58.1)	100 (100 to 100)	8.3 (5 to 15.5)	80.4 (30 to 100)
First seizure type, <i>n</i> (%)					
BTC	103 (46.8)	26 (56.5)	25 (55.6)	35 (46.1)	17 (32.1)
FOC	67 (30.5)	8 (17.4)	13 (28.9)	32 (42.1)	14 (26.4)
TON	50 (22.7)	10 (21.7)	6 (13.3)	25 (32.9)	9 (17.0)
FOC impaired	35 (15.9)	3 (6.5)	7 (15.6)	19 (25.0)	6 (11.3)
FOC to BTC	35 (15.9)	5 (10.9)	10 (22.2)	13 (17.1)	7 (13.2)
CLO	31 (14.1)	2 (4.3)	5 (11.1)	14 (18.4)	10 (18.9)
MYO	29 (13.2)	3 (6.5)	3 (6.7)	15 (19.7)	8 (15.1)
ABS ^a	28 (12.7)	3 (6.5)	1 (2.2)	7 (9.2)	17 (32.1)
FOC aware ^a	23 (10.5)	1 (2.2)	0 (.0)	17 (22.4)	5 (9.4)
Atypical ABS ^a	14 (6.4)	3 (6.5)	0 (.0)	1 (1.3)	10 (18.9)
ATO	13 (5.9)	1 (2.2)	0 (.0)	6 (7.9)	6 (11.3)
Motor FOC	13 (5.9)	1 (2.2)	3 (6.7)	4 (5.3)	5 (9.4)
Other	31 (14.1)	3 (6.5)	5 (11.1)	12 (15.8)	11 (20.8)
Unknown	32 (14.5)	8 (17.4)	5 (11.1)	11 (14.5)	8 (15.1)
Seizure ever, <i>n</i> (%)					
Convulsive	209 (95.0)	45 (97.8)	43 (95.6)	75 (98.7)	46 (86.8)
Absence ^a	35 (15.9)	5 (10.9)	1 (2.2)	7 (9.2)	22 (41.5)
Generalized onset	149 (67.7)	33 (71.7)	30 (66.7)	50 (65.8)	36 (67.9)
Infantile spasms	17 (7.7)	3 (6.5)	1 (2.2)	11 (14.5)	2 (3.8)

Abbreviations: ABS, absence; ATO, atonic; BTC, bilateral tonic-clonic; CLO, clonic; DD, developmental disability; DE, developmental encephalopathy; DEE, developmental and epileptic encephalopathy; EE, epileptic encephalopathy; FOC, focal; GOF, gain of function; ID, intellectual disability; IQR, interquartile range; LOF, loss of function; MYO, myoclonic; SZ, seizure; TON, tonic.

^a*p* < .0006.

TABLE 2 Frequency of best and worst ASMs based on caregiver scoring.

		Clinical subgroups			
		DE, <i>n</i> = 46	EE, <i>n</i> = 45	DEE, <i>n</i> = 76	LOF+, <i>n</i> = 53
All, <i>n</i> = 220					
Best ASMs, <i>n</i> (%)					
OXC	56 (25.5)	18 (39.1)	12 (26.7)	21 (27.6)	5 (9.4)
CBZ	38 (17.3)	9 (19.6)	11 (24.4)	13 (17.1)	5 (9.4)
LCM	38 (17.3)	13 (28.3)	4 (8.9)	14 (18.4)	7 (13.2)
CLB	37 (16.8)	6 (13.0)	5 (11.1)	17 (22.4)	9 (17.0)
PHT	34 (15.5)	10 (21.7)	4 (8.9)	16 (21.1)	4 (7.5)
LTG	30 (13.6)	4 (8.7)	6 (13.3)	13 (17.1)	7 (13.2)
VPA	26 (11.8)	8 (17.4)	3 (6.7)	11 (14.5)	4 (7.5)
CLZ	21 (9.5)	4 (8.7)	2 (4.4)	11 (14.5)	4 (7.5)
TPM	21 (9.5)	3 (6.5)	4 (8.9)	11 (14.5)	3 (5.7)
PBT	18 (8.2)	4 (8.7)	6 (13.3)	6 (7.9)	2 (3.8)
LEV	15 (6.8)	1 (2.2)	4 (8.9)	3 (3.9)	7 (13.2)
ZNS	13 (5.9)	4 (8.7)	1 (2.2)	3 (3.9)	5 (9.4)
RFN	7 (3.2)	1 (2.2)	0 (.0)	5 (6.6)	1 (1.9)
ACTH	6 (2.7)	2 (4.3)	0 (.0)	3 (3.9)	1 (1.9)
ESL	6 (2.7)	0 (.0)	3 (6.7)	2 (2.6)	1 (1.9)
ETX	5 (2.3)	0 (.0)	0 (.0)	0 (.0)	5 (9.4)
GBP	4 (1.8)	0 (.0)	0 (.0)	4 (5.3)	0 (.0)
VGB	4 (1.8)	2 (4.3)	0 (.0)	2 (2.6)	0 (.0)
Worst ASMs, <i>n</i> (%)					
LEV	80 (36.4)	17 (37.0)	15 (33.3)	28 (36.8)	20 (37.7)
VPA	17 (7.7)	2 (4.3)	3 (6.7)	4 (5.3)	8 (15.1)
TPM	16 (7.3)	3 (6.5)	4 (8.9)	6 (7.9)	3 (5.7)
CLB	15 (6.8)	6 (13.0)	1 (2.2)	6 (7.9)	2 (3.8)
LTG	14 (6.4)	0 (.0)	1 (2.2)	5 (6.6)	8 (15.1)
LCM	13 (5.9)	3 (6.5)	3 (6.7)	3 (3.9)	4 (7.5)
PHT	12 (5.5)	2 (4.3)	2 (4.4)	5 (6.6)	3 (5.7)
OXC	10 (4.5)	1 (2.2)	2 (4.4)	2 (2.6)	5 (9.4)
PBT	10 (4.5)	3 (6.5)	5 (11.1)	2 (2.6)	0 (.0)
CLZ	9 (4.1)	3 (6.5)	1 (2.2)	3 (3.9)	2 (3.8)
VGB	8 (3.6)	1 (2.2)	1 (2.2)	6 (7.9)	0 (.0)
CBZ	6 (2.7)	0 (.0)	1 (2.2)	3 (3.9)	2 (3.8)
ACTH	4 (1.8)	0 (.0)	0 (.0)	3 (3.9)	1 (1.9)
ZNS	4 (1.8)	1 (2.2)	0 (.0)	1 (1.3)	2 (3.8)
ETX	3 (1.4)	1 (2.2)	1 (2.2)	1 (1.3)	0 (.0)
RFN	3 (1.4)	0 (.0)	1 (2.2)	2 (2.6)	0 (.0)
ESL	2 (.9)	0 (.0)	0 (.0)	1 (1.3)	1 (1.9)
GBP	1 (.5)	1 (2.2)	0 (.0)	0 (.0)	0 (.0)
Score, mean ± SD					
LEV	−.52 ± .93	−.53 ± .77	−.51 ± .99	−.54 ± .84	−.47 ± 1.14
VGB	−.08 ± .73	.54 ± 1.35	−.43 ± .75	−.15 ± .61	.00 ± .00
CBZ	.57 ± .94	.64 ± .76	.98 ± 1.02	.44 ± .95	.28 ± .98
OXC	.54 ± .92	.89 ± .83	.61 ± .95	.56 ± .86	.02 ± .92
ESL ^a	.47 ± 1.05	.00 ± .00	1.35 ± .00	.38 ± 1.15	.22 ± 1.69

TABLE 2 (Continued)

	All, <i>n</i> = 220	Clinical subgroups			
		DE, <i>n</i> = 46	EE, <i>n</i> = 45	DEE, <i>n</i> = 76	LOF+, <i>n</i> = 53
PHT	.42 ± .95	.84 ± 1.07	.31 ± .86	.40 ± .92	.14 ± .89
LCM	.41 ± .99	.56 ± 1.04	.15 ± .98	.49 ± .95	.25 ± 1.05
ZNS	.35 ± 1.02	.59 ± 1.36	.28 ± .69	.18 ± .80	.49 ± 1.33
LTG	.34 ± 1.01	.42 ± .66	.63 ± .98	.49 ± 1.06	−.06 ± 1.08
CLB	.31 ± .94	.01 ± .94	.36 ± .84	.33 ± .94	.64 ± .98
RFN	.27 ± .94	.68 ± .95	−1.35 ± NA	.29 ± .95	.45 ± .78
CLZ	.26 ± .84	.09 ± .83	.26 ± .93	.41 ± .88	.18 ± .78
GBP	.23 ± .70	−.43 ± .75	.00 ± NA	.43 ± .66	.00 ± NA
PBT	.17 ± .79	.16 ± .92	.21 ± 1.18	.14 ± .59	.27 ± .63
ETX	.16 ± 1.09	−1.15 ± NA	−1.85 ± NA	−.75 ± 1.06	.63 ± .75
ACTH ^a	.14 ± 1.03	1.18 ± 1.03	.00 ± .00	.03 ± .94	−.17 ± 1.61
VPA	.14 ± .95	.39 ± .99	.00 ± .93	.27 ± .92	−.19 ± .92
TPM	.08 ± .86	−.03 ± .78	.07 ± .97	.15 ± .88	.06 ± .90

Abbreviations: ACTH, adrenocorticotrophic hormone; ASM, antiseizure medication; CBZ, carbamazepine; CLB, clobazam; CLZ, clonazepam; DE, developmental encephalopathy; DEE, developmental and epileptic encephalopathy; EE, epileptic encephalopathy; ESL, eslicarbazepine; ETX, ethosuximide; GBP, gabapentin; LCM, lacosamide; LEV, levetiracetam; LOF, loss of function; LTG, lamotrigine; OXC, oxcarbazepine; PBT, phenobarbital; PHT, phenytoin; RFN, rufinamide; TPM, topiramate; VGB, vigabatrin; VPA, valproic acid; ZNS, zonisamide.

^a*p* < .0006.

2.2 | Treatment profiles

Individuals were classified according to whether they were currently (i.e., at the time of inclusion) maintained on a single antiseizure medication (ASM; monotherapy), two ASMs (dual therapy), or three or more ASMs (polytherapy). ASMs were grouped by mechanism of action, and their frequencies among patients on monotherapy, dual therapy, or polytherapy were calculated. Each medication was given a score between −1 and 1 based on caregiver-reported effects on seizure frequency, seizure duration, adverse side effects, and altered alertness. Improvements or worsening in seizure frequency, seizure duration, adverse effects, and alertness counted as $\pm .35$, $\pm .35$, $\pm .15$, and $\pm .15$, respectively. For example, a patient reporting that a medication reduced both seizure frequency and duration, but negatively affected alertness, would have a total score of .55. These scores informed final decisions on best and worst ASMs.

2.3 | Algorithm construction and evaluation

Seventeen ASMs were selected for training the algorithm: carbamazepine (CBZ), clobazam (CLB), clonazepam (CLZ), eslicarbazepine (ESL), ethosuximide (ETX), gabapentin, lacosamide (LCM), lamotrigine (LTG), levetiracetam (LEV), oxcarbazepine (OXC), phenobarbital (PBT), phenytoin

(PHT), rufinamide, topiramate (TPM), valproate (VPA), vigabatrin (VGB), and zonisamide. The dataset was randomly divided into 70% training and 30% test sets, stratified by clinical subgroup determined by the neural network to ensure appropriate representation in each run. The features for best and worst ASM were converted into two 17-column outcome matrices. Two 6-layer neural network algorithms were constructed, one for best ASM and one for worst ASM. Accuracy and categorical cross-entropy were used to evaluate the performance of each output across 100 epochs or until the model converged. Accuracy was determined by taking the top five best ASMs and top three worst ASMs as compared with the caregiver-reported best and worst ASMs for each patient. The algorithm for best ASM was further evaluated by counting the number of predictions in the top three that were (1) reported as best (beneficial), (2) never prescribed (untested), (3) prescribed but not reported as best or worst (ineffective), and (4) reported as worst (detrimental). The neural network was subset across five different seeds to ensure the performance was not the result of a favorable training split.

2.4 | Clinician's Game

A two-phase survey was developed utilizing the clinical profile of 12 randomly selected individuals split into two groups who had been prescribed at least 10 ASMs over

their lifetime. Phase 1 had clinicians compete against the ML algorithm to recommend three ASMs for the individual based on their clinical profile, which included age at seizure onset, seizure types at initial presentation, causal SCN8A variant and other variants of uncertain significance, and developmental quotient. Phase 2 gave clinicians the clinical profile of each patient in addition to outputs from each of the three algorithms (i.e., variant consequence, clinical subgroup, top three ASMs). Clinicians were then asked to recommend only one ASM from the three ML recommendations or a different ASM if they disagreed with the recommendations. Responses were evaluated to compare how concordant the top choices of these clinicians were relative to those selected by the ML algorithm, and whether their performance was augmented with the additional aid of the ML algorithm.

This survey was conducted using the first iteration of this model, which improved during the revision process. It was not feasible to repeat the Clinician's Game, and results from the original model have been maintained.

2.5 | Entropy of medication landscapes

To characterize the predictability of ASM use, statistical entropy was calculated for the Registry cohort with 30 ASMs and the recommendations provided by the clinicians and algorithm with 17 ASMs. Entropy is defined as $H = -\sum(p(x) * \log_2(p(x)))$ where H is the entropy of the system and $p(x)$ is the probability of an ASM being prescribed. Statistical entropy can be understood as a measure of uncertainty in a system where higher values indicate less order. Here, a higher entropy indicates higher uncertainty in prescription practices.

3 | RESULTS

3.1 | Frequency of current and weaned ASMs

Of the 301 Registry participants analyzed, 30 different ASMs with a range of mechanisms of action (MOAs) were reported (Figure 1A). The median number of current prescriptions was 2 (quartile 1 = 1, quartile 3 = 3) ASMs, and the median number of weaned prescriptions was 5 (quartile 1 = 2, quartile 3 = 9) ASMs. A total of 83 patients were on monotherapy (27.6%), 70 were on dual therapy (23.3%), and 148 were on polytherapy (49.2%). The four most frequently prescribed ASMs ($\geq 20\%$) included two sodium channel blockers (SCBs; OXC, LCM), a γ -aminobutyric acidergic (GABAergic) drug (CLB), and one ASM with multiple MOAs (VPA; Figure 1A). The four ASMs with

the highest rate of weaning included LEV and three drugs typically prescribed for short periods of time to treat infantile spasms (IS): prednisolone, dexamethasone, and VGB.¹⁵ Of the 83 subjects maintained on monotherapy, 24 were on OXC and 11 were on CBZ (Figure 1A). Other ASMs used as monotherapy in multiple patients included LCM ($n=6$), LTG ($n=6$), ETX ($n=6$), VPA ($n=5$), CLB ($n=5$), PHT ($n=3$), and LEV ($n=2$; Figure 1A). Of the 70 subjects on dual therapy, 16 were on VPA and 14 each were on OXC and LCM (Figure 1A). CBZ also had one of the highest rates of weaning, and the oft-weaned LEV was commonly taken by patients on dual therapy ($n=10$).

3.2 | ASM frequencies by phenotypic subgroup

The rank order for best and worst ASMs differed with marginally statistical significance among the three phenotypic subgroups characterized by gain-of-function (GOF) variants (Kruskal–Wallis $p=.042$ and $.038$, respectively; Table 2). Although OXC was most often ranked best ASM for all three of these phenotypic subgroups, there were notable differences in the rank order of the following best ASMs. For DE, LCM (28.3%) and PHT (21.7%) followed OXC (39.1%), whereas CBZ (24.4%) was the only other ASM after OXC (26.7%) to reach a frequency of $\geq 20\%$ in the EE subgroup (Table 2). For DEE, CLB (22.4) and PHT (21.1) followed OXC (27.6%). In the loss of function-positive (LOF+) subgroup, CLB was most frequently ranked best ASM (17.0%). LEV dominated as most frequently ranked worst ASM, reaching a frequency of $>30\%$ for all four phenotypic subgroups. In the DEE subgroup there was no clear second worst ranked ASM after LEV, whereas VPA and LTG (15.1% each) followed LEV in the list of worst ASMs in the LOF+ subgroup.

3.3 | Algorithm-based ASM recommendations

The neural network average accuracy for best and worst ASMs were $.76 \pm .03$ and $.33 \pm .06$, respectively; average categorical cross-entropy was $7.49 \pm .52$ (Table 3, left). The highest performing seed was selected for application in the Clinician's Game. The results from each seed are shown in Figures S3–S7. Evaluating the top three recommended ASMs across all five seeds resulted in an average of 116.2 ± 1.8 beneficial, 155.6 ± 5.4 ineffective, 388.2 ± 5.4 untested, and 0 detrimental recommendations (Table 3, right).

Across five seeds, the algorithm consistently identified OXC, LCM, CBZ, LTG, CLB, and PHT as ASMs likely to

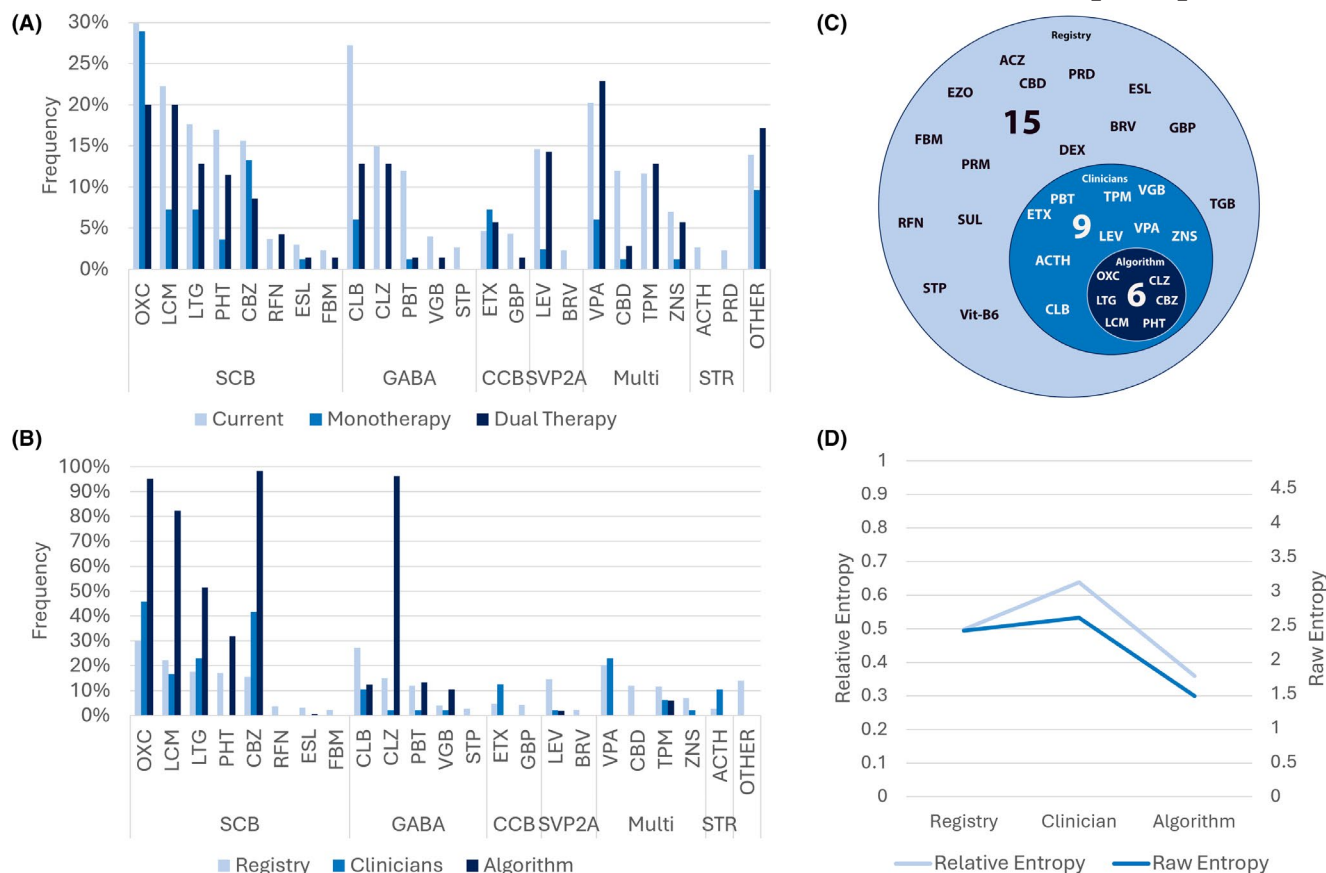


FIGURE 1 Prescription landscape of antiseizure medications (ASMs) in SCN8A-related epilepsies. (A) Current prescriptions of ASMs reported in the International SCN8A Patient Registry (Registry), including those used in monotherapy and dual therapy. (B) Frequency of ASMs reported in the Registry, and those recommended by clinicians and the algorithm (see text). (C) ASMs reported in the Registry (largest circle), recommended by clinicians, and recommended by the algorithm (smallest circle). (D) Statistical entropy for the ASMs in the Registry and those recommended by clinicians and the algorithm (see text). Relative entropy is defined as raw entropy divided by maximum entropy for each system. ACTH, adrenocorticotrophic hormone; ACZ, acetazolamide; BRV, brivaracetam; CBD, cannabidiol; CBZ, carbamazepine; CCB, calcium channel blockers; CLB, clobazam; CLZ, clonazepam; DEX, dexamethasone; ESL, eslicarbazepine; ETX, ethosuximide; EZO, ezogabine; FBM, felbamate; GABA, γ -aminobutyric acid; GBP, gabapentin; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PBT, phenobarbital; PHT, phenytoin; PRD, prednisone; PRM, primidone; RFN, rufinamide; SCB, sodium channel blockers; STP, stiripentol; STR, steroids; SUL, sulthiame; SVP2A, synaptic vesicle protein 2A; TGB, tiagabine; TPM, topiramate; VGB, vigabatrin; Vit-B6, vitamin B6; VPA, valproic acid; ZNS, zonisamide.

be effective for >25% of the population (Figures 1C,D, 2, and S3–S7; Table S5). OXC was identified as the best ASM choice for 745 of 1100 (67.7%) recommendations and appeared in the top five recommendations 1047 times. CBZ, CLZ, and LCM, although less frequently recommended as the best ASM (259/1100, 42/1100, and 11/1100, respectively), were each recommended in the top five for >80% of the population (Figure 2, Table S5). Of these, CBZ and CLZ were most often ranked as the second and third options, respectively, followed by CBZ and LCM. When weighting each medication by the rank of the recommendation, the order of recommendations was OXC, CBZ, CLZ, LCM, LTG, and PHT (Table S5). Other ASMs were recommended at lower rates: PBT (147/1100), CLB (137/1100), VGB (116/1100), TPM (64/1100), LEV (19/1100), and ESL

(5/1100). As expected, LEV was almost always identified as a detrimental ASM (109/1100), followed by TPM (907/1100), CLZ (539/1100), LCM (380/1100), and VGB (283/1100; Figure 2, Table S5).

3.4 | Neural network improves likelihood of selecting beneficial ASM

In phase 1, 38.8% (7/18) of the algorithm recommendations were beneficial and none was detrimental, whereas 22.2% (16/72) and 8.3% (6/72) of clinician recommendations were beneficial or detrimental, respectively. In phase 2, 38.8% of the algorithm recommendations were beneficial, with at least one of the three recommendations

TABLE 3 Results of neural network across five seeds used to subset the population for training.

Seed	Best ASM accuracy	Worst ASM accuracy	Categorical cross-entropy	Beneficial	Ineffective	Untested	Detrimental
1024	.82	.38	7.6	116	163	381	0
1028	.73	.27	7.3	116	156	388	0
1080	.74	.41	8.3	119	154	387	0
2024	.76	.27	6.8	114	157	389	0
2025	.77	.33	7.5	116	148	396	0
Average	.76	.33	7.49	116.2	155.6	388.2	0
SD	.03	.06	.52	1.8	5.4	5.4	0

Abbreviation: ASM, antiseizure medication.

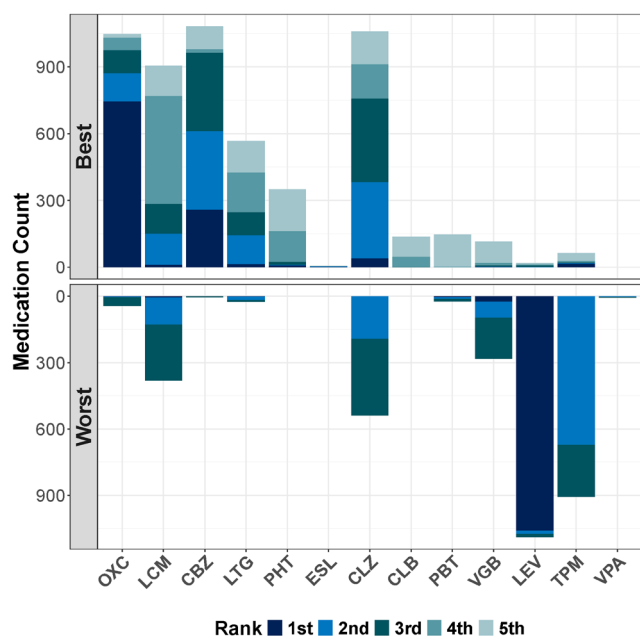


FIGURE 2 Algorithm performance and recommendations. Ranking of antiseizure medications (ASMs) recommended by the algorithm is shown. The leftmost six ASMs are sodium channel blockers (CBZ, carbamazepine; ESL, eslicarbazepine; LCM, lacosamide; LTG, lamotrigine; OXC, oxcarbazepine; PHT, phenytoin); the next four ASMs are γ -aminobutyric acidergic drugs (CLB, clobazam; CLZ, clonazepam; PBT, phenobarbital; VGB, vigabatrin); levetiracetam (LEV) is a synaptic vesicle protein 2A modulator; topiramate (TPM) and valproic acid (VPA) have multiple mechanisms of action.

being beneficial for all patients (Table 4). When informed by output from the algorithm, there was a marginally statistically significant increase in beneficial clinician recommendations to 45.8% (11/24, two-sided Fisher exact test $p=.036$, one-sided Fisher exact test $p=.027$, odds ratio=2.92). In one instance, all clinicians chose ASMs that differed from the recommendations of the algorithm; one of these was detrimental (Table 4, Patient 7).

Conversely, a single clinician selected a beneficial ASM not recommended by the algorithm (Table 4, Patient 12). All other recommendations not counted as beneficial or detrimental were considered neutral, as they were either never prescribed for the patient or were only marginally effective. Clinicians who participated in the game were actively treating a median of 8 patients and spent an average of 3 h each week reading SCN8A literature.

3.5 | Algorithm increases consistency in choosing first-line therapies

Entropy was calculated for the medication landscape of the entire Registry, the recommendations from phase 1 of the Clinician's Game, and the recommendations from the algorithm. The relative entropy (e.g., observed entropy/maximum entropy) was .497, .642, and .359 for Registry, clinician recommendations, and model recommendations, respectively (Figure 1D).

4 | DISCUSSION

Despite the availability of more than 30 ASMs, there is limited consensus regarding optimal treatment regimens for individuals with SCN8A-RE,^{1,4} many of whom present with complex seizure profiles and high rates of refractory epilepsy.¹⁻³ Given the small patient population and the limited consensus on best practices, clinicians still find themselves in the difficult position of choosing the best first-line and adjunctive treatments. This work was motivated by the opportunity to make use of caregiver-reported rankings of best and worst ASMs in the Registry, which were based on a combination metric including changes in seizure burden, side effects, and alertness.² This study is among the first to utilize ML methods^{16,17} to recommend ASMs based on the early clinical profile of patients with a rare pediatric epilepsy.⁹

TABLE 4 Results from the Clinician's Game.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12
ML prediction (ranked)												
Prediction 1	LCM	OXC	OXC	OXC	OXC	OXC	OXC	CBZ	LCM	OXC	OXC	CBZ
Prediction 2	OXC	LTG	LCM	LCM	LCM	LCM	LCM	LTG	OXC	LCM	LCM	LTG
Prediction 3	CBZ	CBZ	LTG	LTG	LTG	CLZ	LTG	PHT	CBZ	LTG	CBZ	LCM
Clinician recommendations (unranked)												
Clinician 1												
Prediction 1	CLB	CBZ	CBZ	CBZ	ETX	CBZ	CLZ	CBZ	OXC	OXC	OXC	LTG
Prediction 2	LTG	LCM	OXC	OXC	LTG	OXC	NA	NA	NA	NA	NA	NA
Prediction 3	OXC	OXC	VGB	VPA	VPA	VPA	NA	NA	NA	NA	NA	NA
Clinician 2												
Prediction 1	CBZ	CBZ	ACTH	ACTH	ETX	CLB	ETX	CBZ	OXC	OXC	OXC	ETX
Prediction 2	LCM	LCM	CBZ	LTG	LTG	LTG	NA	NA	NA	NA	NA	NA
Prediction 3	OXC	OXC	OXC	VPA	VPA	VPA	NA	NA	NA	NA	NA	NA
Clinician 3												
Prediction 1	CLB	CLB	ACTH	ACTH	CLB	LTG	ETX	LTG	OXC	OXC	LCM	CBZ
Prediction 2	TPM	OXC	LTG	CBZ	ETX	TPM	NA	NA	NA	NA	NA	NA
Prediction 3	VPA	VPA	TPM	LTG	VPA	ZNS	NA	NA	NA	NA	NA	NA
Clinician 4												
Prediction 1	LEV	CBZ	CBZ	ACTH	CBZ	CBZ	VPA	CBZ	CBZ	CBZ	CBZ	LTG
Prediction 2	PBT	LCM	LCM	CBZ	LCM	LCM	NA	NA	NA	NA	NA	NA
Prediction 3	VPA	OXC	OXC	OXC	OXC	OXC	NA	NA	NA	NA	NA	NA
Caregiver reports (truth set)												
Beneficial	OXC, TPM	OXC, PBT, PHT	LTG, OXC, VPA	CLZ, OXC, VPA	LEV	OXC, LCM	LTG	LTG, OXC	LTG, OXC	LTG, OXC	LCM, PHT	ETX, LTG
Detrimental	LEV, VPA	LCM, LEV	LEV	VGB, LEV, PHT	NA	LEV	VPA	LEV	LEV	LEV, PBT	PBT	LEV, VPA

Note: Clinicians were not required to rank their recommendations for Patients 1–6; recommendations are reported in alphabetical order.

Abbreviations: ACTH, adrenocorticotrophic hormone; CBZ, carbamazepine; CLB, clobazam; CLZ, clonazepam; ETX, ethosuximide; LCM, lacosamide; LEV, levetiracetam; LTG, lamotrigine; ML, machine learning; NA, not applicable; OXC, oxcarbazepine; PBT, phenobarbital; PHT, phenytoin; TPM, topiramate; VGB, vigabatrin; VPA, valproic acid; ZNS, zonisamide.

The study finds that patients were prescribed a wide variety of more than 18 different antiseizure medications with inconsistent usage patterns, indicating a complex and varied medical landscape for seizure treatment. Nearly 60% of patients are taking more than two ASMs (median = 2, quartile 1 = 1, quartile 2 = 3), and many have weaned several additional ASMs (median = 5, quartile 1 = 2, quartile 3 = 9) over the course of only a few years (mean = 4.4 ± 2.3). The results of the study also demonstrate the utility of an ML approach in recommending ASMs that are likely to be beneficial in the early treatment of SCN8A-RE patients, with little risk of recommending detrimental ASMs. In addition, the algorithm expands the number of recommended ASMs from two SCBs identified in a recent consensus process⁴ to five SCBs and a single GABAergic drug. In the following sections, we discuss the ASMs recommended for treatment of newly diagnosed patients and how use of the algorithm may simplify the selection process, improve consistency among clinicians, and eventually streamline the trial and error process that characterizes current clinical practice.

4.1 | SCN8A-RE medication landscape

A total of 37 ASMs were prescribed in a subset of Registry participants ($n = 301$) that spans nearly 10 different mechanistic classes. The analysis of statistical entropy indicates a moderately high level of randomness ($H = .497$ and $.642$ for Registry and clinicians, respectively) in ASM prescriptions (Figure 1D). This result does not necessarily imply a random selection process; rather, it likely reflects the difficulty in predicting the long-term efficacy of ASMs as monotherapies or in combinations. Some non-mutually exclusive factors that may contribute to higher entropy include transient effectiveness of an ASM, weaning of partially effective ASMs in search of better seizure reduction, prescription choices based on insurance company preference or local availability, increased trial and error associated with low exposure to patients with this rare condition, and/or complex cellular mechanisms implicating both excitatory and inhibitory neuron activity as drivers of hyperexcitability.^{18,19} Despite these uncertainties, there are well-established guidelines for treating IS¹⁵ and absence seizures,²⁰ which affect ~25% and ~16% of the SCN8A-RE population, respectively. However, the process of deciding on best first-line and adjunctive therapies is still quite complicated given the combination of seizure types experienced by this population.

The high rate of polypharmacy also complicates efforts to identify effective ASMs. Thus, it is important not only to develop our understanding of effective combinations of ASMs but also to identify which features are predictive of

an individual responding well to monotherapy. The application of the ML algorithm has served to narrow the list of ASMs to a more manageable set that is likely to be beneficial in the early treatment of patients with SCN8A-RE. This may ultimately lead to more consistency (less entropy) in choosing initial treatments.

4.2 | Mechanisms of action of recommended ASMs

Long-term treatment with any medication may have adverse effects due to toxicity of metabolic intermediates and interactions with other medications. This risk is compounded when multiple ASMs are concurrently prescribed, increasing the likelihood of long-term detrimental effects. For example, polypharmacy with various ion channel blockers and/or GABAergic drugs can lead to a range of adverse effects.^{21–23} With this in mind, the mechanism of action of the ASMs selected by the algorithm should be considered.

The top recommended ASMs likely to be of benefit to patients with newly diagnosed SCN8A-RE associated with GOF variants include five SCBs (OXC, CBZ, LCM, LTG, PHT) and a single GABAergic drug (CLZ; Figure 1C). With the additional finding of LEV as the most detrimental ASM of the 17 considered, these results mirror and extend those of a recent modified Delphi consensus process.⁴ These preferences were also replicated in phase 1 of the Clinician's Game, where OXC and CBZ were recommended the most by the four participants and LEV was only recommended once. Aside from these, only VPA was recommended more than 33% of the time. Interestingly, the top-ranked ASMs used as a monotherapy paralleled the rank order of those on the top recommended list (Figure 1A).

Four of the five recommended SCBs (OXC, CBZ, PHT, and LTG) primarily act through fast inactivation, whereas LCM acts through a novel slow inactivation mechanism.²⁴ Notably, the former four SCBs and VPA block high-frequency repetitive spike firing, which is believed to occur during the spread of seizure activity, without affecting ordinary ongoing neural activity.²⁵ Given the low rates of monotherapy, combination approaches may be necessary to effectively manage the complex and difficult-to-control seizures in patients with SCN8A-RE. As such, ASM combinations should be prioritized to have synergistic mechanisms of action and limited cross-reactivity. For example, LCM may be effective in combination with other SCBs due to complementary effects of enhancing both slow and fast inactivation.²⁴ Another synergism may come from the combined use of an SCB with a GABAergic drug. Cenobamate (CNB)—a

tetrazole-derived carbamate with a dual MOA through its effect on sodium channels and GABA_A receptors at a nonbenzodiazepine site²⁶—has shown promise in reducing seizure burden in SCN8A-RE.²⁷ This is consistent with findings in mouse models indicating that *Scn8a* GOF variants can increase excitation and cause seizures by enhancing persistent current on excitatory neurons and simultaneously causing inhibitory neuron failure and overall inhibitory reduction.²⁸

4.3 | ML to optimize treatment of SCN8A-RE

This study provides a foundation for future work leveraging ML with health data to optimize clinical management of SCN8A-RE and other epilepsies with similar data resources. The constructed algorithm streamlines the selection of ASMs by focusing the initial trial and error process on a narrowed list of options. Although the intended outcome is to expedite the identification of an effective treatment regimen, the current algorithm does not provide guidance on the optimal order of prescribing ASMs or on the best combination of ASMs to prescribe.

The algorithm was trained on a dataset with sufficient sample sizes to generate an initial performance benchmark. As databases grow in size and more granular data on seizure frequency and medication interactions become available, the algorithm will continue to learn and improve its accuracy, as well as improve in its ability to recommend beneficial ASMs as first line, as adjunctive, or in combinations. The algorithm will also improve as better, more efficacious treatment options become available. For example, the set of ASMs investigated in this study does not contain newer ASMs such as CNB, which require more data to assess. A prospective study would help to further validate the algorithm, especially one in which detailed seizure frequency and duration data were collected prior to and after prescription of a recommended ASM.

4.4 | Assessing ASM efficacy: Clinical versus caregiver perspectives

It is important to highlight the different lenses through which clinicians and caregivers may assess the benefits or detriments of particular ASMs. Clinicians typically use standardized metrics like $\geq 50\%$ seizure reduction, seizure freedom rates, or changes on electroencephalographic recordings,²⁹ whereas caregivers tend to base their assessment on factors that also include changes in developmental trajectory and overall quality of life.³⁰ Therefore,

we have attempted to characterize performance in terms of how closely ASM selection was aligned between clinicians and the algorithm, which was trained on a caregiver-based composite measure incorporating both seizure control and quality of life metrics. This is consistent with US Food and Drug Administration guidance emphasizing the need to focus on disease features most important to patients in clinical trials.³

The study also points to limitations in the availability of high-quality, high-resolution data on seizure frequency. Currently, measures of seizure frequency are collected via electronic medical records (EMRs) or Registry updates, both of which are infrequently reported and overly reliant on recall. This challenges that process of identifying critical associations between changes in seizure burden and various environmental variables (i.e., illnesses, poor sleep quality, etc.). This highlights the need to incorporate procedures to collect daily seizure data (e.g., via electronic seizure diaries) that can be integrated with EMR and Registry data, which in turn would allow for greater potential to infer the effect of particular ASMs.

4.5 | Limitations and future directions

Despite promising results, there are a number of limitations that should be considered. For example, several potentially beneficial ASMs may have been overlooked due to infrequent prescriptions (e.g., ETX for absence seizures). In addition, the set of ASMs investigated in this study does not contain newer ASMs such as CNB, which require more data to assess. The size of the study population limits the ability for robust learning, particularly with the wide variety of medications considered. Prospective studies in which more granular seizure and medication data are collected will facilitate improvement in the ability of ML to identify effective ASMs used individually and in combination with others. The algorithm showed a slight tendency to recommend SCBs for patients with variants with LOF effects, which seemingly contradicts standard practice.⁴ This was in part due to the occasional recommendation of LTG in the LOF+ subgroup, an ASM that is occasionally prescribed for absence seizures (i.e., in combination with VPA).³¹ Of relevance is that many SCN8A patients in the LOF+ subgroup experience absence seizures.¹ It is important to note that the majority of the predictions across all five seeds were untested, representing a substantial number of recommendations that could be beneficial, ineffective, or even detrimental for patients in this study.

This study also raises questions that should be addressed in future research. One of the benefits of the current approach is that it considers outcome measures that

go beyond seizure control. However, more work is needed to compare these results with clinician-based metrics that are centered strictly on seizure reduction. Another area of interest is the question of treatment response variability among phenotypic subgroups. The higher rates of monotherapy in the DE and EE subgroups are consistent with higher levels of seizure resistance and more severe outcomes for DEE patients.¹⁴ Preliminary data also support the hypothesis that DE patients are generally more responsive to treatment with any SCB, whereas EE patients appear to respond more specifically to OXC and CBZ.¹⁴ Another possible future subject is the study of the impact of IS on medication response. The presence of IS often reflects a more severe phenotype, and future studies are needed to determine whether ASM recommendations differ for patients with or without IS. This study ultimately lays the groundwork for future development of ML algorithms to recommend ASMs and strengthens the case for applying these methods to other rare diseases to optimize treatment in the early stages after diagnosis.

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CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

All relevant data and code for replication are available at [10.5281/zenodo.15003253](https://doi.org/10.5281/zenodo.15003253). Requests for additional deidentified data will be considered upon request to the corresponding author.

ETHICS STATEMENT

The study was approved by the University of Arizona Institutional Review Board (#1603487278). 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.

PATIENT CONSENT STATEMENT

All caregivers of individuals with SCN8A-RE consented to participate prior to filling out the questionnaire.

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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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