Real-World Evidence of *KCNQ2* Disease Management as Generated Through a Novel Data Platform

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RATIONALE

- Mutations of the *KCNQ2* gene, which codes for the potassium $K_v7.2/7.3$ channel, are among the top 10 childhood genetic epilepsies[1,2]
- Variants in the *KCNQ2* gene underlie a spectrum of rare neonatal-onset epilepsies with varying severity, from self-limited forms to a more severe developmental and epileptic encephalopathy (*KCNQ2*-DEE)[1,2]
- Owing to its rarity, recommendations for managing patients with *KCNQ2*-DEE are based upon case series with often limited longitudinal data, and no treatments are specifically approved for *KCNQ2*-DEE[3,4]
- The objective of this study was to evaluate real-world data from a cohort of patients with *KCNQ2* epilepsy obtained via a novel data platform that aggregates patient medical records, creating a complete picture of patients and their disease management

METHODS

- Invitae's Ciitizen platform is a patient/caregiver-consented platform that collects medical records by leveraging the Health Insurance Portability and Accountability Act of 1996 right of access
- Medical records are imported into the platform for document preprocessing. Through a series of artificial intelligence services, document attributes are determined and subsequently verified by clinicians
- The data platform supports systematic capture of patient phenotypes, medical encounters, and therapeutic interventions
- Data completeness and recency were verified through a minimum of 3 rounds of human review based on encounter type and date. Patients who were missing critical medical records related to their neurologic phenotype were excluded from the analysis
- The data from patients who completed data capture before October 2022 were included in the analysis
- Data were extracted from the medical records of 44 patients captured to date with a molecular diagnosis and clinical presentation consistent with *KCNQ2*-related disorders
- All personal, identifying information about the family or its members was excluded
- Extracted data were harmonized by use of standard terminologies and validated through standardized review. Cohort features were analyzed using descriptive statistics

RESULTS

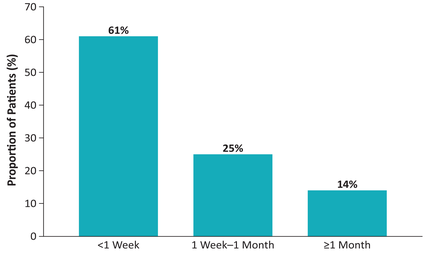
Table 1. Cohort Demographics

Characteristic (N=44)	
Age at last data capture	
Mean	7.2 y
Median	4.7 y
Range	11 mo–30 y
Sex	
Female, n (%)	24 (55%)
Male, n (%)	20 (45%)
KCNQ2 gene variants	35 different variants reported • 29 variants reported once • 6 variants reported more than once —S122L, V132M, R210H, R233W, A265V, G281R

Timing of Diagnosis

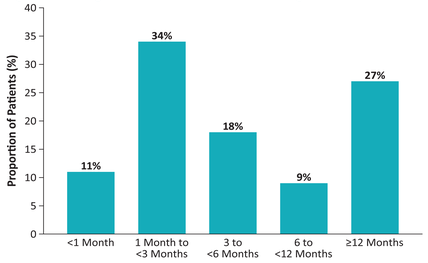
- The majority of patients (86%) were diagnosed with epilepsy within the first month of life (**Figure 1**)

Figure 1. Timing of Initial Epilepsy Diagnosis



- In comparison, only 11% of patients achieved a diagnosis of "*KCNQ2*-related disorder" within the first month of life, and within the first 6 months of life, only 63% of patients were diagnosed (**Figure 2**)

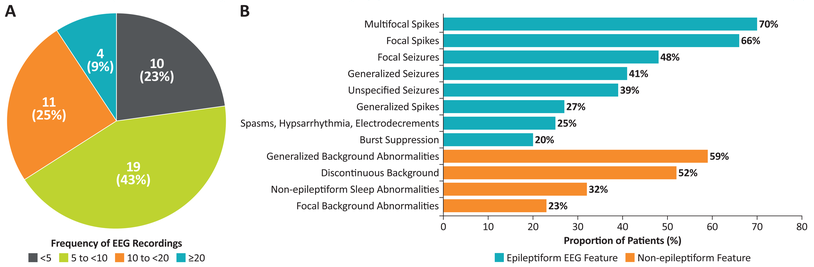
Figure 2. Timing of *KCNQ2*-Related Disorder Diagnosis



Electroencephalogram (EEG) Recordings

- Before the age of 6, the 44 patients had a total of 406 unique EEG recordings (**Figure 3**)

Figure 3. Frequency of EEG Recordings Before 6 Years of Age (A) and Most Common EEG Features Documented in the Medical Record (B)



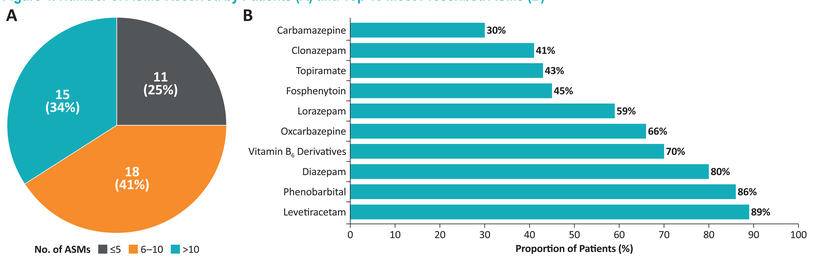
EEG, electroencephalogram.

- Focal seizures were reported in 48% of patients, and 41% of patients reported generalized seizures. 39% of patients had seizures that were not specified as focal or generalized (**Figure 3B**)
- The most observed epileptiform abnormalities were interictal multifocal spikes in 70% of patients and focal spikes in 66% of patients
- The most observed nonepileptiform abnormalities were generalized background abnormalities (59%) and discontinuous background (52%)

Use of Antiseizure Medications (ASMs)

- There were 32 unique ASMs documented, averaging a mean of 9.2 (range 3–26) ASMs per patient taken over the course of their disease with 34% of patients having taken >10 ASMs (**Figure 4**)
- Levetiracetam and phenobarbital were the most commonly prescribed ASMs, taken by >80% of patients

Figure 4. Number of ASMs Received by Patients (A) and Top 10 Most Prescribed ASMs (B)

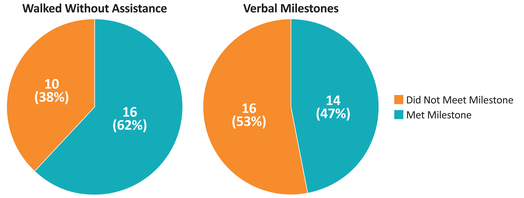


ASM, antiseizure medication.

Developmental Milestones

- Attainment of developmental milestones before 3 years of age was evaluated in patients where data were available
- Among the patients, 62% (16/26) walked without assistance and 47% (14/30) met the language milestones of the ability to use at least one word or verbal communication before 3 years of age (**Figure 5**)

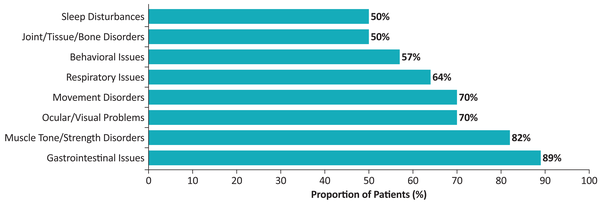
Figure 5. Walking and Language Development Before 3 Years of Age



Comorbidities

- Most patients had comorbid phenotypes as categorized in **Figure 6**
- The most common comorbidities were gastrointestinal issues (89%, including feeding tube dependency in 50% of patients), muscle tone and strength disorders (82%, including muscle weakness, spasticity, and appendicular hypertonia), ocular and visual problems (70%), and movement disorders (70%)

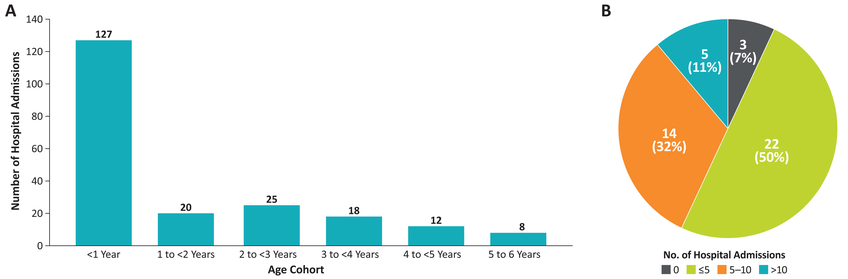
Figure 6. Most Common Comordities



Hospital Admissions

- The burden of hospital admissions was extremely high during the first year of life compared to subsequent years (**Figure 7**)
- Half of the patients (22/44) had 5 or more hospital admissions prior to 6 years of age
- Before 6 years of age, patients spent a total of 1274 days in the hospital

Figure 7. Hospital Admissions (A) and Admission Frequency (B) Before 6 Years of Age



CONCLUSIONS

- This novel platform has identified an emerging cohort of patients with *KCNQ2* epilepsy of varying clinical severity and demonstrates the value of standardized medical record collection in genetically defined cohorts
- The evaluation of the unbiased, real-world data collected via this platform provides unique insights into the patient journey, expands our understanding of rare epilepsy syndromes including *KCNQ2*-DEE, and may better inform treatment strategies and prognosis
- Interrogation of complete medical records for patients with rare genetic epilepsies can provide a more complete picture of the management strategy, common pitfalls, and clinical challenges experienced by this patient population

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DISCLOSURES Noam Butterfield, Celene Grayson, Lindy Jiang, and Cynthia Harden are employees of and own stock or stock options in Xenon Pharmaceuticals Inc. Brianna Murray, Catherine Schlechter, and Geoffrey Beek are employees of and own stock in Invitae Corporation.

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