I, Caitlin Campbell, hereby submit this original work as part of the requirements for the degree of Master of Science in Genetic Counseling.

It is entitled:
Detection of Causative Variants Using Multigene Panels in a Pediatric Population with Epilepsy

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Detection of Causative Variants Using Multigene Panels in a Pediatric Population with Epilepsy

A thesis submitted to the
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ABSTRACT

Objective: Guidelines for ordering genetic testing for epilepsy have not been developed and there is little information available on the various genetic testing options for epilepsy. Specifically, few studies address the yield of epilepsy multigene panels. The purpose of this study was to determine the yield of epilepsy panels among a pediatric population, as well as to identify clinical predictors of obtaining a genetic diagnosis using epilepsy panels.

Methods: This retrospective medical record review examined data of 117 pediatric epilepsy patients at a large tertiary referral center who had at least one epilepsy panel of any type ordered between January 1st, 2009 and December 31st, 2013. The association of clinical predictors with epilepsy panel results was analyzed using the chi-square test, Fisher’s exact test, and Wilcoxon rank-sum test.

Results: Of 124 epilepsy panels ordered, 17 (13.7%) received a causative result. Tonic or atonic seizures detected on EEG (p=0.04) were significantly associated with causative results. A higher proportion of children with myoclonic seizures on EEG had a causative panel result, which trended toward significance (p=0.06). Microcephaly, age of onset of epilepsy, developmental delay, drug resistant epilepsy, congenital malformations, and abnormal brain MRI results were not found to be useful predictors. The number of genes on the multigene panel did not correlate with diagnostic yield. Of the 17 participants with causative results, eight had mutations in sodium or potassium channel genes.

Significance: This study had a comparable yield to other epilepsy panel studies and is currently the largest study examining clinical characteristics of patients with epilepsy panel testing. This study identified that certain seizure types (tonic or atonic seizures on EEG) are clinical predictors of panel results, however further studies are needed to confirm these clinical predictors and clarify the utility of various ordering practices for genetic testing in epilepsy.

Keywords: Molecular diagnostic yield, Clinical predictors, Genetic testing, Channelopathy.
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# TABLE OF CONTENTS

LIST OF TABLES AND FIGURES ........................................................................................................ vi

INTRODUCTION .......................................................................................................................... 1

METHODS .................................................................................................................................. 4

RESULTS ...................................................................................................................................... 9

DISCUSSION ............................................................................................................................. 12

REFERENCES ............................................................................................................................ 18
LIST OF TABLES AND FIGURES

Table 1. Causative Panel Results and Clinical Characteristics ........................................ 21

Table 2. Clinical Predictors of Panel Results .................................................................. 24

Figure 1. Classification of Variants ................................................................................ 25

Figure 2. Number of Genes by Year ............................................................................ 26

Figure 3. Number of Genes by Panel Group .................................................................. 27

Appendix 1: Data Collection Form .................................................................................. 28
INTRODUCTION

Epilepsy is a common disorder affecting 1% of the general population and about 0.5% of the pediatric population. Causes of epilepsy include structural and metabolic abnormalities, genetic factors, and unknown factors. The genetics of epilepsy is complex. Genetic epilepsy disorders exhibit significant genetic heterogeneity, variable expressivity of seizures, and reduced penetrance.

In addition to traditional methods used in the workup for epilepsy, such as EEG, genetic testing in the form of single gene tests, multigene panels, microarray, and whole exome sequencing (WES) is also available to diagnose the etiology of seizures. Unless a specific gene is suspected, the single gene approach is not very effective for genetically heterogeneous disorders like epilepsy due to phenotypic variability and overlap between genetic and non-genetic epilepsies. The benefits of multigene testing include reducing time, cost, and the need to identify a single gene. However, there can be greater uncertainty with multigene panels due to the increased frequency of variants of uncertain significance (VUSs).

Array comparative genomic hybridization (CGH) and single nucleotide polymorphism (SNP) microarray have a diagnostic yield of 8-21% when performed to evaluate for genetic etiologies of epilepsy. Array CGH and SNP microarray detect copy number variants, whereas multigene panels and WES detect mutations in individual genes. WES has a yield in general of approximately 25% and a reported yield for epilepsy-related developmental disorders of 34%. WES also has lower coverage of target genes, is more expensive, and results in more VUSs than multigene panels.
Genetic testing for epilepsy can lead to an accurate diagnosis of the etiology for seizures, which is important for management and prognosis. This is especially important in the pediatric population because prompt diagnosis and treatment can affect long-term development. Genetic testing also has the potential to inform reproductive choices, reduce the length of the diagnostic odyssey, prevent additional expensive or invasive testing, and increase adherence to medical advice. Despite the discernible benefits, there is still some debate of the utility of genetic testing for epilepsy because of the uncertainty about which patients would benefit.

Guidelines for ordering genetic testing in epilepsy have not been developed and there is unfamiliarity among neurologists with the types of genetic testing available, when to offer testing, and the most appropriate tests to order for patients with epilepsy. Genetic tests, in general, are frequently ordered incorrectly, which can be minimized by the involvement of genetic counselors. In a limited survey of 163 neurologists and 372 psychiatrists, Salm et al. showed that only 33% felt confident ordering genetic testing. Among those who had previously ordered genetic testing, only 63.8% felt confident. Although 74.1% of neurologists had ordered genetic testing in the last six months, only 51% had access to a geneticist or genetic counselor to refer their patients. With the frequency of genetic testing ordered in discomfort by clinicians, more involvement of genetics professionals and the creation of guidelines could be beneficial.

The limited number of studies of epilepsy panels has shown a yield of between 9-48% using panels of various sizes. Each of these studies either had a small sample size or did not look at detailed clinical information.
Due to the limited studies of the yield of epilepsy panels and the uncertainty in what testing to order for epilepsy patients, more information is needed on the outcomes of using epilepsy panels. The purpose of this study was to determine the likelihood of obtaining a genetic diagnosis using epilepsy panels in a pediatric population with epilepsy. Additionally, this study aimed to identify clinical predictors that affect that likelihood. Clinical predictors found to significantly affect the yield could aid in identifying which patients would be more likely to benefit from genetic testing utilizing multigene epilepsy panels.
METHODS

Study Design

This quantitative and comparative cohort study is a retrospective medical record review of pediatric epilepsy patients who have had at least one epilepsy multigene panel test ordered at CCHMC between January 1st, 2009 and December 31st, 2013. CCHMC is a large tertiary referral center. Data was collected from the CCHMC electronic medical record (EMR) and managed using REDCap (Research Electronic Data Capture). This study was reviewed by the Cincinnati Children’s Hospital Medical Center (CCHMC) Institutional Review Board and was granted a waiver of the informed consent process and a waiver of HIPAA authorization.

Study Population

CCHMC patients were included in this study if they had an epilepsy diagnosis as documented by an ICD-9 code of 345.xx, were younger than 18 years old at the time of epilepsy multigene panel testing, had seen a CCHMC neurologist, geneticist, and/or genetic counselor, and had an epilepsy panel ordered between January 1st, 2009 and December 31st, 2013. Based on the study inclusion criteria, 117 patients met all study criteria.

Out of the 117 eligible participants, seven had two epilepsy panels ordered with at least one of the panels ordered within the inclusion criteria time frame. For these seven participants each panel was counted as a separate participant, resulting in a final count of 124 participants. Each panel was counted as a separate participant because the panels were ordered at different times and the characteristics of the participants and their epilepsy had changed over time.
Classification of Panel Results

For each participant, the result of the epilepsy panel was classified as a causative result or a negative result based on the laboratory-issued report and clinical interpretation (Figure 1).

Measures of Clinical Predictors

Data abstracted from the EMR included demographic information, type of epilepsy panel ordered, number of genes on epilepsy panel, date of blood draw, date of birth (to calculate age at blood draw), epilepsy panel results, parental testing results, number of antiepileptic drugs (AEDs) tried, age of onset of epilepsy, EEG patterns, brain MRI results, seizure types, history of prolonged seizures, congenital malformations, family history of epilepsy, ordering provider, providers seen, and previous genetic testing.

Demographic information included sex, ethnicity, and race as listed in the EMR. Due to the low number of non-white participants, racial background was categorized as white or non-white.

All participants had seen a neurologist, genetic counselor, and/or geneticist at CCHMC. If a participant had seen a geneticist, the presence or absence of dysmorphic features was recorded based on the geneticist’s clinical documentation.

The number of AEDs tried, head circumference, documented seizure types, and age of onset of epilepsy was collected from the most recent Neurology or Genetics clinic note before testing was ordered.

Epilepsy was classified as drug resistant if three or more AEDs had been tried. Drug resistant epilepsy is defined by the ILAE as “failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination)
to achieve sustained seizure freedom.”

Head circumference, when available, was classified as microcephaly (< 3rd %ile), normal (3rd %ile to 97th %ile), or macrocephaly (>97th %ile). The age-based percentiles were obtained from the EMR Growth Chart based on the World Health Organization (WHO) head circumference-for-age standards. For participants over the age of two at testing, the age-based percentiles were calculated based on the head circumference charts in The Handbook of Physical Measurements. Seizures were categorized into the following types: absence, myoclonic, tonic, clonic, atonic, tonic-clonic, focal, epileptic spasms, neonatal, temperature sensitive, febrile, and unclassified. Age of onset of epilepsy was collected in months for less than two years of age and in years for greater than or equal to two years of age.

Congenital malformations were abstracted from the EMR and classified as cardiovascular, gastrointestinal, genitourinary, ophthalmological, otolaryngological, neurological, or musculoskeletal. As a result of the small number of participants with congenital malformations, the presence or absence of any congenital malformations was examined.

The variables of developmental delay and developmental regression were both classified as present, absent, or not available.

EEG abnormalities, when EEG results were available, were classified as interictal background, interictal epileptiform, and ictal abnormalities. Background pattern classification categories were burst suppression, slow-mild, slow-moderate, slow-severe, hypsarrhythmia, and normal. Epileptiform pattern categories were focal, generalized/diffuse, multifocal (at least three different areas involving both hemispheres), and none. Ictal pattern categories were
absence, myoclonic, tonic, clonic, atonic, tonic-clonic, focal, epileptic spasms, neonatal, unclassified, and none.

Brain MRI results were classified as normal or abnormal (collected as abnormal/indicative of epilepsy or abnormal/not indicative of epilepsy) based on the MRI criteria from the National Institutes of Health (NIH) National Institute of Neurological Disorders and Stroke (NINDS) Common Data Elements for Epilepsy.\textsuperscript{33}

**Classification of Epilepsy Panels**

Providers at CCHMC order a variety of epilepsy multigene panels from different genetic testing companies. As shown in Figure 3, the 14 types of panels were categorized into five groups to examine the yield of panels that test for similar genes, regardless of company. Epilepsy panels that tested for a substantial number of the same genes were often testing for comparable phenotypes, so the groups are based on phenotype.

For each panel ordered, resulting variants were classified as “negative” or “causative” (Figure 1).

**Data Analysis**

For categorical data the chi-square test was used to analyze the association of clinical predictors with epilepsy panel results. The Fisher’s exact test was used instead of the chi-square test when expected cell frequencies were less than five. For non-normally distributed continuous data the Wilcoxon rank-sum test was used. Categorical data was summarized using percentages and frequencies and non-normal continuous data was summarized using median and range. Logistic regression was used to look at the relationship between the numbers of
genes on panels and the year tested. A nominal p-value of $\alpha \leq 0.05$ was used. Data were analyzed using JMP statistical software (SAS, Cary, NC).
RESULTS

Panel Results

Of the 124 epilepsy panels ordered, seven participants (5.6%) had pathogenic results, 81 participants (65.3%) had benign results, and 36 participants (29.0%) had VUS results. Of the 36 participants with VUS results, the VUSs were classified as presumed causative in 10 participants (27.8%). After grouping the presumed causative VUSs with the pathogenic results, a total of 17 participants (13.7%) had causative panel results. The characteristics of participants with a causative result, including the mutation(s) found, can be viewed in Table 1.

Two of the seven individuals in whom two separate panels had been performed had causative results identified on the second panel (29%).

Clinical Predictors of Panel Results

A variety of clinical predictors were analyzed to examine the association with epilepsy panel results (Table 2). The clinical characteristics that were associated with abnormal results were tonic seizures detected on EEG (p=0.01), tonic or atonic seizures detected on EEG (p=0.04), and congenital malformations (p=0.02). There was a significant association between panel results and whether or not a participant had seen a genetic counselor or geneticist (p=0.05). Additionally, myoclonic seizures detected on EEG (p=0.06), and age at testing (p=0.08) were trending towards significance. There was no significant association found for microcephaly, age of onset of epilepsy, developmental delay, and drug resistant epilepsy.
Congenital malformations included Ebstein's anomaly of the tricuspid valve, hypospadias, ectopic ureters, scoliosis, macroglossia, thumb joint contracture, ankyloglossia, and cleft palate/Pierre Robin sequence.

**Characteristics of Epilepsy Panels**

As shown in Figure 2, the number of genes tested on panels increased significantly over time (p<0.001). There was no significant relationship between number of genes on panel and panel results (Table 2).

Figure 3 shows the panel group categories and the number of genes on each panel. The overall yield of causative results was 13.7%. Based on these panel groups, the yield is 3/43 (7.0%) for the febrile seizure panel group, 0/7 (0.0%) for the epileptic encephalopathy panel group, 2/11 (18.2%) for the myoclonic/adolescent panel group, 11/58 (19.0%) for the infantile/childhood/comprehensive panel group, and 1/5 (20.0%) for the extensive panel group.

**Demographic and Clinical Characteristics**

Inclusion criteria for the study were met by 117 children, who were counted as 124 participants as two epilepsy multigene panels had been performed in seven of the participants. Out of the 124 participants, eight (6.5%) were deceased at the time of data collection. Information on race and sex is available in Table 2.

All but one participant had seen a neurologist. Frequently, epilepsy panels were ordered with collaboration between a genetic counselor and/or geneticist and a neurologist as evidenced by clinical documentation of discussions of testing, but a neurologist was the ordering provider 74.2% of the time. In terms of genetics providers, 63.7% of participants had
seen a genetic counselor, but only 35.5% had seen a geneticist. Of the 44 participants that had seen a geneticist, six (13.6%) were noted to have dysmorphic features.

As shown in Table 2, the majority of participants had normal brain MRI results (90/117, 76.9%), developmental delay (94/123, 75.8%), drug resistant epilepsy (81/123, 65.9%), and young ages of onset of epilepsy (median=8 months old). Some participants did not have EMR data available on brain MRI results, developmental delay, and number of medications tried. Additionally, most participants had previous genetic testing before the epilepsy panel (77/124, 62.1%). The most frequent types of testing ordered were microarray (59/124, 47.6%), single gene testing (37/124, 29.8%), and chromosomes (35/124, 28.2%).
DISCUSSION

Panel Results

The overall yield of a causative result in our study was 14% (17/124), which was comparable to the yield of most other studies of epilepsy panels of between 15% and 21%. Our yield was lower than the 48% yield found in a limited study of 33 adults and children using a panel of 265 genes, however the differences between these studies are likely due to differences in the sample populations and sample sizes.

The studies by Bradbury et al., Aradhya et al., and Wang et al. used panels that would fall into the infantile/childhood/comprehensive panel group of this study. The yields in those studies of 11-20%, 16%, and 21%, respectively, are similar to the 19% yield of the infantile/childhood/comprehensive panel group. These yields are also similar to the myoclonic/adolescent panel group (18%) and the extensive panel group (20%).

The yield in this study of 14% is also similar to the yield of 8-21% for microarray for epilepsy. The yield was 19% (11/59) for participants who had previous microarray testing, suggesting that multigene panels are beneficial after normal microarray results. Additionally, WES might be useful after negative multigene panel results, as suggested by Bradbury et al. by a yield of about 40% when both types of testing were utilized, which means there could be greater than a 40% yield when utilizing microarray, multigene panels, and WES in sequence for epilepsy.

The VUS rate of 29% in our sample population was similar to the VUS rates of previous epilepsy panel studies of 30% and 39%.
Of the 17 participants with causative results, almost half had mutations in genes related to potassium and sodium channels (Table 1). Out of the 17 participants with causative results, medication changes were made in three patients due to results of multigene panels.

**Clinical Predictors of Panel Results**

Both tonic and atonic (p=0.04) and myoclonic (p=0.06) seizures on EEG were predictive of causative results. These seizure types, while difficult to distinguish from each other clinically, should be considered as a group as a positive predictor of diagnostic utility for epilepsy multigene panels. Age of onset of epilepsy, the presence of developmental delay, and drug resistant epilepsy were not associated with an increase in yield, however this may be because of the high proportion of our study population who had these factors. Anecdotally, epilepsy multigene panels tend to be ordered at CCHMC on patients with younger ages of onset of seizures, developmental delay, and drug resistant epilepsy so many participants had these features.

There was a rate of congenital malformations of 24% in the causative group, which is higher than the background rate of birth defects of approximately 3-5%\textsuperscript{34}. The significant difference in the occurrence of congenital malformations (p=0.02) could be a result of the small number of causative results (17 participants). Of the four participants with congenital malformations that had causative results, only one participant had a congenital malformation related to their identified genetic diagnosis, which was scoliosis in a participant with a MECP2 mutation.\textsuperscript{35} In the other three cases, there has been no reported association between the congenital malformation(s) and the respective mutation(s). For the congenital malformations found in participants with negative results, it is unknown if the malformations were sporadic or
related to an unidentified genetic disorder. In the Hrabik study of the diagnostic yield in patients with epilepsy using SNP microarray, there was a significant association of a clinically significant result in patients with congenital malformations, especially in musculoskeletal and cardiovascular systems. The results of the Hrabik study and this study suggest that epilepsy patients with congenital malformations might be more likely to have epilepsy related to a chromosomal abnormality, but that congenital malformations are not as helpful in identifying a single gene epilepsy condition.

Although the association of abnormal brain MRI results with panel results was close to significance, the abnormal MRI results included predominantly non-specific MRI findings. There was only one participant with an abnormal MRI result that correlated with an epileptogenic process.

In this study population there was a high percentage of participants with developmental delay (76%, 94/123), of which 27% (25/94) had severe developmental delay, characterized by documentation that the individual was not walking or talking by two years of age. A possible explanation for the high rate of developmental delay is that clinicians were more likely to order testing in participants with developmental delay, especially significant developmental delay. However, there was no significant difference in results between those with and without developmental delay.

**Characteristics of Epilepsy Panels**

The number of genes included on the multigene panels increased significantly over time (Figure 2). Although the number of genes increased, this increase was not associated with a higher yield. The lack of difference in yield could be due to the small sample size, small number
of extensive panels ordered, and the limited number of participants with causative results. The larger number of genes would be unlikely to make a difference in yield if many of the additional genes were for disorders of very low incidence or were unrelated to the patient’s phenotype. In a study comparing multigene panels and WES there was a yield of 34% for WES in epilepsy-related developmental disorders, in which only 10% of the mutations found were in genes included on the epilepsy panels. The high percentage of genes not found on the epilepsy panels that were detected by WES suggests that there are a large number of genes of low prevalence monogenic epilepsies: a multigene panel would not increase the yield much by adding a small fraction of these genes.

For the seven individuals in whom two separate panels had been performed, all had negative results on the first panel. Two out of seven individuals (29%) had causative results identified on the second panel. Three of the second panels ordered were extensive panels of 489 genes, of which one was causative. These ordering practices suggest that the very large panels were used as a second-tier panel. However, there are no current guidelines or studies on common ordering practices for epilepsy, so it is unclear whether a larger panel or WES would be a more effective testing strategy after a negative epilepsy panel.

Demographic and Clinical Characteristics

The study population consisted of a majority of non-Hispanic white participants and is likely different than the racial composition of the general pediatric epilepsy population in the United States, although cross-sectional epidemiological data is not available. However, this study was performed at CCHMC, which is a pediatric hospital that is the sole provider of tertiary
care in that particular geographic region, so it is likely that most children with epilepsy living in the nearby region received care at CCHMC.

**Role of Genetics Providers**

The significant association between causative panel results and participants being seen by a genetic counselor or geneticist (p=0.03) could be due to many factors. One possibility is that patients were referred to a genetic counselor or geneticist because the neurologist was suspicious of a genetic disorder. Alternatively, it is possible that genetics providers are better at discerning which patients with epilepsy are more likely to have a genetic disorder and what testing to order. It has previously been shown that there is discomfort among neurologists ordering genetic testing,²⁷ so neurologists in this study might also have had some discomfort in ordering genetic testing for epilepsy.

**Limitations**

One of the limitations of this study was the number of participants, although this is the largest study looking at clinical characteristics of patients with epilepsy multigene panel testing. Larger studies of up to 1600 participants²⁸ have limited clinical information available about their sample populations. Since all types of epilepsy panels were included in this study, the results reflect yield of epilepsy multigene panels overall, but are not specific to a type of panel or phenotype. The pattern of genetic testing ordered at CCHMC might be different than at other institutions and is likely to vary across providers, although CCHMC is a large institution with numerous ordering providers. Furthermore, the epilepsy panels had differing numbers of genes, were testing for different phenotypes, and were ordered from numerous genetic testing
companies. To account for these differences, we analyzed the effect of the number of genes and looked at differences in yield between the panel types. Additionally, seven of the individuals were counted as two participants because they had two panels ordered at different time points, which could have affected our data. The VUSs were sorted into presumed causative and presumed benign categories using clinical expertise, although some of the classifications could be incorrect.

**Future Directions/Implications for Future Research**

In future studies, it would be beneficial to have a larger sample population to examine both the yield of epilepsy panels of all types and the clinical predictors of results, especially looking at seizure types. Considering the frequent genetic testing performed on participants before having an epilepsy panel ordered, including 30% of participants with at least one single gene test, a cost analysis would be useful to examine the most cost effective testing strategy for epilepsy. In order to develop a testing algorithm, further studies should be performed rigorously examining the differences in benefit of single gene testing, multigene panels, and WES for epilepsy.

**Conclusion**

The overall yield of epilepsy panels was 14% in this study, which varied by the type of panel ordered. There were certain clinical predictors that increase the likelihood of obtaining a causative result with epilepsy panels, which included tonic or atonic seizures on EEG. By further studying clinical predictors of testing results, we might be able to more adequately discern which patients would be more likely to benefit from epilepsy panel testing.
REFERENCES


### Table 1. Causative Panel Results and Clinical Characteristics

<table>
<thead>
<tr>
<th>ID</th>
<th>Mutation</th>
<th>Classification</th>
<th>Number of Genes on Panel</th>
<th>Age at Testing</th>
<th>Age of Onset</th>
<th>Seizure types</th>
<th>EEG Findings</th>
<th>Congenital Malformations</th>
<th>Previous Testing</th>
<th>Management Implications</th>
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<tbody>
<tr>
<td>2</td>
<td>KCNQ2 c.1625 C&gt;G</td>
<td>Presumed Causative VUS</td>
<td>51</td>
<td>0 mo</td>
<td>0 mo</td>
<td>Neonatal</td>
<td>Multifocal, neonatal seizures</td>
<td>None</td>
<td>None</td>
<td>No further diagnostic testing</td>
</tr>
<tr>
<td>19</td>
<td>ARX c.1399 G&gt;T</td>
<td>Pathogenic</td>
<td>38</td>
<td>4 mo</td>
<td>4 mo</td>
<td>Epileptic spasms</td>
<td>Hypsarrhythmia, multifocal, epileptic spasms</td>
<td>None</td>
<td>Microarray</td>
<td>No further diagnostic testing</td>
</tr>
<tr>
<td>25</td>
<td>CDKL5 c.577 G&gt;A</td>
<td>Presumed Causative VUS</td>
<td>38</td>
<td>20 mo</td>
<td>0 mo</td>
<td>Epileptic spasms, unclassified</td>
<td>Hypsarrhythmia, multifocal, epileptic spasms</td>
<td>None</td>
<td>Chromosomes, microarray</td>
<td>Both parents tested (de novo), change in medication, no further diagnostic testing</td>
</tr>
<tr>
<td>28</td>
<td>GRIN2A c.2907 C&gt;G</td>
<td>Presumed Causative VUS</td>
<td>51</td>
<td>5 yo</td>
<td>18 mo</td>
<td>Myoclonic, febrile, unclassified</td>
<td>Generalized/ diffuse</td>
<td>Scoliosis</td>
<td>Chromosomes, microarray</td>
<td>Both parents tested (GRIN2A maternal and KCNQ3 paternal), change in medication, no further diagnostic testing</td>
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<tr>
<td>32</td>
<td>KCNQ2 c.1742 G&gt;T</td>
<td>Presumed Causative VUS</td>
<td>38</td>
<td>1 mo</td>
<td>0 mo</td>
<td>Neonatal</td>
<td>Multifocal</td>
<td>None</td>
<td>Microarray</td>
<td>No further diagnostic testing</td>
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<td>35</td>
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<td>Pathogenic</td>
<td>38</td>
<td>4 mo</td>
<td>2 mo</td>
<td>Epileptic spasms</td>
<td>Moderate slowing, hypsarrhythmia, multifocal, tonic seizures</td>
<td>None</td>
<td>Chromosomes, microarray</td>
<td>Both parents tested (de novo), no further diagnostic testing</td>
</tr>
<tr>
<td>39</td>
<td>CLN6 c.297+1 G&gt;A</td>
<td>Presumed Causative VUS</td>
<td>38</td>
<td>2 mo</td>
<td>1 mo</td>
<td>Tonic</td>
<td>Mild slowing, multifocal, tonic seizures</td>
<td>Macroglossia, thumb joint contracture</td>
<td>Microarray, Beckwith-Wiedemann testing</td>
<td>Maternal testing, further diagnostic testing (conjunctival biopsy results consistent with NCL)</td>
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<tr>
<td>ID</td>
<td>Gene</td>
<td>Mutation</td>
<td>Status</td>
<td>Age</td>
<td>Age at Onset</td>
<td>Developmental History</td>
<td>Seizure History</td>
<td>Diagnosis</td>
<td>Additional Comments</td>
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<tr>
<td>40</td>
<td>SCN1A</td>
<td>c.4410dupG</td>
<td>Pathogenic</td>
<td>3</td>
<td>13 mo</td>
<td>Tonic-clonic, febrile</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>No further diagnostic testing, change in medication</td>
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<tr>
<td>46</td>
<td>MECP2</td>
<td>c.1290dupC</td>
<td>Pathogenic</td>
<td>40</td>
<td>7 yo</td>
<td>Tonic, atonic</td>
<td>Moderate slowing, multifocal, myoclonic and tonic seizures</td>
<td>Scoliosis</td>
<td>None</td>
<td>No further diagnostic testing</td>
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<tr>
<td>62</td>
<td>SCN1A</td>
<td>c.677 C&gt;T</td>
<td>Pathogenic</td>
<td>38</td>
<td>3 yo</td>
<td>Myoclonic, tonic, tonic-clonic</td>
<td>Focal, tonic seizures</td>
<td>None</td>
<td>None</td>
<td>No further diagnostic testing</td>
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<td>70</td>
<td>SCN1A</td>
<td>c.896 A&gt;G</td>
<td>Presumed Causative VUS</td>
<td>4</td>
<td>18 mo</td>
<td>Absence, tonic-clonic, unclassified</td>
<td>None</td>
<td>None</td>
<td>Microarray</td>
<td>Both parents tested (de novo), no further diagnostic testing</td>
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<tr>
<td>82</td>
<td>EPM1 allele 1</td>
<td>1: 85 repeats</td>
<td>Pathogenic</td>
<td>5</td>
<td>12 yo</td>
<td>Myoclonic, unclassified</td>
<td>Mild slowing, multifocal, myoclonic seizures</td>
<td>None</td>
<td>Chromosomes, microarray, Complete Ataxia Panel</td>
<td>No further diagnostic testing</td>
</tr>
<tr>
<td>86</td>
<td>CHRNA2</td>
<td>c.503 C&gt;T</td>
<td>Presumed Causative VUS</td>
<td>53</td>
<td>4 yo</td>
<td>Myoclonic, tonic-clonic</td>
<td>Mild slowing, generalized/ diffuse, myoclonic seizures</td>
<td>Hypospadias</td>
<td>None</td>
<td>Both parents tested (paternal), testing of other family members, no further diagnostic testing</td>
</tr>
<tr>
<td>89</td>
<td>CLN5</td>
<td>c.1137 G&gt;T</td>
<td>Presumed Causative VUS</td>
<td>38</td>
<td>4 yo</td>
<td>Absence, tonic-clonic, epileptic spasms</td>
<td>Focal, generalized/ diffuse, epileptic spasms</td>
<td>None</td>
<td>Chromosomes, microarray</td>
<td>Further diagnostic testing performed (conjunctival biopsy)</td>
</tr>
<tr>
<td>92</td>
<td>SCN9A</td>
<td>c.2215 A&gt;G</td>
<td>Presumed Causative VUS</td>
<td>6</td>
<td>6 yo</td>
<td>Absence, tonic-clonic, febrile</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Unknown</td>
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<tr>
<td>137</td>
<td>TPP1 c.509-1</td>
<td>Pathogenic</td>
<td>12</td>
<td>3 yo</td>
<td>18 mo</td>
<td>Myoclonic, clonic</td>
<td>Mild slowing, focal, generalized/ diffuse</td>
<td>None</td>
<td>Microarray, Febrile Seizures Panel</td>
<td>Unknown (deceased)</td>
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<td>G&gt;C</td>
<td></td>
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<tr>
<td></td>
<td>c.622 C&gt;T</td>
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<tr>
<td>138</td>
<td>KCNQ2 c.1657</td>
<td>Presumed Causative VUS</td>
<td>489</td>
<td>4 yo</td>
<td>0 mo</td>
<td>Myoclonic, tonic</td>
<td>Moderate slowing, generalized/ diffuse, multifocal, myoclonic and tonic seizures</td>
<td>None</td>
<td>Microarray, CDKL5 sequencing, Early Infantile Epileptic Encephalopathy Panel</td>
<td>Both parents tested (de novo), no further diagnostic testing performed</td>
</tr>
<tr>
<td>Clinical Predictors</td>
<td>Causative Panel Result</td>
<td>Negative Panel Result</td>
<td>p-value</td>
<td>Odds Ratio</td>
<td></td>
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<tr>
<td>---------------------------------------------------------</td>
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</tr>
<tr>
<td>Congenital Malformations</td>
<td>23.53% (4/17)</td>
<td>4.67% (5/107)</td>
<td>0.02*</td>
<td>6.28</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Malformation Related to Diagnosis</td>
<td>1/4</td>
<td>3/4</td>
<td></td>
<td></td>
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<tr>
<td>Malformation Not Related to Diagnosis</td>
<td></td>
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</tr>
<tr>
<td>Tonic or Atonic Seizures on EEG</td>
<td>29.41% (5/17)</td>
<td>11.32% (12/106)</td>
<td>0.04*</td>
<td>3.26</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Saw Genetic Counselor or Geneticist</td>
<td>88.24% (15/17)</td>
<td>62.62% (67/107)</td>
<td>0.05*</td>
<td>4.48</td>
<td></td>
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</tr>
<tr>
<td>Myoclonic Seizures on EEG</td>
<td>23.53% (4/17)</td>
<td>8.49% (9/106)</td>
<td>0.06</td>
<td>3.35</td>
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</tr>
<tr>
<td>Abnormal Brain MRI</td>
<td>41.18% (7/17)</td>
<td>20.00% (20/100)</td>
<td>0.06</td>
<td>2.80</td>
<td></td>
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<tr>
<td>Abnormal/Indicative</td>
<td>0/17</td>
<td>1/100</td>
<td></td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>Abnormal/Not Indicative</td>
<td>7/17</td>
<td>19/100</td>
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</tr>
<tr>
<td>Age at Testing</td>
<td>3.1yo (0-12.4yo)†</td>
<td>3.9yo (0-17.6yo)†</td>
<td>0.08</td>
<td>N/A</td>
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<tr>
<td>Microcephaly</td>
<td>5.88% (1/17)</td>
<td>21.36% (22/103)</td>
<td>0.13</td>
<td>0.23</td>
<td></td>
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</tr>
<tr>
<td>Age of Onset of Epilepsy</td>
<td>4mo (0-9yo)†</td>
<td>8.5mo (0-14yo)†</td>
<td>0.14</td>
<td>N/A</td>
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</tr>
<tr>
<td>Developmental Regression</td>
<td>37.50% (6/16)</td>
<td>21.59% (19/88)</td>
<td>0.17</td>
<td>2.18</td>
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</tr>
<tr>
<td>Developmental Delay</td>
<td>64.71% (11/17)</td>
<td>78.30% (83/106)</td>
<td>0.22</td>
<td>0.51</td>
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<tr>
<td>Sex- Female</td>
<td>64.71% (11/17)</td>
<td>51.40% (55/107)</td>
<td>0.31</td>
<td>1.73</td>
<td></td>
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</tr>
<tr>
<td>Epileptic Spasms</td>
<td>23.53% (4/17)</td>
<td>17.76% (19/107)</td>
<td>0.52</td>
<td>1.43</td>
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</tr>
<tr>
<td>Myoclonic Seizures</td>
<td>64.71% (11/17)</td>
<td>71.03% (76/107)</td>
<td>0.60</td>
<td>1.34</td>
<td></td>
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</tr>
<tr>
<td>High Number of Genes on Panel (&gt;=50 genes)</td>
<td>23.53% (4/17)</td>
<td>18.69% (20/107)</td>
<td>0.74</td>
<td>1.34</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Tonic or Atonic Seizures</td>
<td>29.41% (5/17)</td>
<td>26.17% (28/107)</td>
<td>0.78</td>
<td>1.18</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Drug Resistant Epilepsy (&gt;=3 medications tried)</td>
<td>64.71% (11/17)</td>
<td>66.04% (70/106)</td>
<td>0.91</td>
<td>0.94</td>
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</tr>
<tr>
<td>Race- White</td>
<td>88.24% (15/17)</td>
<td>84.11% (90/107)</td>
<td>1.00</td>
<td>1.42</td>
<td></td>
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</tr>
</tbody>
</table>

p-values from chi-square test, Fisher’s exact test, or Wilcoxon rank-sum test (2-tailed unless otherwise specified)
Categorical data summarized using percentages and frequencies
†Non-normal continuous data summarized using median and range
Abbreviations: mo=months old, yo=years old, abnormal/indicative= abnormal brain MRI indicative of epilepsy, abnormal/not indicative=abnormal brain MRI not indicative of epilepsy
*Nominally significant
Figure 1. Classification of Variants

Figure 1 shows the variant classification process. When an epilepsy panel was ordered, a report was issued from a CLIA-certified genetic testing laboratory that classified each genetic alteration as pathogenic, benign, or a variant of uncertain significance (VUS). VUSs were also sometimes classified as likely benign or likely pathogenic. When a VUS was issued on the report, a team of clinicians including a neurologist and genetic counselor discussed the case to determine if the VUS was presumed causative or presumed negative. If the team of clinicians who initially saw the patient had included their impressions in the EMR, these impressions were used to classify each VUS for the purposes of this study. If no impressions were included in the EMR, then the authors used clinical correlation to classify the VUS. The VUSs were classified as presumed causative or presumed negative using the clinical characteristics of each participant. Several factors were considered when classifying each VUS as presumed causative or negative, including the patient’s phenotype, expected phenotype of the condition of interest, the inheritance of the gene, whether the VUS was inherited or de novo, how the VUS tracked with epilepsy in the family, and the penetrance and variable expressivity of the phenotype of interest. After classifying the VUSs as presumed causative or presumed negative, the VUSs were grouped with the other panel results. The causative results group includes the pathogenic results and the presumed causative VUSs. The negative results group includes the benign results and the presumed negative VUSs.
Figure 2. Number of Genes by Year

Figure 2 shows the number of genes ordered by year. The size of each circle represents the number of participants that had that number of genes ordered in that year. The numbers of genes are grouped into categories in order to maximize the ability to see all data points.
Figure 3 shows the number of genes on each panel. The number of genes on each panel is recorded as the largest number reported for that panel because the number of genes on the same panel changed slightly over time.
Appendix 1: Data Collection Form

Data Collection Form

Record ID

Patient Identifier

Is patient deceased?  
- Yes
- No

If patient is deceased, what was the cause of death?

Results Review - Laboratory Results - Laboratory Testing - Send Out Other

Patient has two panels that were collected as two patients?  
- Yes
- No

If has two panels collected as two patients, what is the record ID for the other panel?

Ordering Provider
- Neurology
- Genetics
- Not available
- Other

If selected ordering provider as ‘Other’, specify ordering provider:

What is the company and panel name?
- 1- Transgenomic Male Febrile Seizure Panel
- 2- Transgenomic Female Febrile Seizure Panel
- 3- Transgenomic Febrile Seizure Panel
- 4- University of Chicago Early Infantile Epileptic Encephalopathy Panel
- 5- Athena Epilepsy Associated with Fever Evaluation
- 6- Athena Myoclonus Epilepsy Evaluation
- 7- Medical Neurogenetics Comprehensive Epilepsy NextGen DNA Sequencing Panel
- 8- Medical Neurogenetics Epileptic Encephalopathy NextGen DNA Sequencing Panel
- 9- GeneDx Childhood-Onset Epilepsy Panel
- 10- GeneDx Comprehensive Epilepsy Panel
- 11- GeneDx Infantile Epilepsy Panel
- 12- GeneDx Progressive Myoclonic Epilepsy Panel
- 13- GeneDx Adolescent Epilepsy Panel
- 14- Courtagen epiSEEK Comprehensive Sequence Analysis for Epilepsy and Seizure Disorders
- 15- ARUP Progressive Myoclonic Epilepsy Panel

What is the panel outcome/result classified as?
- Positive
- Negative

Panel Company
- Transgenomic
- University of Chicago
- Athena
- Medical Neurogenetics
- GeneDx
- Courtagen
- Other

If selected panel company as ‘Other’, specify company and panel type:
| If  Transgenomic, select panel type: | ○ Comprehensive Epilepsy Evaluation NGS Panel (Transgenomic)  
| | ○ Male Febrile Seizure Panel (Transgenomic)  
| | ○ Female Febrile Seizure Panel (Transgenomic)  
| | ○ Other (Transgenomic)  

| If University of Chicago, select panel type: | ○ Early Infantile Epileptic Encephalopathy Panel (University of Chicago)  
| | ○ Infantile and Childhood Epilepsy Panel (University of Chicago)  
| | ○ Other (University of Chicago)  

| If Athena, select panel type: | ○ Advanced Epilepsy Evaluation (Athena)  
| | ○ Epilepsy Advanced Sequencing Evaluation- Generalized, Absence, Focal, and Myoclonic Epilepsies (Athena)  
| | ○ Epilepsy Advanced Sequencing Evaluation- Epileptic Encephalopathies (Athena)  
| | ○ Epilepsy Advanced Sequencing Evaluation- Infantile Spasms (Athena)  
| | ○ Epilepsy Advanced Sequencing Evaluation - Neuronal Migration Disorders (Athena)  
| | ○ Epilepsy Advanced Sequencing Evaluation - Epilepsy in X-Linked Intellectual Disability (Athena)  
| | ○ Epilepsy Advanced Sequencing Evaluation - Neuronal Ceroid Lipofuscinosis (Athena)  
| | ○ Epilepsy Advanced Sequencing Evaluation - Epilepsy with Migraine (Athena)  
| | ○ Epilepsy Advanced Sequencing Evaluation - Syndromic Disorders (Athena)  
| | ○ Epilepsy Associated with Fever Evaluation (not NGS) (Athena)  
| | ○ Myoclonus Epilepsy Evaluation (not NGS?) (Athena)  
| | ○ Other (Athena)  

| If Medical Neurogenetics, select panel type: | ○ Comprehensive Epilepsy NextGen DNA Sequencing Panel (Medical Neurogenetics)  
| | ○ Epileptic Encephalopathy NextGen DNA Sequencing Panel (Medical Neurogenetics)  
| | ○ Other (Medical Neurogenetics)  

| If GeneDx, select panel type: | ○ Childhood-Onset Epilepsy Panel (GeneDx)  
| | ○ Comprehensive Epilepsy Panel (GeneDx)  
| | ○ Infantile Epilepsy Panel (GeneDx)  
| | ○ Progressive Myoclonic Epilepsy Panel (GeneDx)  
| | ○ Adolescent Epilepsy Panel (GeneDx)  
| | ○ Other (GeneDx)  

| If Courtagen, select panel type: | ○ epiSEEK Comprehensive Sequence Analysis for Epilepsy and Seizure Disorders (Courtagen)  
| | ○ epiSEEK Infancy and Childhood Epilepsy Panel (Courtagen)  
| | ○ Other (Courtagen)  

| If selected panel type as 'Other', specify panel name: |  

| Number of Genes on Panel |  
| Date Blood Drawn |  

| Gene Panel Result | ○ Positive/Pathogenic  
| | ○ Negative/Benign  
| | ○ VUS  

| If gene panel result is 'Positive/Pathogenic', specify gene and mutation: |  

If gene panel result is ‘Positive/Pathogenic’, specify the diagnosis or syndrome (if in result report):

If gene panel result is ‘VUS’, specify VUS: (and save report)

Relevant VUS(s):

The VUS is classified as:
- Not likely pathogenic (report states or there was further negative testing for recessive condition with one VUS)
- Uncertain
- Likely pathogenic

Results Review- Laboratory Results- Genetic Testing

(Panel test date = [date_blood])

Other Genetic Testing Ordered Before Panel Testing on [date_blood] (check all that apply)
- None
- Chromosomes
- Microarray (SNP microarray or array CGH)
- SCN1A testing
- Other single gene testing
- Whole exome sequencing
- Other panel testing
- Other

If selected 'Other panel testing' for Other Genetic Testing, specify panel:

If selected 'Other' for Other Genetic Testing, specify test:

If selected 'Other single gene testing', specify which gene(s):

Specify any abnormal genetic testing results other than panel results:

Results Review- Radiology- MRI

Brain MRI Classification (Most recent MRI before panel testing. If stable, look at previous MRI) (Panel test date = [date_blood])
- Normal
- Abnormal/Indicative
- Abnormal/Not Indicative
- Inconclusive
- Unclear- Needs further review
- Not available

MRI needs further review?
- Yes
- No

If Brain MRI results need further review, specify (copy most recent impression before panel testing):
**Problem List**

Structural Malformations (based on Problem List). Check all that apply:
- Cardiovascular
- Gastrointestinal
- Genitourinary
- Ophthalmological
- Otolaryngological (ENT)
- Neurological
- Musculoskeletal
- Other
- Unclear- Needs further review
- None

If Cardiovascular malformations, specify: ___________________________________________
If Gastrointestinal malformations, specify: ___________________________________________
If Genitourinary malformations, specify: ___________________________________________
If Ophthalmological malformations, specify: _________________________________________
If Otolaryngological (ENT) malformations, specify: _________________________________
If Neurological malformations, specify: ___________________________________________
If Musculoskeletal malformations, specify: _________________________________________
If ‘Other’ malformations or ‘Unclear-needs further review’, specify: ___________________

Other relevant features or findings: ________________________________________________

Does the patient have epileptic encephalopathy as a diagnosis code? (Problem List)
- Yes
- No

Does the patient have an autism spectrum disorder as a diagnosis code? (Problem List)
- Yes
- No

Does this patient have cortical visual impairment? (Problem List)
- Yes
- No

Does this patient have EDS hypermobile type or hypermobility syndrome? (Problem List)
- Yes
- No

**Demographics- Contact Info and Clinical Info**

Date of Birth

Sex
- Male
- Female

Ethnicity
- Hispanic
- Non-Hispanic
- Unknown

Race
- White or Caucasian
- Black or African American
- Asian or Pacific Islander
- American Indian or Alaskan Native
- Other
- Unknown
### Chart Review - Genetics

<table>
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<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seen Genetic Counselor?</td>
<td>Yes, No, Not available</td>
</tr>
<tr>
<td>Seen Geneticist?</td>
<td>Yes, No, Not available</td>
</tr>
<tr>
<td>If have seen geneticist, were dysmorphic features noted?</td>
<td>Yes, No, Not available</td>
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</table>

### Genetics Note / Media (Pedigree) OR Neuro Note

<table>
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<tr>
<th>Question</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Family History of Seizures/Epilepsy (at least one first or second degree relative)</td>
<td>Yes, No, Not available</td>
</tr>
<tr>
<td>Family History of Febrile Seizures (at least one first or second degree relative)</td>
<td>Yes, No, Not available</td>
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</table>

### Chart Review - Encounters

<table>
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<th>Question</th>
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<tbody>
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<td>Seen Neurologist?</td>
<td>Yes, No, Not available</td>
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### Head Circumference (Growth Chart or Neuro Note)

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<th>Options</th>
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<tbody>
<tr>
<td>Normal</td>
<td>Microcephaly (&lt; 3rd %ile)</td>
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</tbody>
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### Neurology or Genetics Note

| Epilepsy Syndrome BEFORE panel testing (if listed in neuro note) (Panel test date = [date_blood]) | |
| Age of Onset of Epilepsy | Less than 2 years old, 2 years old or older, Not available |
| If the age of onset of epilepsy is greater than or equal to 2 years of age, specify age of onset in YEARS | |
| If the age of onset of epilepsy is less than 2 years of age, specify age of onset in MONTHS | |
Seizure Types (check all that apply) (Panel test date = [date_blood])
- absence
- myoclonic
- tonic
- clonic
- atonic
- tonic-clonic
- focal
- epileptic spasms
- neonatal seizures
- temperature sensitive
- febrile seizures
- unclassified

History of Prolonged Seizures or Status Epilepticus? (seizures lasting longer than 5 minutes)
- Yes
- No
- Not available

Number of AEDs Tried up until panel testing (In Neuro note) (Panel test date = [date_blood])

---

**Development - Neuro or Genetics Notes**

Does the patient have hypotonia?
- Yes
- No

Does the patient have ataxia?
- Yes
- No

Developmental Delay?
- No developmental delay
- Developmental delay
- Not available

Age at testing in years (automatic calculation for developmental delay severity question) = date blood drawn - date of birth

If developmental delay is present, what is the severity?
- At least 2 yrs old at testing - nonverbal and nonambulatory at 2 yrs of age or older
- At least 2 yrs old at testing - verbal or ambulatory by 2 yrs of age
- Younger than 2 yrs old at testing, but have records for age 2 or older - nonverbal and nonambulatory at 2 yrs of age or older
- Younger than 2 yrs old at testing, but have records for age 2 or older - verbal or ambulatory by 2 yrs of age
- Younger than 2 yrs old at testing and no records available for age 2 yrs or older
- Not available

If developmental delay is present, when was the onset of the developmental delay?
- Onset before epilepsy onset
- Onset with or after epilepsy onset
- Not available

Developmental Regression?
- Yes
- No
- Not available
Neuro or Genetics Notes for parental testing/ management changes. For parental testing, search parents' names, phone #s, or updated pedigree.

If gene panel result is 'Positive/Pathogenic' or 'VUS', was there parental testing? (will only include the positive VUSs after classified)

- Maternal testing
- Paternal testing
- Both parents tested
- Neither parent tested/ Not available

If parental testing was performed, specify results of parental testing. Mutation is:

- De novo
- Maternal
- Paternal
- Multiple VUSs- maternal and paternal
- Unknown (including if only one parent tested)

If gene panel result is 'Positive/Pathogenic' or 'VUS', was testing performed on family members other than the parents after result received? (will only include positive VUSs after classified)

- Yes
- No
- Not available

If gene panel result is 'Positive/Pathogenic' or 'VUS', was there a change in medications after result received? (will only include positive VUSs after classified) (Panel test date = [date_blood])

- Yes
- No
- Not available

If gene panel result is 'Positive/Pathogenic' or 'VUS', was further diagnostic testing performed after result received? (will only include positive VUSs after classified) (Panel test date = [date_blood])

- Yes
- No
- Not available

Chart Review- Procedures- EEG

(Panel test date = [date_blood])

EEG Background Patterns (most recent EEG before panel testing)- check all that apply:

- Normal
- Burst Suppression
- Slow-mild
- Slow-moderate
- Slow-severe
- Hypsarrhythmia
- Not available

EEG Epileptiform Patterns (most recent EEG before panel testing)- check all that apply:

- None
- Focal
- Generalized/diffuse
- Multifocal (3 different areas involving both hemispheres)
- Not available

Seizure Types noted during EEG- check all that apply:
(look in description if type is unclear in impression)

- None
- absence
- myoclonic
- tonic
- clonic
- atonic
- tonic-clonic
- focal
- epileptic spasms
- neonatal seizures
- temperature sensitive
- febrile seizures
- unclassified
EEG needs further review?  

☐ Yes  
☐ No

If EEG needs further review, copy Impression: