In the United States Court of Federal Claims
OFFICE OF SPECIAL MASTERS

CHARLISE ELLIS, parent and next friend of X.G., a minor,	*	No. 13-336V
	*	Special Master Christian J. Moran
Petitioner,	*	
	*	Filed: September 6, 2018
v.	*	
	*	Entitlement, seizure disorder, genetic condition
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	
	*	
Respondent.	*	

Richard Gage, Richard Gage, P.C., Cheyenne, WY, for petitioner;
Darryl R. Wishard, United States Dep't of Justice, Washington, DC, for respondent.

PUBLISHED DECISION DENYING COMPENSATION[1]

Charlene Ellis is the mother of X.G., a boy with multiple health problems, which began before his birth.[2] At conception, he had a genetic mutation. When Ms. Ellis was pregnant with X.G., she became infected with the cytomegalovirus (CMV) and CMV can cause adverse consequences. Early in his life, before the eight-month vaccinations of concern here, X.G. had some evidence of developmental delay and he continues to suffer from delayed development.

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[1] The E-Government Act, 44 U.S.C. § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services), requires that the Court post this decision on its website. Pursuant to Vaccine Rule 18(b), the parties have 14 days to file a motion proposing redaction of medical information or other information described in 42 U.S.C. § 300aa-12(d)(4). Any redactions ordered by the special master will appear in the document posted on the website.

[2] The caption reflects that the minor's name has been changed to initials. This decision refers to him by these initials. When this decision quotes medical records, the term "X.G." is used even when his actual name appears in the medical record.

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Ms. Ellis does not claim that any vaccine caused X.G.'s delayed development. Rather, Ms. Ellis alleges that a set of vaccinations, most notably the diphtheria-tetanus-acellular pertussis (DTaP) vaccination, caused him to suffer a seizure disorder. Ms. Ellis's claim is grounded in the (undisputed) temporal sequence that the DTaP vaccination occurred one day before X.G.'s first seizure. To assist her in prosecuting her claim, Ms. Ellis retained a pediatric neurologist, Marcel Kinsbourne.

The Secretary does not agree that the DTaP vaccination affected X.G. adversely. For his part, the Secretary relies upon a practicing pediatric neurologist, Elaine Wirrell. Dr. Wirrell opines that either the CMV infection or the genetic mutation could have caused (and mostly likely did cause) X.G.'s seizure disorder. Dr. Wirrell further disputes the theory of causation.

The parties agreed to submit this matter on the papers. The better evidence is consistent with the Secretary's position. The Secretary has established that either the CMV infection or the genetic mutation was the likely cause of X.G.'s seizure disorder. This finding is consistent with the medical literature and consistent with the opinion of Dr. Wirrell. Dr. Wirrell is more qualified than Dr. Kinsbourne. Her reports are comprehensive, address points in depth, and are supported by medical literature. In contrast, Dr. Kinsbourne's reports overlook or skirt around issues and contain opinions not consistent with medical literature. Thus, the undersigned credits Dr. Wirrell's opinion rather than Dr. Kinsbourne's opinion. To the limited extent that the treating doctors have expressed opinions about the cause of X.G.'s problems, they align with Dr. Wirrell. Finally, Ms. Ellis has not established, on a more-likely-than-not basis, that the vaccination either caused or significantly aggravated X.G.'s seizure disorder.

I. Facts

A. Gestation, Birth, and Neonatal Course

X.G.'s very early medical history is reviewed in some detail because, as one of his doctors later said, his "prenatal and perinatal courses were complicated." Exhibit 45 at 76.

On January 6, 2010, Ms. Ellis went to an office of Planned Parenthood, seeking a pregnancy test. She reported that her last menstrual period was on November 9, 2009. Exhibit 1 at 12. (These dates help estimate stages of fetal

development.) The pregnancy test was positive for the child Ms. Ellis would name X.G.

1. Genetic Mutations

At conception, X.G. had a mutation in a gene known as MED13L and a mutation in a gene known as LMNA. Exhibit 58 at 11, 23.[3] As relevant to this case, the more significant gene is MED13L.

When the genetic testing was done in 2016, Ms. Ellis was tested, but X.G.'s father was not. The genetic testing on Ms. Ellis revealed that she did not have the MED13L mutation. The absence of genetic testing for X.G.'s father meant that Ambry Genetics could not determine whether X.G.'s "alteration occurred in a *de novo* fashion." Exhibit 58 at 14.

X.G.'s genotype was heterozygous, meaning he had different alleles. Exhibit 58 at 11; see also Dorland's Illustrated Medical Dictionary at 857 (32nd ed. 2012) (defining heterozygosity). X.G.'s alteration type was a missense. Exhibit 58 at 11. A missense mutation is one in which the genes encode a different amino acid. Dorland's at 1169.

Ambry Genetics classified X.G.'s genetic mutation as a "variant of uncertain significance." "Overall, the evidence suggests that the identified MED13L alteration is possibly the cause of the patient's clinical symptoms." Exhibit 58 at 11. The Ambry Genetics report references 11 articles about the MED13L gene.

After referencing some of these articles, Dr. Kinsbourne opined that "The likelihood of a child with a MED13L variant having seizures without further provocation is somewhat elevated relative to the general population, but is far from meeting the more-likely-than-not standard." Exhibit 59 at 2. Dr. Wirrell, however, took a different view. She stated "the literature provides supportive evidence that MED13L is in fact an independent risk factor for epilepsy." Exhibit KK at 1.

Based upon some of the material that Ambry Genetics cited, the Genetic and Rare Disease Information Center of the National Institutes of Health stated: "Other

[3] Although the mutations have been present in X.G. since his conception, they were not discovered until testing in 2016. Exhibit 58 (exome testing by Ambry Genetics).

features of MED13L haploinsufficiency syndrome include … recurrent seizures (epilepsy)." Court Exhibit 1001.

Notwithstanding this genetic mutation, Ms. Ellis's pregnancy appeared to continue normally for a while. See exhibit D (Dr. Wirrell report) at 2-3 for a detailed summary of events during the pregnancy. But, an ultrasound performed in the 28th week of the pregnancy revealed that fetal growth was less than expected. Exhibit 2.2 at 40-41 / pdf 5-6. Dr. Wirrell used this information to conclude that Ms. Ellis became infected with CMV before this ultrasound. Exhibit AA at 3.[4]

2. CMV infections

CMV infections are either asymptomatic or symptomatic with approximately 90 percent deemed asymptomatic. Exhibit C (Congenital cytomegalovirus, Medline Plus Medical Encyclopedia, U.S. National Library of Medicine, National Institutes of Health (Dec. 16, 2013), http://www.nlm.nih.gov/medlineplus/ency/article/001343.htm). Unfortunately, X.G.'s CMV infection fell into the rarer category of symptomatic infections. According to the Centers for Disease Control and Prevention, signs of an in utero CMV infection that may be present at birth include: "premature birth," "small size at birth," "small head size," and "seizures." Exhibit B (Congenital CMV Infection, Centers for Disease Control and Prevention (Dec. 16, 2013), http://www.cdc.gov/cmw/congenital-infection.html) at 1.

The severity of an in utero CMV infection depends upon many factors, including the time the virus is acquired. Exhibit G (Vlatka Mejaški Bošnjak et al., Malformations of Cortical Development in Children with Congenital Cytomegalovirus Infection – A Study of Nine Children with Proven Congenital Cytomegalovirus Infection, 35 Suppl. 1 Coll. Antropol. 229 (2011)) at 230. The time of initial infection is significant because of the stages of fetal development.

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[4] Similar to the discovery of X.G.'s genetic mutations in 2016, the doctors did not know that Ms. Ellis had a CMV infection until she gave birth to X.G. Importantly, the experts agree that X.G. suffered an in utero CMV infection. Exhibit 20 (Dr. Kinsbourne) at 1.

As to the timing of the CMV infection, there is no overt disagreement between the experts. As stated in the text, Dr. Wirrell places the CMV infection before the 28-week ultrasound. Although Dr. Kinsbourne wrote reports after this report from Dr. Wirrell, he did not propose a different date of infection or otherwise challenge Dr. Wirrell's opinion on this point.

Although the experts did not explain how the brain develops in utero as well as they could have, the referenced articles provide helpful background information. "Three distinct but overlapping processes are involved in the development of the cerebral cortex, namely neuronal and later, glial proliferation, neuronal migration and cortical organization." Exhibit 50 (Renzo Guerrini et al., Epilepsy and malformations of the cerebral cortex, 5 (Suppl 2) Epileptic Disord. S9 (2003)) at S10. "Neurons are formed from about 8 weeks gestational age until 16 to 20 weeks (exact timing is not clearly established); their migration to the cerebral cortex continues until about 24 to 26 weeks and is followed by a period of cortical organization." Exhibit EE (A. James Barkovich and Camilla E. Lindan, Congenital Cytomegalovirus Infection of the Brain: Imaging Analysis and Embryologic Considerations, 15 Am. J. Neuroradiol. 703 (1994)) at 709. Neuronal migration usually occurs in the second trimester and an injury in the second trimester may cause polymicrogyria. Exhibit 41 (Chapter 20, Viral, Protozoan, and Related Intracranial Infections in Joseph J. Volpe, Neurology of the Newborn 675 (3rd ed. 1995)) at 677.[5]

A symptomatic congenital CMV infection can cause various consequences. See exhibit W (Kathleen R. Fink et al., Neuroimaging of Pediatric Central Nervous System Cytomegalovirus Infection, 30 RadioGraphics 1779 (2010)). For X.G., the CMV infection probably caused two different problems: a migration disorder and microcephaly.

Migration disorder. An MRI from September 2012, when X.G. was approximately two years old, showed that he suffered from a migration anomaly. Exhibit 8 at 1-2; see also exhibit 18 (Dr. Kinsbourne's report) at 2. Migration disorders can be classified into different types, including polymicrogyria. Exhibit I (Ana Alarcon et al., Clinical, Biochemical, and Neuroimaging Findings Predict Long-Term Neurodevelopmental Outcome in Symptomatic Congenital Cytomegalovirus Infection, 163 (No. 3) J. Pediatrics 828 (2013)) at 830.

Migration disorders are associated with epilepsy. In one study, 19 patients had a migration disorder from a CMV infection and six of them suffered from epilepsy. Exhibit 35 (Yasuhiro Suzuki et al., Epilepsy in patients with congenital

[5] Polymicrogyria is "a developmental anomaly of the brain characterized by development of numerous small convolutions (microgyri), causing mental retardation." Dorland's at 1490. Later testing will show that X.G. suffered from polymicrogyria.

cytomegalovirus infection, 30 Brain & Development 420 (2008)) at 422 (table 2). In another study involving more than 300 patients, the researchers found that the most common clinical sequelae to polymicrogyria were epileptic seizures, which affected 78 percent of the patients. Exhibit 54 (Richard J. Leventer et al., Clinical and imaging heterogeneity of polymicrogyria: a study of 328 patients, 133 Brain 1415 (2010)) at 1415. These researchers presented a chart showing that of 132 patients with polymicrogyria and epilepsy, 91 patients had their first seizure between zero and 5 years. Id. at 1423 (figure 8). Another chart presents information about the age of presentation, which is not necessarily a seizure, in narrower intervals.

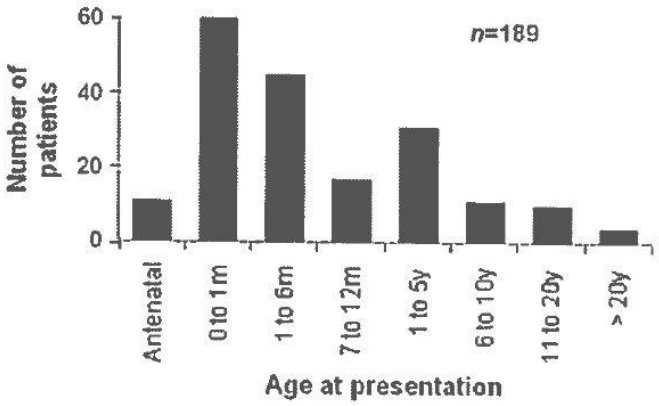

Figure 7 Distribution of ages at presentation in 189 patients with polymicrogyria.

Id. at 1423.

On the other hand, a study of 14 patients with symptomatic congenital cytomegalovirus infection found "no correlation between migration disorders … and epilepsy." Exhibit J (Renzo Manara et al., Brain magnetic resonance findings in symptomatic congenital cytomegalovirus infection, 41 Pediatr. Radiol. 962 (2011)) at 967.

Microcephaly. In a study of 102 patients with symptomatic congenital CMV infection, approximately half (54 patients or 53 percent) had microcephaly. Exhibit 21 (Suresh B. Boppana et al., Symptomatic congenital cytomegalovirus infection: neonatal morbidity and mortality, 11 Pediatr. Infect. Dis. J. 93 (1992)) at 93.

Microcephaly, in turn, is associated with epilepsy. For example, Manara and others, who had found no correlation between migration disorders in epilepsy,

concluded that "microcephaly is the most specific predictor for severe neurological sequelae." Exhibit J (Manara) at 963. They explained that microcephaly "can be considered an indirect sign of severe nervous tissue loss resulting from an early damage to the germinal matrix, which is known to be selectively vulnerable to CMV infection." Id. at 967.

Data about CMV infections and seizure disorders are found in at least two studies. Dr. Kinsbourne pointed to Boppana. Exhibit 20 at 1. In Boppana, of 105 patients with symptomatic congenital CMV infection, 7 (or approximately 7 percent) had seizures. Exhibit 21 (Boppana) at 95 (table 2). An increased frequency of seizures was reported by Alarcon and group. Exhibit I at 830. There, 8 of 23 (or 34 percent) children born with symptomatic congenital CMV infection had seizures.[6] Id. (table I).

3. Remainder of Prenatal Development and Birth

As previously noted, the May 28, 2010 ultrasound showed a slightly small fetus. The next ultrasound, which was performed on July 30, 2010, also showed a small fetus. Exhibit 2.2 at 38-39 / pdf 3-4; see also exhibit D (Dr. Wirrell's report) at 3 (summarizing results of this ultrasound). Following this ultrasound, Ms. Ellis was evaluated for intrauterine growth restriction on August 2, 2010. At this prenatal visit, the doctor, whose name is not legible, sent Ms. Ellis to the hospital "for delivery today." Exhibit 2.1 at 17; accord id. at 10.

The delivery summary records that X.G. was born on August 3, 2010. Exhibit 2.1 at 16. Due in part to deep decelerations, Ms. Ellis underwent an emergency Caesarean-section. Exhibit 3.3 at 126-27 / pdf 27-28. In the report from the operation, the doctor commented that there was a "true knot" in X.G.'s umbilical cord. Id. A handwritten note from a doctor who consulted in the Caesarean-section (Dr. Shibili) added that the cord was around X.G.'s chest. Exhibit 4.1 at 6.[7]

X.G.'s Apgar scores were 9 and 9. Exhibit 2.1 at 16. His birth weight was 2,435 grams (5 pounds 6 ounces). His length was 19 inches and his head circumference was 30 centimeters. Exhibit 4.1 at 4. The neonatologist ordered a

[6] The denominator is 23 because 3 of the initial group of 26 children died.

[7] Another record identifies Dr. Shibili as a neonatologist. Exhibit 2.1 at 16.

series of tests. Exhibit 4.1 at 6. As Dr. Wirrell outlines, many tests turned out normal. See exhibit D at 3-4.

However, one test showed abnormal results. X.G.'s urine tested positive for CMV infection. Exhibit 4.1 at 26. Again, because the CMV infection is so significant, it bears repeating that the experts agree that X.G. had a CMV infection in utero. Exhibit 20 at 1.

Because of X.G.'s intrauterine growth retardation, he was sent for an ultrasound of his head. The impression was "mild hydrocephalus." Exhibit 4.2 at 41 / pdf 6. Hydrocephalus is "a condition marked by dilation of the cerebral ventricles." Dorland's at 877. The interpreting radiologist's impression continued: "Cystic change is seen in the caudothalamic notch bilaterally consistent with subependymal germinal matrix hemorrhages, possibly in utero." Exhibit 4.2 at 41 / pdf 6.

In light of the detection of CMV, at discharge Ms. Ellis was directed to follow up with a pediatric neurologist and a pediatric ophthalmologist. Exhibit 4.1 at 5.

Before continuing to the remainder of X.G.'s medical history, it should be emphasized that X.G. was born with the two conditions that Dr. Wirrell identifies as the likely causes of his seizure disorder: a genetic mutation and a congenital CMV infection. When Dr. Kinsbourne wrote his first report, doctors did not know about the genetic mutation. Yet, at the time of Dr. Kinsbourne's first report, doctors had identified the X.G.'s in utero CMV infection. Without identifying the in utero CMV infection as the cause of X.G.'s problems, Dr. Kinsbourne still recognized that X.G. had problems before the vaccination. He wrote: "X.G. sustained severe prenatal cortical damage, which led to deranged development of cortex and secondary microcephaly." Exhibit 18 at 2. The unfortunate nature of this "severe prenatal cortical damage" became apparent in the ensuing months.

B. Medical Records from One Month (Sept. 2010) through Seven Months (March 2011)

On September 29, 2010, the Suffolk County Department of Health Services administered a set of vaccinations to X.G. Exhibit 14 at 52, 64 (vaccination chart). The handwritten notes suggest that this visit was relatively routine. Although the doctors ordered a repeat of the New York State newborn screen, the results were normal. Id. at 45, 52.

X.G. saw pediatric neurologists on October 28, 2010. One pediatric neurologist was a fellow, Julia Holtmann, and the other was the chief of pediatric neurology, Joseph Maytal. Dr. Holtmann, who primarily authored the report, described some parts of X.G.'s history including his premature birth. Dr. Holtmann stated the reason for the visit was the ultrasound, performed when X.G. was two-days old. Dr. Holtmann's report does not mention CMV. For X.G.'s history in the approximately three months since his birth, Dr. Holtmann recorded that he "has been well. He feeds well. He appears to hear and see well." Exhibit 7 at 1. In the neurologic examination, Dr. Holtmann stated that X.G. "makes good eye contact. He tracks 90 degrees. . . . He turns his head when his name is being called." Id. at 2. The physical examination showed that X.G. "was small but proportionate," with his length in the 25th percentile, his weight in the third percentile, and his head circumference in the third percentile. Id. The impression of the treating neurologists was that X.G. "currently appears to grow and develop appropriately." Id. They recommended another follow up with ultrasound in one month and planned to follow X.G. closely. Id. at 3.

X.G. returned to his pediatrician at Suffolk County on December 20, 2010. He was given a second set of vaccines. Exhibit 14 at 52, 64. The handwritten notes from this appointment are not easily read. Id. at 51.[8]

The next medical record suggests that the pediatrician (Dr. Malki) referred X.G. to a pediatric neurologist due to "intermittent arching of back" and, apparently, was requesting early intervention. Exhibit 7 at 11. This appointment took place at Schneider Children's Hospital, part of the North Shore-Long Island Jewish Health System on January 6, 2011. The pediatric neurologists noted that X.G. had a history of intrauterine growth retardation and germinal matrix hemorrhages with hydrocephalus. They did not mention CMV in their note. The

[8] X.G. was also treated at Mid-Suffolk Pediatrics and Ms. Ellis obtained a transcription of some handwritten records from Mid-Suffolk Pediatrics. Although the Mid-Suffolk Pediatrics material includes the Suffolk County December 20, 2010 record, the person who transcribed the handwriting also had difficulties understanding each word on the Suffolk Country record. See exhibit 42 at 3 (referencing page 11).

examination appears basically normal, except the motor exam says mild increased tone. They recommended early intervention and follow up in two months. Id.[9]

The record appears not to contain any report of a follow up appointment with Dr. Holtmann, Dr. Maytal, who saw X.G. on October 28, 2010, or the pediatric neurologists from Schneider Children's Hospital. Instead, the next visit appears to be a visit for routine care at Suffolk County on April 8, 2011.

C. DTaP Vaccination and Onset of Seizures (April 2011)

In this appointment, Ms. Ellis provided a history in which she described X.G. as "grasping, holding toys, throwing toys."[10] Exhibit 14 at 59. He turns his head, he recognizes people, and says about 4-6 words, including "Da, hi, Ma, what, [and] stop." The notes from the doctor's examination are not entirely legible. However, the doctor clearly has written "delayed development." Exhibit 14 at 59. The doctor also ordered another set of vaccinations. Id. X.G. received his third dose of the Pediatrix vaccine, which contains the diphtheria-tetanus-acellular pertussis (DTaP), inactivated polio, and hepatitis B vaccines. X.G. also received his second dose of haemophilus influenzae B, and his third dose of the pneumococcal conjugate vaccine. Id. at 64 (vaccination chart). Dr. Kinsbourne bases his causal opinion on the DTaP vaccine.

On the next day, April 9, 2011, an ambulance brought X.G. to the emergency department of Good Samaritan Hospital. His parents reported that except for receiving vaccinations yesterday, he was otherwise in good health. He came to the emergency department because "His eyes rolled back and he was shaking." Exhibit 5.2 at 152 / pdf 65. X.G. did not vomit, did not have a fever, and did not have a runny nose. Id. Under past medical history, the doctor has recorded "Born at 34 weeks GA [gestational age], unremarkable neonatal course." Id. The emergency department doctor admitted X.G. to the hospital.

In the hospital, another doctor (Oleg Goloubenko) obtained a slightly different history. Dr. Goloubenko's history begins with the vaccinations from a day earlier. He records that some vaccines were given for a third time and that for

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[9] Ms. Ellis attested that X.G. did not receive any early intervention services before April 2011. Exhibit 17 (affidavit, signed Jan. 6, 2014).

[10] The first two words of this line appear to read "crawling, position."

the first two doses, X.G. developed "low-grade fever." Exhibit 5.2 at 148 / pdf 61.[11] But, "today, no history of fever before he developed convulsions." Id.

Dr. Goloubenko recorded that X.G. was apparently in good health this morning. Then, in the afternoon, he became less active and smiled less. While in a car going shopping, "all of a sudden, he developed jerking movements in his upper and lower extremities, whole body associated with rigidity and eyes and head deviation to the right." "Convulsions lasted for two minutes and then stopped on [their] own."

In the emergency department, X.G. had a second episode and was given Ativan. Then, Dr. Goloubenko was present for a third episode, lasting 15-20 seconds. Id. In addition to ordering additional studies, Dr. Goloubenko requested a consultation with a neurologist. Id. at 150 / pdf 63.

One of the tests was a CT of the brain without contrast. The interpreting radiologist, Wan Kim, found "a diffuse mild dilation of the ventricles as well as a widened subarachnoid space as well as prominent sulci." Dr. Kim continued: "It could be physiological at this age group with underdeveloped CSF resorption function of the granulation. But, it appears to be unusually more prominent." Exhibit 5.2 at 143 / pdf 56.

On April 10, 2011, Mikhail Mirer, who is identified as a pediatric neurologist, consulted. Dr. Mirer stated that X.G.'s past medical history included birth at 34 weeks of gestational age, hydrocephalus, and a sonogram. Dr. Mirer also records that X.G. "was followed by [a] neurologist every two months since birth. As per mother there were no major concerns except the history of hydrocephalus. Child was not recently sick." Exhibit 5.2 at 166 / pdf 79.[12] Dr. Mirer conducted a physical examination. Dr. Mirer's impression was that X.G. is "an 8-month-old boy with history of prematurity, hydrocephalus, [and] new onset seizures." Id. at 167 / pdf 80. Dr. Mirer's plan noted that he had reviewed the CT scan from yesterday that "showed hydrocephalus [with] no other abnormalities." Dr. Mirer recommended continuing phenobarbital. Dr. Mirer noted that X.G. was

[11] The Suffolk County records appear not to mention the low grade fevers from the first two sets of vaccinations.

[12] As previously mentioned, it appears that neurologists saw X.G. twice: on October 28, 2010, and on January 6, 2011. These visits are approximately two months apart.

getting an MRI today and Dr. Mirer wanted the "radiologist to compare the old head sonogram to the recent brain imaging to see if there is a worsening of the ventricular dilatation. . . . The child will be scheduled to get the EEG as well." Id.

The MRI without contrast took place on April 10, 2011 and indicates that X.G.'s history included hydrocephalus. The radiologist's impression was that the MRI showed abnormalities. Specifically, "Lateral ventricular prominence out of proportion to the adjacent sulci, particularly at the temporal horns. This can reflect a degree of hydrocephalus although there is no current evidence of transependymal flow CSF to suggest an acute process. Findings may also potentially represent anatomic variation." Exhibit 5.2 at 145 / pdf 58.[13]

According to a record from April 22, 2011, X.G. was discharged on April 11, 2011. His parents were instructed to give him phenobarbital four times per day and to follow up with Dr. Mirer. Exhibit 5.1 at 3.

A handwritten note from Suffolk County Department of Health Services indicated that Ms. Ellis was having difficulty scheduling the follow up appointment with a neurologist. It appears that some doctors were not in her insurance company's list of providers. Exhibit 14 at 58.

These obstacles did not completely defeat X.G.'s parents in their pursuit of medical care for their child. On April 20, 2011, X.G. was seen by a pediatrician for Suffolk County. The chief complaint states: eight-month old male "seen [at] Good Sam. Hospital 4/9/11 for seizures. Here for [follow up] and lab work." The current medications included phenobarbital 1 tsp. 2x daily. The doctor's notes, which are again difficult to read, indicate that X.G. had had "no further seizures." The doctor also indicates that X.G. has an appointment with a pediatric neurologist on May 26, 2011, and the pediatrician wanted the results of laboratory studies to be faxed to Dr. Mirer. Exhibit 14 at 57. Although blood was drawn during the appointment on April 20, 2011 (see exhibit 14 at 60-62), the experts did not attribute any significance to these results.

Later, on April 20, 2011, at approximately 10:30 PM, Ms. Ellis brought X.G. to the Emergency Department at Southside Hospital. She informed the triage nurse that X.G. has been "having seizure activity every hour, lasting approx. 1 min

[13] Although Dr. Mirer had requested that the radiologist review previous studies, the report does not mention any of the previous imaging.

and then gradually lasting longer, since 430 pm." Exhibit 15 at 45. The triage nurse also reported a "similar episode last week, went to good sam given phenobarbital rx." Id. The emergency department doctor's notes state "[patient] was started on phenobarbital – compliant with meds." Id. at 46. The emergency department doctor gave Ativan and arranged for a transfer to Good Samaritan Hospital. Id. at 48.

A doctor at Good Samaritan Hospital, Mercy Drew, saw him and dictated a report at 4:50 AM on April 21, 2011. The history that Dr. Drew obtained was slightly different from the report given in the emergency department with respect to the events on April 20, 2011.

> As per mom the patient had a cough in morning so he [sic, "she" might have been intended] sent the child [to] the primary care physician who had seen the child and [the doctor] sent him home and on the way to get groceries the patient started to have a seizure, generalized tonic clonic involving all extremities, lasted about 10 minutes, no tongue biting, no incontinence, associated with eyes rolling, no vomiting. Seizure aborted on its own with postictal state. As per mom the patient had six more seizure episodes with one every hour and after the sixth episode she decided to go to South Side Hospital.

Exhibit 5.1 at 28.

For X.G.'s history a few weeks earlier, Dr. Drew's history is again a little different. Dr. Drew accurately records that X.G. was "first admitted to Good Samaritan PICU on the 9th of April 2011." She also states that he had "CT scan, MRI, and EEG done which revealed hydrocephalus." Id. As noted above, an EEG does not appear in the records from Good Samaritan. Nevertheless, the CT scan and MRI did reveal hydrocephalus. Dr. Drew further states that a neurologist prescribed phenobarbital in two divided doses. Dr. Drew states: "Mother did not follow up with Neurology and has not been giving medications consistently. She has given four days out of the ten days the baby has been out of the hospital because she did not like giving medication to the child she said." Id. Dr. Drew stated that the study of phenobarbital conducted at South Side Hospital "was 6.4, which is low. Normal level is supposed to be 15 to 40." Id. at 29. Dr. Drew conducted a physical examination, prescribed seizure precautions, admitted X.G. to

the PICU, and ordered labs, including phenobarbital levels in the morning. Id. at 29-30.

In the PICU, someone completed a "growth and development assessment." The form contains three columns, with one column containing various milestones. Each milestone is associated with two boxes that could be checked, one for "exam" and the other for "history." The person who filled out the form placed an X in the history box for every milestone through 6-9 months. There are no X's in the "exam" column. Exhibit 5.1 at 14.

Later on April 21, 2011, Dr. Mirer saw X.G. again. Dr. Mirer commented that: "Parents were given direct instructions about the dosage and the schedule of the medication, however, the parents decided to stop the medication because child remained seizure-free. On admission, the phenobarbital level was 6 which is below therapeutic." Id. at 32. Dr. Mirer's physical exam of X.G. seemed normal. His plan was to explain to the parents the importance of giving the phenobarbital, to schedule a follow up appointment, and to arrange for further communication if there were more seizures. Id.

X.G. underwent another CT scan of his brain on April 22, 2011. The interpreting radiologist, Dr. Kim, found no significant change from the CT scan on April 9, 2011. Id. at 24.

Later on April 22, 2011, X.G. was discharged. The discharge summary emphasized that Dr. Mirer "feels this is a compliance issue and the patient needs to take his phenobarbital twice a day on a daily basis without missing a dose. The patient also needs to follow up with a neurologist either himself or other neurologist at LIJ." Id. at 3.

On April 28, 2011, X.G. saw a pediatrician from Suffolk County. X.G.'s mother and father told Dr. Rodriguez that X.G. has a history of seizures and hydrocephalus. Under development, Dr. Rodriguez has noted that by history, he is "not sitting by himself." Exhibit 9 at 6. Dr. Rodriguez's plan was for X.G. to follow up with the service from Good Samaritan Hospital. Id.

D. Remainder of 2011

On May 5, 2011, X.G. returned to Schneider Children's Hospital of the North Shore-Long Island Jewish Health System, where he had been seen on January 6, 2011. The interval history indicates that X.G. has had "2 seizures since

last visit. [First] one was April 9, [second] one week later" and contains an accurate recitation about details. For development, the person obtaining the history recorded that X.G. "can roll, tracks, hears, can pull to sit but not sit up [with] support." For the neurological examination, the doctor indicated that X.G. had increased "tone throughout, moves [extremities] spont[aneously]." The pediatric neurologists recommended screening for hearing problems, an ophthalmologic examination, and a routine EEG. Exhibit 7 at 10.[14]

The EEG took place on May 23, 2011, and appears to have lasted for approximately 20 minutes. The doctors who interpreted the EEG, Dr. Maytal and Dr. Patricia Krief, stated that the EEG showed spikes, indicating "the presence of a potentially epileptogenic focus over the left central head region." Exhibit 7 at 17-18.[15]

In the Suffolk County records, there is a page titled "Pediatric Problem List." It contains four entries with the most recent being May 17, 2011. There, someone has written: "[history of] seizure 4/9/11. [Follow up] Ped. Neurology. No flu shot. [History of] seizures." Exhibit 14 at 66.[16]

On June 24, 2011, Ms. Ellis brought X.G. to the Southside Hospital Emergency Department because X.G. "had 3 seizures today." Exhibit 15 at 31. Ms. Ellis informed the doctor that X.G. takes phenobarbital for his seizures and "she is compliant." Id. at 32. After learning that X.G. had been transferred from Southside to Good Samaritan Hospital in April, the doctor arranged a transfer to Cohen Children's Medical Center. Id. at 31-35. The labs at Southside measured X.G.'s phenobarbital at 10.7, when the expected range was 15.0 to 40.0. Id. at 36.

At the Cohen Children's Medical Center, X.G. was examined by one doctor upon admission. Exhibit 16.1 at 8. It also appears that an EEG was performed on June 24, 2011, although an actual record from the EEG is not readily apparent. See exhibit 16.1 at 21 (indicating that X.G.'s father is amenable to an EEG),

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[14] The doctor's signature is not legible but it could read "Dr. Kan."

[15] The EEG took place at the Steven & Alexandra Cohen Children's Medical Center of NY, part of North Shore-Long Island Jewish Health Services.

[16] This notation appears to be the only record in which a treating doctor linked the seizures to a vaccination.

exhibit 16.2 at 66 / pdf 14 (indicating a video EEG was explained). The June 24, 2011 EEG showed left "central spikes, occ. [left] temporal spikes." Exhibit 16.1 at 9; accord exhibit 7 at 8.

A pediatric neurologist (Dr. Malbari) consulted. Her notes states: "Phenobarbital level found to be subtherapeutic. [Patient] now [status post] bolus and increase of phenobarbital dose. . . . [Patient] doing well, will [discharge] home after wife gets out of work. [Follow up] in clinic." Id. at 9. The discharge summary also states that X.G. was to follow up with neurology. Id. at 27.

This follow-up appointment took place with Dr. Malbari at Cohen Children's Medical Center. For history, Dr. Malbari mentions that X.G. had "microcephaly, epilepsy, IUGR? [intrauterine growth restriction], urine CMV (+)." He has been doing better after the dose of phenobarbital was increased. For development, X.G. babbles and rolls over, but he cannot sit without support. Exhibit 7 at 8.[17] The plan was to continue the phenobarbital, to have an appointment with an ophthalmologist, to request records from Good Samaritan Hospital, to repeat the MRI because of the focal findings on the EEG, and to follow up in three months. Id. at 9.

E. Records from 2012 through 2017

After the July 2011 visit at Cohen's Children's Medical Center, the routine medical records generally contribute relatively little information about the cause of X.G.'s seizures. Thus, although all the medical records have been reviewed, the remaining discussion omits some of them and summarizes others more briefly.

The seizure in June 2011 was X.G.'s last until April 2012, when he was being weaned from phenobarbital and was starting Keppra. See exhibit 14 at 14 (noting history), 32 (lab values); see also exhibit 7 at 4-5 (recommendation to change medication). In June 2012, X.G. went to Mid-Suffolk Pediatrics and the pediatricians started to catch X.G. up on his vaccinations by giving him varicella vaccine and Pentacel. Exhibit 14 at 8. Two months later, the pediatricians administered two more vaccines: hepatitis A vaccine and Prevnar 13. Id. at 6.

[17] In this context, Dr. Malbari mentions "EI [early intervention] evaluated yesterday." However, a report from any evaluation from early July 2011 is not readily apparent in the record.

On September 21, 2012, X.G. underwent an MRI of the brain without contrast at the North Shore-Long Island Jewish Health System. The radiologists listed X.G.'s history as a "2-year-old with seizures and microcephaly" and they did not have access to any previous MRIs. The MRI revealed: "A wide spread neuronal migration anomaly involv[ing] both cerebral hemispheres, with multiple areas of cortical thickening/cortical dysplasia, undersulcation, and blurring of the gray matter white matter junction." Exhibit 8 at 1. Because this MRI showed "neuronal migration," Dr. Wirrell and Dr. Harum discussed its significance extensively.

X.G. continued to experience seizures periodically. He had one on November 18, 2012 (exhibit 15 at 2), and another on January 10, 2013 (exhibit 10 at 8).

On April 16, 2013, X.G. had his first visit at the office of his new pediatricians, Weill Cornell Physicians. The first doctor to see him was Matthew Marks. Dr. Marks began his notes by stating that X.G.'s care was being transferred from Mid-Suffolk pediatrics, where he was last seen at 2 years old.[18] X.G. was now 32 months old. Dr. Marks recounts most of the salient events in X.G.'s life, although Dr. Marks did not mention the in utero CMV. See exhibit 13 at 22-23. Dr. Marks made various referrals, including a referral for gastrointestinal problems, neurology, child development, orthopedics, and dentistry. Id. at 24.

Dr. Marks's referral for an orthopedic consultation was to the Hospital for Special Surgery, which took place on May 9, 2013. Dr. Venu Nemani from the spina bifida and pediatric orthopedic clinic of the Hospital for Special Surgery saw him. The reason for the consultation was developmental delay and not walking. The history that Dr. Nemani obtained states that X.G.'s "birth history included an anoxic brain injury when the umbilical cord was found to be in a knot." Exhibit 13 at 6.[19] Dr. Nemani does not mention the CMV infection. Dr. Nemani notes that X.G.'s seizures began the day after receiving routine vaccines. After conducting a physical examination, Dr. Nemani determined that X.G. suffers from "global developmental delay after [an] anoxic brain injury at birth with some features of

[18] Dr. Marks provides additional context for this change in pediatricians. Apparently, Ms. Ellis lost her job on Long Island after Hurricane Sandy and moved her family to the Bronx. Exhibit 13 at 23.

[19] This appears to be the first reference to an anoxic brain injury due to the umbilical cord.

mixed tone cerebral palsy although he has not been formerly diagnosed with this by his neurologist." Exhibit 13 at 8. Dr. Nemani recommended a brace and prescribed physical therapy, occupational therapy and speech therapy. Id.

After the visit at the Hospital for Special Care, X.G. returned to Weill Cornell on May 24, 2013.[20] Dr. Ryan Kearney begins the history of present illness by noting that X.G. had "growth arrest at 34 weeks gestation in the setting of urine CMV+ culture." X.G. was "eventually born via stat-section for NRFHT [potentially, non-reassuring fetal heart tracing] thought secondary to true knot in the umbilical cord." Exhibit 45 at 7. Although Dr. Tierney mentions the seizures at approximately eight months of age, Dr. Tierney did not associate them with vaccinations. Id. at 1. Dr. Tierney assessed X.G. as suffering from "global developmental delays, hypotonic [cerebral palsy], hydrocephalus without shunting, seizure disorder on Keppra, [and] MRI evidence of dysgenesis." Dr. Tierney opined that X.G.'s "constellation of findings appears consistent with antenatal CMV infection and possible concomitant antenatal seminal event secondary to true knot in cord." Dr. Tierney recommended follow-up in two months. Id. at 10.

On August 9, 2013, X.G. returned to Weill Cornell. He saw a pediatrician and had lab work done. Exhibit 45 at 17, 21-25. On October 22, 2013, Dr. Marks saw X.G. again. Dr. Marks noted that X.G.'s immunizations were not up to date and that Ms. Ellis thought the immunizations precipitated his first seizure. Exhibit 45 at 26-30. In another visit on January 29, 2014, the doctor noted that Ms. Ellis was refusing more immunizations. Id. at 31-35.

On March 21, 2014, Matthew McCarthy, a pediatrician at Weill Cornell, saw X.G. Dr. McCarthy referred the family to pediatric genetics and ordered an EEG. Id. at 36-41.

A four-year old checkup took place on September 2, 2014, with Denver Brown, a pediatrician. Dr. Brown noted that Ms. Ellis did not show up for the EEG, which had been ordered in March, and that the referral for genetics was still outstanding. In X.G.'s history, Dr. Brown stated that he had a seizure about one month ago. Dr. Brown administered another dose of the DTaP and IPV vaccines and again referred X.G. to neurology and genetics. Exhibit 45 at 42-48.

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[20] Whether this visit was with a pediatrician, a neurologist, or a pediatric neurologist is not entirely clear.

A continuous video EEG from October 31, 2014, was abnormal. Id. at 76.

In March 2015, Ms. Ellis was working with a school to develop an Individualized Education Plan for X.G. in kindergarten. At this time, his developmental age was approximately 18 months. His seizures were "fairly well controlled on Keppra." Exhibit 45 at 60-64 (record from Jennifer Cross, pediatrician with specialty in child development).

It appears that Dr. Cross again referred X.G. for genetic testing because on May 24, 2016, Lilian Cohen, a medical geneticist at Weill Cornell, examined X.G. at Dr. Cross's request. Dr. Cohen recommended whole exome sequencing. Exhibit 58 at 29-33. Ms. Ellis consented to this genetic testing on June 15, 2016. Id. at 6.

Ambry Genetics issued its report identifying the alteration in the MED13L and LMNA genes on September 6, 2016. Exhibit 58 at 11, 23. X.G. was approximately 6 years old when these genetic mutations, which were present in him since conception, were discovered.

On March 24, 2017, a 32-minute video EEG was abnormal. The EEG showed abundant epileptiform discharges. Exhibit 45 at 83-84. On the day of the video EEG, another pediatric neurologist, Eric James Mallack, saw X.G. for his seizures. Dr. Mallack recorded that the "last seizure [was] 3 weeks ago, 4 months ago was last seizure prior to that." Dr. Mallack also stated that X.G. was diagnosed with MED13L syndrome based upon the Ambry testing. Id. at 75.

The records from March 24, 2017, are the most recent medical records filed.

II. Procedural History, including Expert Reports

Through her attorney, Ms. Ellis filed her petition on May 17, 2013. The relatively skeletal petition alleges that the April 8, 2011 vaccinations caused or significantly aggravated X.G.'s seizure disorder and developmental delays. Ms. Ellis periodically filed medical records until November 4, 2013, when she filed her statement of completion.

The Secretary reviewed this material in his report filed pursuant to Vaccine Rule 4, on November 22, 2013. The Secretary's summary of medical records noted that X.G. was born with microcephaly, suffered from intrauterine growth retardation, and tested positive for CMV. Resp't's Rep. at 2. The Secretary also identified medical records in which doctors were concerned about X.G.'s

development before he was vaccinated. Resp't's Rep. at 3-4 (citing Dr. Holtmann's October 28, 2010 record, the December 20, 2010 pediatrician's record, the January 16, 2011 referral to early intervention, and the April 8, 2011 diagnosis of developmental delay). Ultimately, the Secretary recommended against compensation, because Ms. Ellis did not meet her burden of proof. In particular, Ms. Ellis had not presented a report from a treating doctor who opined that a vaccination harmed X.G. and had not presented an opinion from a specially retained expert on the same subject. Resp't's Rep. at 11-14. Moreover, the Secretary identified the congenital CMV infection as an alternative explanation for X.G.'s developmental delays and seizures.

In the ensuing status conference, the parties discussed the issues in the case including whether Ms. Ellis would proceed on a significant aggravation theory. Ms. Ellis requested 75 days to produce an expert report because of the complicated issues.

Ms. Ellis filed the first report from Dr. Kinsbourne on May 12, 2014. Exhibit 18. This report is relatively brief, approximately 3 ½ pages long. Dr. Kinsbourne did not discuss the CMV infection. Dr. Kinsbourne also omitted any discussion of the medical records in which a doctor expressed concerns about X.G.'s development from October 20, 2010 through April 8, 2011. Dr. Kinsbourne opined that the acellular pertussis vaccination significantly aggravated X.G.'s pre-existing condition and caused him to suffer a severe refractory seizure disorder. Exhibit 18 at 4.

Ms. Ellis was instructed to obtain a supplemental expert report from Dr. Kinsbourne. Based upon Loving v. Sec'y of Health & Human Servs., 86 Fed. Cl. 135, 144 (2009), Ms. Ellis was directed to have Dr. Kinsbourne express an opinion as to how X.G. would have developed "but-for" the vaccination. Order, issued May 14, 2014.

Ms. Ellis responded by filing a 1 ½ page report from Dr. Kinsbourne. Dr. Kinsbourne stated that X.G.'s "brain injuries are consistent" with congenital CMV infections. With respect to the question of how X.G. would have developed but-for the vaccinations, Dr. Kinsbourne stated: "we cannot know whether X.G. would have joined the minority of affected children who become epileptic had he not receive DTaP vaccination that ushered in his seizure disorder." Exhibit 20 at 1.

Ms. Ellis was again instructed to obtain a supplemental report. Dr. Kinsbourne was expected to provide an opinion that differentiated disabilities due

to the congenital CMV infection from injuries induced by the vaccination. Order, issued June 25, 2014.

This process took a relatively lengthy amount of time. On September 3, 2014, Ms. Ellis's attorney represented that he was attempting to retain a specialist in pediatric infectious diseases with knowledge about CMV infections, Karen Harum. Mr. Gage represented that although Dr. Harum has good qualifications as a medical doctor, she did not have much experience as an expert in the Vaccine Program. To guide Dr. Harum and any other experts, the undersigned proposed a set of instructions. Order, issued February 3, 2015. On March 6, 2015, Ms. Ellis represented that Dr. Harum will opine about CMV exposure and Dr. Kinsbourne will address how the acellular pertussis vaccine can cause an encephalopathy – a neurologic topic.

Ms. Ellis filed the first report from Dr. Harum on May 1, 2015. Primarily because X.G. had an eight-month history of "mostly normal" development, Dr. Harum expected that X.G. would have had a much better outcome. Exhibit 30 at 3-4.[21] Later, Dr. Harum expanded on her opinions in a report that more closely tracked the structure set out in the Instructions. Exhibit 32.

Ms. Ellis also filed a supplemental report from Dr. Kinsbourne that more directly addressed the elements of a significant aggravation claim. Exhibit 38. In response to all these reports, the Secretary filed a single report from Dr. Wirrell. Exhibit D. Dr. Wirrell's first report was approximately 12 ½ pages. Her recitation of facts from the medical records was both detailed and accurate. See exhibit D at 2-8.

Dr. Wirrell's opinion was that X.G.'s congenital CMV infection caused a malformation of cortical development, which made the risk of developing epilepsy very likely (over 80-90 percent). Exhibit D at 13. In addition, Dr. Wirrell challenged many assertions made by Dr. Kinsbourne and Dr. Harum.

Dr. Wirrell brings out that an infant's brain is poorly myelinated. Myelination is a process that is most pronounced in the first 2-3 years of life. Until

[21] When Ms. Ellis obtained Dr. Harum's report, Ms. Ellis was alleging that the vaccination significantly aggravated X.G.'s seizure disorder and developmental delay. As discussed below, after X.G.'s genetic mutation was discovered, Ms. Ellis withdrew her claim regarding developmental delay. Consequently, some of Dr. Harum's opinions are no longer relevant.

myelination become sufficiently advanced, infants and toddlers cannot accomplish complex motor coordination such as walking and talking. Therefore, impairments in an infant's brain may not become apparent for several months or even 1-2 years. Exhibit D at 12.

The myelination process is one reason why Dr. Wirrell disagrees with Dr. Harum's assertion that X.G. was "nearly normal" at 8 months of age. In addition, in Dr. Wirrell's view, the "medical records provided contradict this statement, as there are several references to developmental delay, as well as the findings of jitteriness, increased tone, and tendency to arch his back, which are in keeping with early signs of motor delay." Exhibit D at 12.

Dr. Wirrell also addressed the temporal sequence in which X.G.'s first seizure closely followed his vaccinations. "[I]n children like X.G., with an underlying predisposition to epilepsy due to a severe brain malformation, intercurrent illness, fever or other psychological or physiological stressors may lower the seizure threshold, unmasking epilepsy. However, such illnesses or stressors are NOT the cause of the epilepsy, but simply lower the seizure threshold such that epilepsy is unmasked." Exhibit D at 12.

Dr. Wirrell's report provoked additional questions for Dr. Harum and Dr. Kinsbourne. See order, issued Sept. 11, 2015. While responses to those questions were pending, another status conference was held. In an October 9, 2015 status conference, the parties arranged for a schedule for the remainder of the case, although the parties did not maintain the schedule. The parties planned for a hearing to be held on March 8-9, 2016, with associated pre-hearing deadlines.

Dr. Harum answered the questions asked in the September 11, 2015 order in a report dated November 5, 2015. Dr. Harum addressed how the process of myelination affects MRI imaging. She stated:

> Because the brain MRI performed at 25 months of age identifies a migrational anomaly that was not identified on the brain MRI at 8 months of age, I am led to believe that the migrational anomaly is not that significant. Without the opportunity to see the brain MRI scans for comparison, and without the ability to judge the quality of the studies, I can surmise that the migrational anomaly identified at 25 months of age was of a milder nature, and

> only became visible after a more mature pattern of myelination had surpassed.

Exhibit 39 at 1-2. Dr. Harum's reference to seeing the MRI images started the parties on a relatively unproductive detour.

In a November 12, 2015 status report, Ms. Ellis contended that a "'battle ground' in this case is what the MRI's do, or do not, show." Thus, Ms. Ellis planned to obtain the MRI images, to transmit them to a pediatric neuroradiologist at Stanford University (Dr. Barnes), and to obtain a report from him. Ms. Ellis further proposed that after Dr. Barnes wrote a report, Dr. Kinsbourne would answer the questions posed in the September 11, 2015 order. Then, Dr. Wirrell would respond. Ms. Ellis further offered that all these steps could fit within the schedule leading to a hearing on March 8-9, 2016.

These plans, however, went awry. By January 6, 2016, Mr. Gage had obtained the MRI images from the April 10, 2011 MRI at Good Samaritan Hospital. Exhibit 5.2 at pdf 58. However, Mr. Gage was having difficulty obtaining images for the September 22, 2012 MRI from North Shore-Long Island Jewish Health System. Exhibit 8 at 2. Without the images, Dr. Barnes could not write his report. Thus, the schedule for the March 8-9, 2016 hearing was cancelled. Order, issued Jan. 7, 2016.

After more complications in obtaining the images from the 2012 MRI, Mr. Gage received them and sent them to Dr. Barnes. Dr. Barnes eventually told Dr. Kinsbourne that X.G. "had polymicrogyria, which is diffuse throughout both cerebral hemispheres." Exhibit 43 (report from Dr. Kinsbourne). Dr. Barnes also told Dr. Kinsbourne that he (Dr. Barnes) was overcommitted and could not write a report. Id.

In an August 30, 2016 status conference, the parties discussed the information that Dr. Barnes had provided via Dr. Kinsbourne. Dr. Barnes did not add meaningful information to the point Dr. Harum had raised in her November 5, 2015 report. There, Dr. Harum said that the migrational abnormality apparent on the 2012 MRI was not that significant in part because it was not apparent on the 2010 MRI. Exhibit 39 at 1. About ten months later, Dr. Barnes had not commented about any differences between the two MRIs, or, more precisely, Dr. Kinsbourne did not have any comment from Dr. Barnes in Dr. Kinsbourne's report. See exhibit 43.

Although Ms. Ellis decided not to obtain a report from a neuroradiologist, the Secretary wanted to give his expert, Dr. Wirrell, a chance to review the MRI images. She provided her opinion in a report filed as exhibit V on September 6, 2016.

Dr. Wirrell begins with a review of the more recent MRI, which was conducted on September 21, 2012. Dr. Wirrell interprets the MRI images as showing that X.G. has "diffuse polymicrogyria, maximal in the perisylvian regions, diffuse white matter loss, ventriculomegaly, and cerebral atrophy, all of which would be consistent with a CMV infection in the late second trimester." Exhibit V at 2.

Dr. Wirrell then reviews the earlier MRI, which was taken when X.G. was eight-months old on April 10, 2011. Dr. Wirrell explains developmental features of children, particularly children under one year of age, make obtaining clear information about brain disease difficult. Exhibit V at 2.

Dr. Wirrell further explains that "it is my opinion that the diffuse malformation of cortical development, along with associated white matter changes and cerebral atrophy, resulting from CMV infection in the late second semester, are the cause of [X.G.'s] epilepsy and developmental delay. These changes clearly predate his immunization." Id. at 3. Dr. Wirrell identifies two major risk factors in children with symptomatic congenital CMV that correlate highly with epilepsy: first, "underlying malformations of cortical development," and, second, "evidence of cortical atrophy, indicated by microcephaly and/or ventriculomegaly." Because X.G. had both risk factors, his risk of developing epilepsy was exceedingly high, and likely over 90%. Id. at 4.

Dr. Wirrell also repeated her previously expressed opinion about the temporal relationship between the vaccination and the seizures. "In children who are predisposed to epilepsy as a result of a severe structural brain abnormality, concurrent physiologic stressors, such as illness, fever, sleep deprivation or vaccination could temporarily lower the subthreshold even further, and this is likely the reason for X.G. presenting with the first seizure within a day of his vaccination.… In such cases, the vaccine or febrile illness is not causal, but simply unmasks the inherent predisposition to epilepsy. I do not believe that the immunization in any way exacerbated his underlying CMV infection, caused or exacerbated his underlying epilepsy or developmental delay, or exacerbated any structural changes to his brain." Id.

After the parties informally communicated mutually convenient dates for a hearing on August 23-24, 2017, the undersigned issued an order for that event. The order also required Ms. Ellis to submit updated medical records, Ms. Ellis to file a pre-hearing brief, and the Secretary to file a pre-hearing brief. Orders, issued Sept. 21, 2016, Oct. 28, 2016. On November 14, 2016, a status conference was held to discuss the content expected in the forthcoming briefs.

After the reminders about the need to file updated medical records, Ms. Ellis filed records from the Hospital for Special Surgery and Weill Cornell (exhibits 44-45) on April 21, 2017. Collectively, these medical records provide information about X.G. from May 2013 through March 2017.

Also, on April 21, 2017, Ms. Ellis filed her prehearing brief and supplemental reports from Dr. Harum (exhibit 46) and from Dr. Kinsbourne (exhibit 47). Dr. Harum's report is simplistic, consisting of three paragraphs. In the first paragraph, she discusses X.G.'s condition at the age of eight months, before he started to have seizures. In the second paragraph, she describes X.G.'s condition at the age of five years when he had "spastic tetraplegic cerebral palsy and an ongoing variety of seizures on Keppra." Exhibit 46 at 1. In its entirety, the final paragraph reads: "I conclude that X.G.'s condition is significantly worsened by the onset of seizures both in the short-term and in the long term." Id. Dr. Harum has no discussion about the CMV infection and has no discussion about the detection of the MED13L gene mutation (see exhibit 45 at 75). Therefore, this report carries little weight. See Pope v. Sec'y of Health & Human Servs., No. 14-78V, 2017 WL 2460503, at *7 (Fed. Cl. Spec. Mstr. May 1, 2017) (refraining from relying upon a report from Dr. Harum that "contain[ed] very little in the way of expert opinion or analysis").

Dr. Kinsbourne's April 21, 2017 report was partially in response to the September 10, 2015 order. In answering a question about whether the initial set of seizures caused any lasting damage, Dr. Kinsbourne also responded to Dr. Wirrell's opinion about a lower seizure threshold. Dr. Kinsbourne opined that: "It was the lowering of the seizure threshold that did the lasting damage." Dr. Kinsbourne explained: "It did so by setting in motion a sequence of events that resulted in severe epilepsy and severe mental retardation. 'Unmasking a predisposition' amounts to a two-hit process. Susceptibility is provoked into clinical reality by risk factor, the vaccinations. Both of the 'hits,' susceptibility and risk factor, are causal." Exhibit 47 at 3. Like Dr. Harum, Dr. Kinsbourne did not discuss the detection of the MED13L gene mutation.

The Secretary filed a response from Dr. Wirrell only one week later. Dr. Wirrell summarized the information from the updated medical records in exhibits 44 and 45. Exhibit AA at 1-2. Unlike Dr. Harum and Dr. Kinsbourne, Dr. Wirrell discussed the MED13L gene mutation. She stated that the patients with a mutation in their MED13L gene have an increased risk for epilepsy. Therefore, X.G. "has both congenital CMV with diffuse cortical malformations … and … MED13L syndrome which is unrelated to the congenital CMV. Both of these conditions contribute to his significant neurodevelopmental disabilities." Exhibit AA at 2.

On June 30, 2017, Ms. Ellis filed another report from Dr. Kinsbourne. He stated MED13L syndrome "is characterized by developmental delay independent of delay caused by CMV." Exhibit 57. Because X.G. has two independent factors associated with developmental delay, Dr. Kinsbourne could no longer attribute the developmental delay to vaccination. But, Dr. Kinsbourne asserted that "The MED13L syndrome does not feature epilepsy as one of its manifestations. Therefore I continue to adhere to the opinion that … X.G.'s seizure disorder was caused by the DTaP vaccination." Id.

Ms. Ellis filed a motion for a ruling on the record. She stated that she "will no longer be pursuing a claim for developmental delay." She asserted that "Petitioner has submitted all the evidence that petitioner believes the special master needs to issue a ruling in this case on the issue of the introduction of seizures." She requested that the special master allow the parties to submit briefs and to cancel the hearing scheduled for August 2017. Pet'r's Mot., filed July 5, 2017.

This motion was denied without prejudice. The undersigned noted that although Ms. Ellis had requested authority to issue a subpoena to obtain the genetic testing from Ambry Genetics, Ms. Ellis had not filed any reports from Ambry Genetics. In addition, the undersigned filed an excerpt from the website of the National Institutes of Health about MED13L syndrome. According to the Genetic and Rare Diseases Information Center, "other features of MED13L haploinsufficiency syndrome include… recurrent seizures (epilepsy)." Exhibit 1001 at 1. This information from the National Institutes of Health seemed inconsistent with Dr. Kinsbourne's assertion that "The MED13L syndrome does not feature epilepsy as one of its manifestations." Exhibit 57. Finally, the undersigned suggested that the parties may want to retain experts in the field of genetics. This suggestion was more directed to Ms. Ellis because "[i]n the undersigned's experience, Dr. Kinsbourne's credentials in the field of genetics are not particularly strong. See Snyder v. Sec'y of Health & Human Servs., 553 Fed.

App'x 994, 1001-02 (Fed. Cir. 2014) (finding in a SCN1A gene case that the special master was not arbitrary in refraining from crediting Dr. Kinsbourne's opinion)." Order, issued July 11, 2017. Accordingly, the undersigned invited additional evidence on the identified area.

On the day that the undersigned expressed interest in reviewing the report of genetic testing from Ambry Genetics, Ms. Ellis filed the report as Exhibit 58. As discussed extensively above, the testing by Ambry Genetics is the foundation for the finding that X.G. suffers from a MED13L gene mutation.[22]

Once Ms. Ellis filed the genetic testing from Ambry Genetics, Dr. Wirrell promptly presented a report on the MED13L gene. After citing articles, Dr. Wirrell asserted "the literature provides supportive evidence that MED13L is in fact an independent risk factor for epilepsy. While I believe that the diffuse cortical malformation places [X.G.] at [the] highest risk of seizures, the MED13L mutation further leads to a lowering of the seizure threshold, making it very likely that [X.G.] would have developed epilepsy, regardless of any vaccination." Exhibit KK (report filed July 19, 2017) at 1-2.

On August 1, 2017, a status conference was held to discuss the parties' plans for resolving the case. Ms. Ellis declared that she wanted to proceed with the theory that the vaccines contributed to X.G.'s seizures but she did not anticipate getting a geneticist. The parties agreed that after a time for submitting briefs, the case could be submitted on the papers. Thus the hearing scheduled for August 23-24, 2017 was canceled. Order, issued Aug. 2, 2017.

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[22] The circumstances under which Ms. Ellis filed the genetic testing are concerning. First, on November 16, 2016, Ms. Ellis was ordered to provide updated medical records as they became available. Although not spelled out, the undersigned expected that Ms. Ellis would request updated records soon after the order was issued. However, Ms. Ellis did not begin requesting records until March 8, 2017. Pet'r's Status Rep., filed Mar. 31, 2017. Then, after the Weill-Cornell records revealed that genetic testing took place, Ms. Ellis requested records via subpoena. Ambry Genetics produced the records under a cover letter, showing it mailed the records on May 24, 2017. Assuming that Ms. Ellis's attorney received the records within one week of mailing, Ms. Ellis's attorney possessed the records weeks before July 5, 2017, when the petitioner filed a motion for a ruling on record that was premised on an assertion that the special master had all the records necessary to make a decision. But, when Ms. Ellis made this motion, she had not filed the records from Ambry Genetics.

Dr. Kinsbourne addressed the MED13L mutation for a second time in a report dated August 10, 2017. Although Dr. Kinsbourne had earlier declared that "the MED13L syndrome does not feature epilepsy as one of its manifestations," exhibit 57 (emphasis added), Dr. Kinsbourne now said that "The likelihood of a child with a MED13L variant having seizures without further provocation is somewhat elevated relative to the general population, but is far from meeting the more-likely-than-not standard." Exhibit 59 at 2. Dr. Kinsbourne also asserted that "'seizures beget seizures.'" Id.

Dr. Wirrell generally disagreed with Dr. Kinsbourne. Exhibit MM. This report appeared to complete the parties' submission of evidence.

The parties then submitted a series of briefs. Ms. Ellis filed an initial brief, dated November 22, 2017, and a reply brief, dated February 5, 2018. The Secretary filed one brief on December 23, 2017.

After the case became ready for adjudication, the undersigned realized that Dr. Kinsbourne had not properly cited an article that apparently showed that from a group of 35 children with an MED13L mutation, six children had seizures.[23] Reza Asadollahi was the lead author on this paper. Due to its potential significance, the undersigned identified the correct paper, filed it, and permitted the parties to comment on its significance. Order, issued May 15, 2018; court exhibit 1002. The parties filed comments on May 29 and June 6, 2018. The case is (again) ready for adjudication.

III. Standards for Adjudication

A petitioner is required to establish her case by a preponderance of the evidence. 42 U.S.C. § 300aa–13(1)(a). The preponderance of the evidence standard requires a "trier of fact to believe that the existence of a fact is more probable than its nonexistence before [he] may find in favor of the party who has the burden to persuade the judge of the fact's existence." Moberly v. Sec'y of Health & Human Servs., 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010) (citations

[23] Strangely, Ms. Ellis cited this study in her November 22, 2017 brief (page 6) without noticing that the article that Dr. Kinsbourne had cited did not support the proposition for which Dr. Kinsbourne was citing it.

omitted). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Human Servs., 931 F.2d 867, 873 (Fed. Cir. 1991).

Distinguishing between "preponderant evidence" and "medical certainty" is important because a special master should not impose an evidentiary burden that is too high. Andreu v. Sec'y of Health & Human Servs., 569 F.3d 1367, 1379-80 (Fed. Cir. 2009) (reversing special master's decision that petitioners were not entitled to compensation); see also Lampe v. Sec'y of Health & Human Servs., 219 F.3d 1357 (Fed. Cir. 2000); Hodges v. Sec'y of Health & Human Servs., 9 F.3d 958, 961 (Fed. Cir. 1993) (disagreeing with dissenting judge's contention that the special master confused preponderance of the evidence with medical certainty).

As confirmed in W.C. v. Sec'y of Health & Human Servs., 704 F.3d 1352, 1357 (Fed. Cir. 2013), the elements of an off-Table significant aggravation case were stated in Loving. There, the Court blended the test from Althen v. Sec'y of Health & Human Servs., 418 F.3d 1274, 1279 (Fed. Cir. 2005), which defines off-Table causation cases, with a test from Whitecotton v. Sec'y of Health & Human Servs., 81 F.3d 1099, 1107 (Fed. Cir. 1996), which concerns on-Table significant aggravation cases. The resulting test has six components. These are:

> (1) the person's condition prior to administration of the vaccine, (2) the person's current condition (or the condition following the vaccination if that is also pertinent), (3) whether the person's current condition constitutes a "significant aggravation" of the person's condition prior to vaccination, (4) a medical theory causally connecting such a significantly worsened condition to the vaccination, (5) a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation, and (6) a showing of a proximate temporal relationship between the vaccination and the significant aggravation.

Loving, 86 Fed. Cl. at 144.

IV. Analysis

Four overlapping reasons indicate that Ms. Ellis is not entitled to compensation. The foundational reason is that Dr. Wirrell has persuasively explained that either the in utero CMV infection or the genetic mutation — two

factors that are independent from the vaccination — are likely causes of X.G.'s seizure disorder. This reason, in turn, is based upon the subsidiary determination that Dr. Wirrell has much more experience treating children who are like X.G. This background makes her opinions more credible than Dr. Kinsbourne. Next, the weight of opinions from treating doctors align with Dr. Wirrell's opinion. Finally, Ms. Ellis has not established that the vaccinations either caused X.G.'s seizure disorder or significantly aggravated his pre-existing conditions.

A. The Secretary established that X.G.'s seizures were likely due to his genetic mutation and congenital CMV infection.

When petitioners establish the Althen elements, the burden shifts to the Secretary to establish on a more-likely-than-not basis some alternative explanation for the condition affecting the vaccinee. Deribeaux v. Sec'y of Health & Human Servs., 717 F.3d 1363, 1367 (Fed. Cir. 2013). However, this burden-shifting framework does not cause compartmentalization of the evidence. As the Federal Circuit explained in a case involving a child with an SCN1A mutation, "in some cases a sensible assessment of causation cannot be made while ignoring the elephant in the room—the presence of compelling evidence of a different cause for the injury in question." Stone v. Sec'y of Health & Human Servs., 676 F.3d 1373, 1380 (Fed. Cir. 2012). In this situation, "the Secretary's burden [is] to show a sequence of cause and effect that is logical and legally probable, although causation by the unrelated factor need not be established to a medical or scientific certainty." Deribeaux, 717 F.3d at 1368.

Here, the Secretary has identified two factors that are likely to have caused X.G.'s seizure disorder: the congenital CMV infection and the genetic mutation. These factors are both independent of each other and independent of the vaccination.[24] Ms. Ellis did not persuasively rebut either factor. Of the two factors, the CMV infection is more significant.

[24] The presence of more than one alternative factor complicates the analysis because jurisprudence from the Federal Circuit in the context of an SCN1A mutation talks about a "sole substantial factor." See, e.g., Deribeaux, 717 F.3d at 1369. Yet, the Federal Circuit has also stated that the Secretary meets his burden regarding unrelated factors by identifying "a particular such factor (or factors) and presenting sufficient evidence to establish that it was the sole substantial factor in bringing about the injury." Bazan v. Sec'y of Health & Human Servs., 539 F.3d 1347, 1354 (Fed. Cir. 2008).

1. CMV Infection.

As discussed above, the CMV infection probably caused two different consequences for X.G.: a migration disorder (more specifically bilateral perisylvian polymicrogyria) and microcephaly. Dr. Wirrell submitted articles showing that both a migration disorder and microcephaly are associated with epilepsy. Based upon these studies and her own work, Dr. Wirrell estimated X.G.'s likelihood of developing seizures solely based on the infection at more than 80 percent. Exhibit D at 13, exhibit AA at 4. Ms. Ellis did not effectively undermine Dr. Wirrell's opinion.

Microcephaly. To start, Ms. Ellis did not present any argument regarding microcephaly and epilepsy. See Pet'r's Br. filed Nov. 22, 2017, at 5, Pet'r's Reply, filed Feb. 5, 2018.[25] This leaves Dr. Wirrell's point about microcephaly and epilepsy unrebutted.

Polymicrogyria. With respect to polymicrogyria Ms. Ellis did present an argument, just not a persuasive one. Ms. Ellis and Dr. Kinsbourne relied primarily upon a 2008 article by Leventer. Pet'r's Br. filed Nov. 22, 2017, at 5; exhibit 47 (Dr. Kinsbourne's report) at 2. In this article, Leventer and colleagues reviewed different types of malformations of cortical development ("MCD"). Court exhibit 1003 (Richard J. Leventer et al., Malformations of cortical development and epilepsy, 10 Dialogues in Clinical Neuroscience 47 (2008)).[26] The researchers were interested in malformation of cortical development because those abnormalities are associated with seizures. Leventer explained: "The seizures in MCDs arise as a consequence of either malpositioning of normal cortical neurons

[25] At best, Dr. Kinsbourne suggested that when X.G. was born and his head circumference was within the third percentile, X.G.'s microcephaly was marginal. Exhibit 47 at 2. As with much of Dr. Kinsbourne's opinions, this suggestion does not withstand scrutiny. While two articles defined microcephaly differently, under either definition, a head circumference in the third percentile is microcephalic. Boppana, an article Dr. Kinsbourne cited, set a cutoff at 10 percent. Exhibit 21 at 94. Suzuki used 5 percent. Exhibit H at 421.

Moreover, multiple doctors characterized X.G. as microcephalic. Exhibit 7 at 15, exhibit 8 at 1, exhibit 45 at 9.

[26] Although Ms. Ellis cited the 2008 Leventer article in her brief, apparently, she did not realize that she actually filed, as exhibit 54, a different article by Leventer published in 2010. The undersigned has reviewed both the article Ms. Ellis actually filed and the article that she intended to file.

or the presence of abnormal cortical neurons which results in abnormal cortical circuitry and a subsequent imbalance between the excitatory . . . and inhibitory . . . systems which would normally control electrical discharges and … seizures." Id. at 47-48.

The 2008 Leventer article discussed eight types of malformations of cortical development, including polymicrogyria and tuberous sclerosis.[27] Dr. Kinsbourne quoted a portion of the article on polymicrogyria: "The frequency of epilepsy in [polymicrogyria] is 60% to 85%, although seizure onset may not occur until the second decade, however usually between the ages of 4 and 12." Id. at 56. From this premise, Dr. Kinsbourne argues that "X.G.'s seizure onset was far earlier than would have been expected." Exhibit 47 at 2. Building further upon this point, Ms. Ellis contends that "While this statistic may go to damages, it clearly makes the possibility of the microgyria being the sole substantial factor on causing X.G.'s seizures remote." Pet'r's Br. at 5 n.1.

Dr. Wirrell answered this argument by relying upon the 2010 Leventer article that Ms. Ellis had actually filed as exhibit 54. Exhibit AA at 4. Unlike the 2008 Leventer article, which was about different types of cortical malformations, the 2010 Leventer article was about the specific type of cortical malformation affecting X.G. — polymicrogyria. Within the types of polymicrogyria, the relevant one is bilateral perisylvian polymicrogyria because that is the subtype X.G. has. Leventer and colleagues found that "bilateral perisylvian polymicrogyria had a significantly lower age at seizure onset than unilateral perisylvian polymicrogyria (median age of onset 12 months versus 99 months)." Exhibit 54 (Leventer) at 1424. A median age of onset of 12 months is much closer to X.G.'s actual onset (8 months) and effectively refutes Dr. Kinsbourne's assertion that X.G.'s onset was "far earlier" than expected.[28]

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[27] In the Vaccine Program, parents of children with tuberous sclerosis have unsuccessfully claimed that vaccines detrimentally affected their children. See Turner v. Sec'y of Health & Human Servs., 268 F.3d 1334, 1336 (Fed. Cir. 2001); Hanlon v. Sec'y of Health & Human Servs., 191 F.3d 1344 (Fed. Cir. 1999); but see Suel v. Sec'y of Health & Human Servs., 31 Fed. Cl. 1, 9 (1993).

[28] For the expected onset of seizures for polymicrogyria, Dr. Kinsbourne also relied upon a second article exhibit 50 (Guerrini, 2003). The structure of the 2003 Guerrini article shares some similarities with the 2008 Leventer article, which Guerrini co-wrote. In the context of discussing bilateral perisylvian polymicrogyria, Guerrini asserts that "Seizures usually begin between 4 and

2. Genetic Mutation.

In addition to the consequences of the CMV infection, Dr. Wirrell also proposed that the MED13L mutation could be the cause for X.G.'s seizures. However, in her view, the cortical malformation presented a larger risk than the genetic mutation. Exhibit MM.

Overall, the evidence that an MED13L mutation can cause seizures was persuasive. In other words, the Secretary met his burden of establishing, on a more-likely-than-not basis, that MED13L mutations can cause seizures.

Relying upon Dr. Wirrell and various articles, the Secretary argued that a mutation in the MED13L gene can cause seizures. Resp't's Resp., filed Dec. 23, 2017, at 10. In response, Ms. Ellis did not challenge that the MED13L mutation can cause seizures. Rather, as discussed in more detail below, Ms. Ellis's argument is that the interval between the vaccination and the onset of seizures (approximately one day) necessarily implicates the vaccination as contributing to the seizures. See Pet'r's Reply at 2-3.

Ms. Ellis's brief's apparent acquiescence to the point that a mutation in the MED13L gene can cause seizures is consistent with the final position of her expert. In Dr. Kinsbourne's last report, he opined "epileptic activity may occur but is not among the core attributes of disorders associated with MED13L variants. The likelihood of a child with a MED13L variant having seizures without further provocation is somewhat elevated relative to the general population." Exhibit 59 at 2.[29]

Taken with the opinions of Dr. Wirrell, Dr. Kinsbourne's acknowledgment that "epileptic activity may occur . . . with MED13L variants" means that a preponderance of evidence supports a finding that MED13L variants can cause seizures. Nevertheless, it is important to recognize that the evidence does not point in one direction. See Doe 11 v. Sec'y of Health & Human Servs., 601 F.3d 1349, 1355 (Fed. Cir. 2010) (the presence of contrary evidence does not make a special

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12 years of age." Exhibit 50 at S20. However, Guerrini provides no citation for this assertion and Guerrini is not consistent with the more recent study Leventer published in 2010.

[29] Dr. Kinsbourne continues: "but [the relative increase] is far from meeting the more-likely-than-not standard." Exhibit 59 at 2.

master's finding arbitrary). For example, Ambry Genetics stated that the genetic mutation was a "variant of uncertain significance" and the alteration is "possibly the cause of the patient's clinical symptoms." Exhibit 58 at 11. In addition, as Dr. Kinsbourne pointed out, in the studies of children with MED13L mutations, some — but not all — children suffer seizures. The existence of children with MED13L mutations but without seizures demonstrates that MED13L mutations do not always cause seizures.

The undersigned's experience in hearing other cases involving genetic mutations (see Lampe v. Sec'y of Health & Human Servs., 219 F.3d 1357, 1362 (Fed. Cir. 2000)) suggests that some of the differences in outcome could be explained by differences in the genetic mutation. Did the genetic mutation occur in a highly conserved region? X.G.'s genetic mutation "is conserved in available mammalian species except" five rodents, including the prairie vole and mouse. Exhibit 58 at 14. X.G.'s genetic mutation was a missense mutation in which one amino acid was substituted for another. How does this change in amino acids affect the structure, and, therefore, the function of the protein? Have researchers modeled MED13L mutations in animals, and, if so, what has been the outcome? These questions could have been answered, at least in part, by a geneticist, but both parties declined to retained geneticists. See Stone v. Sec'y of Health & Human Servs., No. 04-1041V, 2010 WL 1848220, at *17 (Fed. Cl. Spec. Mstr. Apr. 15, 2010) (listing factors a geneticist considers in "'looking for evidence of causality'"), mot. for rev. granted, 95 Fed. Cl. 233 (2010), compensation denied on remand, 2011 WL 836992 (Fed. Cl. Spec. Mstr. Jan. 20, 2011), mot. for rev. denied, 99 Fed. Cl. 187 (2011), aff'd, 676 F.3d 1373 (Fed. Cir. 2012).

The unanswered questions make the Secretary's case with respect to the genetic mutation less strong than the evidence presented in a case involving a mutation in a different gene, known as SCN1A. There, the Secretary presented the opinion of a board-certified geneticist and the undersigned characterized "the evidence about the causal role of the mutation" as "clear and convincing." Snyder v. Sec'y of Health & Human Servs., No. 07-59V, 2011 WL 3022544, at *12 (Fed. Cl. Spec. Mstr. May 27, 2011), mot. for rev. granted and decision reversed, 102 Fed. Cl. 305 (2011), reinstated, 553 Fed. App'x 994 (Fed. Cir. 2014). Yet, the undersigned noted that the Secretary's burden of proof is not "clear and convincing." Id. at *12 n.7. Thus, in the present case, the weight of the evidence regarding the significance of the genetic mutation may both (1) be less than the evidence presented in Snyder, and (2) exceed the preponderance of the evidence standard.

Of course, X.G.'s case is different from Snyder in at least one other very important respect: X.G. also suffered an in utero CMV infection. As explained above, CMV infections can cause a child to have polymicrogyria and microcephaly, two brain abnormalities associated with seizures. Taken together, the CMV infection and the genetic mutation means that the Secretary has presented a convincing case that the vaccination did not cause X.G.'s seizure disorder. In other words, the Secretary has met his burden of showing that the vaccination was not a substantial factor in the X.G.'s seizure disorder.

In an attempt to counter this finding, Ms. Ellis argued that Dr. Wirrell "has admitted that the April 8, 2011 vaccinations caused the onset of X.G.'s seizures." Pet'r's Pre-Hear'g Br., filed Apr. 23, 2017, at 14; accord Pet'r's Mot., filed Nov. 22, 2017, at 3 (citing exhibit D at 12 and Ex. V at 4). However, Ms. Ellis takes passages of Dr. Wirrell's reports out of context.

Dr. Wirrell actually said the following:

> In children like X.G., with an underlying predisposition to epilepsy due to severe brain malformation, intercurrent illness, fever or other psychological or physiological stressors may lower the seizure threshold, unmasking epilepsy. However, such illnesses or stressors are NOT the cause of the epilepsy, but simply lowers the seizure threshold such that epilepsy is unmasked.

Exhibit D at 12.

Dr. Wirrell expressed a similar opinion in her second report:

> In children who are predisposed to epilepsy as a result of a severe structural brain abnormality, concurrent physiological stressors, such as illness, fever, sleep deprivation or vaccinations could temporarily lower the seizure threshold even further, and this is likely the reason for X.G. presenting with the first seizure within a day of his vaccination. This is similar to the situation of a child with Dravet syndrome due to an SCN1A mutation, where the mutation results in a stronger predisposition to seizures, and the vaccination or febrile illness temporarily reduces that threshold even further, so

> that a seizure occurs. In such cases, the vaccine or febrile illness is not causal, but simply unmasked the inherent predisposition to epilepsy. I do not believe that the immunization in any way exacerbated his underlying CMV infection, caused or exacerbated his underlying epilepsy or developmental delay, or exacerbated any structural changes to his brain.

Exhibit V at 4.

Dr. Wirrell's distinction between a vaccination unmasking a structural malformation, which leads to an initial seizure, and a vaccination being the cause of a seizure disorder has been endorsed by persuasive Vaccine Program precedent (although other cases have rejected that distinction). Ms. Ellis also did not note the language distinction of a vaccination triggering (causative) versus a vaccination unmasking (non-causative), which, admittedly, has not been entirely consistent in the case law. With unmasking, seizures would occur earlier following a vaccination, but the individual's ultimate clinical course would remain the same. The multiple SCN1A cases are illustrative.

In one case, a girl received a set of vaccines, including the DTaP vaccine, at four months and suffered a seizure within seven hours. Faoro v. Sec'y of Health & Human Servs., No. 10-704V, 2016 WL 675491, at *3 (Fed. Cl. Spec. Mstr. Jan. 29, 2016), mot. for rev. denied, 128 Fed. Cl. 61 (2016). During the litigation, doctors discovered that the child had a mutation in her SCN1A gene and she was diagnosed with Dravet syndrome. Id. at *6. Ultimately, the special master found that the child's "SCN1A gene mutation is the reason she has Dravet syndrome and associated neurological symptoms." Id. at *2. The special master recognized that "Although [the child's] vaccinations may have caused a low-grade fever or otherwise triggered her first seizure, neither that initial seizure nor her vaccinations caused or significantly aggravated her Dravet syndrome and resulting neurological complication." Id. The special master also found that the Secretary proved "that the SCN1A mutation—a factor unrelated to the administration of the vaccines—is the agent solely responsible for causing [the girl's] Dravet syndrome and resultant neurological injuries." Id. at *28 (citing cases). This outcome was found to be in accordance with law and neither arbitrary nor capricious. Faoro v. Sec'y of Health & Human Servs., 128 Fed. Cl. 61 (2016).

While the SCN1A cases were decided relatively recently, an early case in the Vaccine Program also demonstrates that in appropriate cases, special masters

have found genetic disorders caused a seizure disorder. Matthew Jordan was born prematurely and suffered from multiple problems, including microcephaly and kidney problems. Jordan v. Sec'y of Health & Human Servs., No. 91-1344V, 1992 WL 300901, at *1-2 (Fed. Cl. Spec. Mstr. Oct. 2, 1992). When Matthew was approximately three-months old, a geneticist stated that Matthew suffered from a "genetic disorder that was inherited in an autosomal recessive pattern."[30] When Matthew was approximately six-months old, he received the third dose of the diphtheria-whole cell pertussis-tetanus (DPT) vaccine and experienced a seizure the evening of the vaccination. Id. at *2.

Matthew's parents brought a claim in the Vaccine Program, alleging that the DPT vaccination caused him to suffer a residual seizure disorder, which was, at that time, listed on the Vaccine Table. The Secretary attempted to rebut the presumption of causation by establishing a factor unrelated to the DPT vaccination, namely the genetic disorder, caused Matthew's seizure disorder. To meet his burden of proof, the Secretary presented opinions from a board-certified pediatric neurologist, Ihor Rak, and a board-certified geneticist, Leslie Raffel. They generally opined that the DPT vaccination did not cause Matthew's seizure disorder. In a passage foreshadowing Dr. Wirrell's opinion in the present case, the special master summarized the geneticist's testimony:

> To explain her prior written statement that DPT could have "unmasked" infantile seizures, Dr. Raffel testified that DPT and/or fever can lower the threshold for seizures. In fact, a febrile reaction to DPT in this case may have precipitated Matthew's first seizure. It was Dr. Raffel's opinion that without the DPT vaccine, Matthew would have had seizures anyway within a week or a month.

Id. at *8.

To counter the Secretary's evidence, Matthew's parents relied upon Dr. Kinsbourne. Much like the present case, Dr. Kinsbourne acknowledged that "a

[30] The geneticist reached this conclusion primarily because Matthew's older sister, Kara, suffered from similar problems. Matthew was being treated in 1989, before human genetic testing became widely available.

neuromigrational disorder raises the risks of seizures beyond the general population." Id. at *9. Nevertheless, Dr. Kinsbourne opined "the only possible cause for Matthew's seizure after the third DPT vaccination was the DPT vaccine." Id. at *8.

The special master found that the Secretary had met the burden of proof.[31] "Each child was prone to seizures and mental retardation. It may well be that the DPT vaccine acted as a trigger for seizures. However, testimony amply supports the claim that the children would have seized ultimately and that their condition would have been the same even absent the DPT vaccination." Id. at *12.

On a motion for review, the Court ruled that the special master's analysis was not arbitrary. Substantial evidence, including the disparity in the experience of the testifying experts, supported the findings. Jordan, 38 Fed. Cl. 148 (1993).

The reasoning in Jordan seems to fit Ms. Ellis's case. In contrast, in some cases in which special masters have rejected a theory that a vaccination simply unmasked an underlying propensity for a seizure, the reasoning is not persuasive. For example, a special master analyzed the Secretary's argument that a child may have had a genetic propensity to have a seizure disorder as presenting the question whether the genetic predisposition was "superseding." Sucher v. Sec'y of Health & Human Servs., No. 07-58V, 2010 WL 1370627 (Fed. Cl. Spec. Mstr. Mar. 15, 2010), at *43. However, in another SCN1A case, the Federal Circuit determined that once a special master found that the genetic mutation was the sole cause of the child's seizure disorder, the special master did not need to analyze potential superseding causes. Stone v. Sec'y of Health & Human Servs., 676 F.3d 1373, 1381 (Fed. Cir. 2012). Thus, following the method of analysis in Sucher seems inapt in the present case.[32]

Federal Circuit precedent also undermines the reasoning in another case in which the special master rejected the Secretary's unmasking theory. The parents

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[31] The special master's analysis begins by noting that "the training and clinical experience of Drs. Rak and Raffel exceed those of Dr. Kinsbourne in the areas of issue in this case: autosomal recessive disorders, neuromigrational defects, and epilepsy." Id. at *12. This was in 1992.

[32] Sucher is also distinguishable because testing for genetic disorders known at that time was negative. Id. at *15. As explained above, X.G. was found to have a genetic disorder, which is associated with seizures.

of Camille Priest alleged that a DPT vaccination caused their daughter to suffer injuries listed on the Vaccine Table: encephalopathy, residual seizure disorder, and hypotensive-hyporesponsive shock collapse. Priest v. Sec'y of Health & Human Servs., No. 95-134V, 1998 WL 928424, at *1 (Fed. Cl. Spec. Mstr. Dec. 7, 1998). The Secretary argued that an undefined metabolic disorder caused Camille's encephalopathy. In the view of the Secretary's experts, the DPT may have placed demands on Camille, but, she "would have had some different stress or intercurrent illness, which would have unmasked her underlying disorder." Id. at *5. The special master found this argument to be "pure speculation. Without knowing what metabolic disorder Camille purportedly has, respondent cannot state what her symptoms would be." Id. at *8.

Priest is different from the present case in at least two overlapping respects. First, after Priest, the Federal Circuit has held that the Secretary's burden on alternative factor is simply a preponderance of the evidence. Deribeaux, 717 F.3d at 1368. The special master's suggestion that the Secretary must "know" the metabolic disorder may indicate that the special master was requiring medical or scientific certainty. Second, although the Secretary could not identify the metabolic disorder in Priest, the two factors affecting X.G. before his vaccination are now known: an in utero CMV infection and a genetic mutation. This knowledge has taken the Secretary's argument out of the realm of "pure speculation." Dr. Wirrell has persuasively opined that seizures are a likely outcome for both factors.

Against Dr. Wirrell's opinion, Dr. Kinsbourne seems to demand proof at a level of scientific certainty. See exhibit 47 at 4 (stating whether X.G. would have developed epilepsy in the absence of cortical malformations was "unknowable"). If "knowing" is understood as meaning "absolutely certain," Dr. Kinsbourne is correct that no one knows whether X.G. would have developed seizures. However, as explained above, the law does not require this level of certainty and, for the reasons explained above, Dr. Wirrell's opinion meets the appropriate burden of proof.[33]

[33] Dr. Kinsbourne's opinion seems to resemble the position the Honorable Judge Newman from the Federal Circuit set forth in a dissent. See Oliver v. Sec'y of Health & Human Servs., No. 2017-2540, 2018 WL 3945586, at *8 (Fed. Cir. Aug. 17, 2018). However, this reasoning

B. Dr. Wirrell is more qualified than Dr. Kinsbourne.

By now, there should be no question that special masters may consider the qualifications and experience of the experts appearing before them. See, e.g., Copenhaver v. Sec'y of Health & Human Servs., 129 Fed. Cl. 176, 183 (2016) (citing cases).

It should also be apparent by now that Dr. Kinsbourne's experience is lacking. Although Dr. Kinsbourne greatly contributed to the field of pediatric neurology, his advancements stopped in 1991, when he stopped practicing pediatric neurology. See exhibit 19 (curriculum vitae). In other words, a person who completed a fellowship in pediatric neurology in 1992 (the year after Dr. Kinsbourne started a different occupation) would have been a practicing pediatric neurologist for more than 20 years by the time Dr. Kinsbourne wrote his first report in 2014. A 20-year practice would make this hypothetical pediatric neurologist an experienced pediatric neurologist. Yet, this is the amount of time during which Dr. Kinsbourne has not routinely treated patients as a pediatric neurologist.

The concerns about Dr. Kinsbourne's lack of current practice in pediatric neurology are neither novel nor, according to appellate authorities, arbitrary. In 2000, — nearly 20 years ago — a special master explained that she could not rely upon Dr. Kinsbourne because, in part, he "has had no clinical experience in ten years." Flanagan v. Sec'y of Health & Human Servs., No. 90–1126V, 2000 WL 1207256, at * 13 (Fed. Cl. Spec. Mstr. Aug. 4, 2000) (emphasis added), mot. for rev. denied, 48 Fed. Cl. 169, 173-74 (2000), aff'd sub nom. Turner v. Sec'y of Health & Human Servs., 268 F.3d 1334, 1338-39 (Fed. Cir. 2001).

The undersigned found that Dr. Kinsbourne's lack of current experience was a factor weighing against his opinion in a case in which the child-vaccinee was found to have an underlying genetic mutation. Snyder, 2011 WL 3022544, at *5-6, *21-22. When the Federal Circuit reinstated that decision, it ruled that the special master did not err in concluding that the Secretary's experts were better qualified than Dr. Kinsbourne.

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was contained in a dissent and the panel majority affirmed a decision finding that an SCN1A mutation was the sole cause of a seizure disorder.

So, too, in this case, Dr. Wirrell's qualifications in pediatric neurology are superior to Dr. Kinsbourne's qualifications.[34] To start with the obvious point, Dr. Wirrell actually practices pediatric neurology. She currently works at the Mayo Clinic as "a child neurologist with a subspecialty in pediatric epilepsy." Exhibit D at 1. Over the past five years, she has treated 150 children with malformations of cortical development and has treated four children with symptomatic congenital CMV infections and comorbid epilepsy. Id.[35]

Dr. Wirrell has also written articles and books on the topic of seizures in infants and children. One notable example is that Dr. Wirrell "co-authored the chapter of Epilepsies in Infancy for the most recent version of Swaiman's Pediatric Neurology: Principles and Practice." Exhibit D at 1. Dr. Wirrell describes the Swaiman treatise as "the most commonly utilized textbook by child neurologists," and special masters also have often cited Swaiman.

Thus, by background alone, Dr. Wirrell is better qualified to discuss the etiology of X.G.'s seizure problem. But, even within the confines of this case, Dr. Wirrell's opinions are more credible.

Problems with Dr. Kinsbourne's reports started in his initial report, which omitted any discussion of the CMV infection, despite his awareness that the CMV infection was an issue. The Secretary's review of the medical records identified the CMV infection and proposed the congenital CMV infection "was responsible for . . . [X.G.'s] development of seizures starting on April 9, 2011." Resp't's Rep.

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[34] As noted in the procedural history, Ms. Ellis also obtained reports from Dr. Harum. Dr. Harum's opinions are generally not relevant because she focused on the theory that the vaccinations contributed to X's developmental delay and Ms. Ellis has decided not to proceed on this theory. Nevertheless, the undersigned has also considered Dr. Harum qualifications. See exhibit 31 (curriculum vitae).

[35] Dr. Wirrell provided information about the number of patients she has treated for different conditions in response to an order, issued June 17, 2015. This order also solicited information about Dr. Kinsbourne's experience in treating patients with a CMV infection that caused a developmental delay. However, Dr. Kinsbourne did not answer this question. See exhibit 38. When Dr. Wirrell was providing this autobiographical information, X.G.'s genetic mutations were not known. Therefore, Dr. Wirrell did not provide any information about treating children with genetic disorders.

at 12-13. Later, the Secretary asserted that the congenital CMV infection "provides an alternate explanation for the onset of his seizures." Id. at 13.

However, Dr. Kinsbourne's recitation of facts involving X.G.'s birth was relatively short (two paragraphs) and did not mention the CMV infection at all. Dr. Kinsbourne opined: "The medical records do not offer any evidence for alternative causation of the seizures." Exhibit 18 at 4. Dr. Kinsbourne's statement, especially after the Secretary had already identified the CMV infection as an "alternate explanation," strains credulity.

Dr. Kinsbourne's second report acknowledges that X.G.'s "prenatal injury was most likely due to a congenital cytomegalovirus (CMV) infection." Exhibit 20 at 1. To discuss symptomatic CMV infections, Dr. Kinsbourne presented one article, exhibit 21 (Boppana). Boppana showed that children with symptomatic CMV infections suffer seizures at a rate "well above population expectations." Exhibit 20 (Dr. Kinsbourne's report) at 1. This information further undermines Dr. Kinsbourne's earlier assertion that there was no alternative explanation for the seizures.

Dr. Kinsbourne's analysis of the significance of the MED13L gene was similar. After information about the mutation was first presented in this case, Dr. Kinsbourne stated, without citing any authority, that the "MED13L syndrome does not feature epilepsy as one of its manifestations." Exhibit 57. The basis for this statement is not at all clear, as it is not consistent with material present in the case at the time when Dr. Kinsbourne offered this statement. The report from Ambry Genetics about X.G. states: "Other features reported in a subset of patients [with MED13L alterations] include . . . epilepsy." Exhibit 58 at 13.

After Dr. Wirrell identified articles linking the mutation to children with epilepsy (exhibit KK), Dr. Kinsbourne took a more nuanced view. He stated "epileptic activity may occur but is not among the core attributes of disorders associated with MED13L variants." Exhibit 59 at 2. The term "core attributes" makes Dr. Kinsbourne's opinion more accurate than his initial statement, which suggested that the MED13L syndrome was not associated with epilepsy at all.

Finally, Dr. Kinsbourne seemed to ignore X.G.'s migrational disorder. To review, the first MRI from April 20, 2011, was done when he was relatively young (less than one year old) and when his brain was still myelinating. This MRI showed some abnormal features. Exhibit 5.2 at 145 / pdf 58. The second MRI

from September 21, 2012, showed a "wide spread neuronal migration anomaly." Exhibit 8 at 1.

Dr. Kinsbourne appears not to have attributed any significance to the migrational disorder. It is true that Dr. Kinsbourne's first report mentions both MRIs (exhibit 18 at 1-2) and his second report acknowledges that X.G.'s prenatal brain injury caused "widespread cortical dysplasia" (exhibit 20 at 1). However, Dr. Kinsbourne's initial reports contain no discussion of the significance of the malformation of X.G.'s brain. From reading Dr. Kinsbourne's first two reports, it appears that this deviation in brain structure was no more than an incidental finding, unrelated to seizures.

Dr. Wirrell's view was different. She opined that X.G.'s structural abnormalities were relevant to his seizures. Citing four studies as examples, Dr. Wirrell offered: "Several studies have shown that neuroimaging abnormalities are highly correlated with development of epilepsy in children with congenital CMV." Exhibit D at 9. Later, Dr. Wirrell emphasized: "The vast majority of children with a diffuse, bilateral malformation of cortical development, most probably caused by symptomatic congenital CMV, would be expected to develop . . . epilepsy, which would have a high risk of being medically intractable." Id. at 10. After Dr. Wirrell reviewed the MRI images, she further confirmed her opinion: "the diffuse malformation of cortical development, along with associated white matter changes and cerebral atrophy, resulting from CMV infection in the late second trimester, are the cause of his epilepsy and developmental delay." Exhibit V at 3.

When Dr. Kinsbourne was ordered to address the studies connecting brain structural anomalies to epilepsy, the discordant approaches of Dr. Kinsbourne versus Dr. Wirrell were illuminated. Dr. Kinsbourne explained that in his earlier reports, he "was referring to the larger group of children with congenital [CMV], most of whom do not have cortical malformations. Dr. Wirrell referred specifically to those who did have such malformations." Exhibit 47 at 1. What Dr. Kinsbourne did not explain was why he chose to base his opinion upon children who were noticeably different from X.G. — children who did not have a cortical malformation. Thus, Dr. Kinsbourne has constructed an "apples to oranges" analysis, and Dr. Wirrell has constructed an "apples to apples" analysis.

Dr. Wirrell's analysis of the significance of X.G.'s MRIs is much more persuasive than Dr. Kinsbourne's skirting of the issue. In connection with the MRIs, it is worth noting that Dr. Kinsbourne never directly challenged Dr.

Wirrell's interpretation of them.[36] Instead, once Dr. Wirrell placed X.G.'s structural brain abnormalities front and center, Dr. Kinsbourne requested help from another doctor, who specializes in neuroradiology (Dr. Barnes). Although Dr. Kinsbourne deserves credit for recognizing the limits of his experience, this acknowledgment simply follows his lack of expertise. Unlike Dr. Kinsbourne, Dr. Wirrell seemed qualified to offer opinions about MRIs. See exhibit V at 2 (noting that Dr. Wirrell reviewed the MRI images).

Overall, because of the undersigned's awareness of Dr. Kinsbourne's lack of clinical practice, especially with respect to treating children with genetic disorders causing seizures, the undersigned suggested that Ms. Ellis should consider obtaining a report from a pediatric geneticist. A person with expertise in pediatric genetics could have helped Ms. Ellis. However, Ms. Ellis chose to stay with Dr. Kinsbourne. Order, issued July 11, 2017. Now, having chosen to rest her case with Dr. Kinsbourne, Ms. Ellis is left with an expert who has not practiced in more than two decades and who did not credibly grapple with the complex issues in X.G.'s case.

In short, Ms. Ellis has failed to present a persuasive case due, in part, to the relative weakness of her expert.

C. X.G.'s Treating Doctors Generally Did Not Associate the Vaccination with His Disabilities

Special masters should consider opinions treating doctors express. Capizzano v. Sec'y of Health & Human Servs., 440 F.3d 1317, 1322 (Fed. Cir. 2006).

Here, overall, the treating doctors tended not to blame the vaccination for X.G.'s seizures. Admittedly, relatively few treating doctors created medical records in which the doctors discussed the cause of X.G.'s seizures. But, most of their statements and their actions seem to suggest that the treating doctors thought that the vaccination did not harm him.

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[36] Ms. Ellis's other expert, Dr. Harum, raised issues about the technical feasibility of the two MRIs. See exhibit 39 at 1-3. However, Dr. Wirrell persuasively refuted these criticisms. Exhibit AA at 3, 7.

In early June 2012, X.G. had a seizure when his phenobarbital level was low. Exhibit 16.2 at 86 / pdf 34. Within a few days, Ms. Ellis and X.G.'s father brought X.G. to Mid-Suffolk Pediatrics to catch up on vaccines. In this context, the doctor recorded that X.G. had had a seizure the past weekend. The doctor also described X.G. as "well appearing." The doctor ordered an additional dose of Pentacel and a dose of the varicella vaccine.[37] The doctor planned to give additional vaccines at his next appointment in July. Exhibit 14 at 8; see also exhibit 42 at 1 (transcription of this record). The dose of DTaP was given, as the doctor ordered, on June 8, 2012. Exhibit 14 at 1 (vaccination record). Then, on August 8, 2012, X.G. received a fourth dose of Prevnar 13 and his first dose of the hepatitis A vaccine. Id.; see also exhibit 14 at 6 (note from office visit), exhibit 42 at 1 (transcription of this record).

As previously mentioned, after Ms. Ellis moved, she transferred X.G.'s care to Weill Cornell. See exhibit 13 at 22, exhibit 45 at 1-5. After obtaining a history, which was more or less accurate (it omitted the vaccinations) and conducting a physical exam, a pediatrician, Ryan Kearney, assessed X.G. as a two-year-old male with "global developmental delays, hypotonic [cerebral palsy], hydrocephalus without shunting, seizure disorder on Keppra, [and] MRI evidence of dysgenesis." Exhibit 45 at 10. With respect to the cause, Dr. Kearney stated: "His constellation of findings appears consistent with antenatal CMV infection and possible concomitant antenatal seminal event secondary to true knot in cord." Id. Although Dr. Kearney's linking of X.G.'s condition to his in utero CMV infection provides some support for Dr. Wirrell's opinion, Dr. Kearney's assessment cannot be dispositive because Dr. Kearney may not have been aware that the DTaP vaccination preceded X.G.'s first seizure by one day.

Dr. Kearney's colleagues at Weill Cornell continued to suggest that X.G. receive updated vaccinations. See exhibit 45 at 21-24 (Aug. 9, 2013 report from a pediatrician, Dr. Rae, who noted that the first seizure occurred "in the context of recently having received Pediarix"), 27 (Oct. 22, 2013 report from a neurologist, Dr. Marks), 32 (Jan. 29, 2014 report from a pediatrician, Dr. Godwin, recommending flu vaccine). However, Ms. Ellis refused some vaccinations, particularly the flu vaccination, as she believed that the flu vaccination precipitated the first seizure. Id. Ms. Ellis relayed that X.G.'s "old neurologist told him not to

[37] A month before the June 2012 appointment, the doctor at Mid-Suffolk Pediatrics had noted "vaccines → seizures (Apr 11)." Exhibit 14 at 9.

have [a flu vaccine] until he gets older." Id. This statement seems corroborated in an early record from Suffolk County in which a doctor appears to have written on May 17, 2011, "No flu shot [history of] seizures." Exhibit 14 at 66; accord exhibit 42 at 3 (transcription referencing page 11).

Ms. Ellis's resistance to authorizing more flu vaccines continued on September 2, 2014, when she brought X.G. for a four-year old checkup. The pediatrician, Denver Brown, wanted X.G. to receive more vaccines but Ms. Ellis refused the flu vaccine. Dr. Brown ordered and Ms. Ellis accepted a dose of Kinrix, which combines the DTaP and IPV vaccines. Exhibit 45 at 47-48.

The final record from a treating doctor relevant to the causation inquiry came after Ambry Genetics conducted genetic testing. On March 24, 2017, a pediatric neurologist, Eric James Mallack, stated that based upon whole-exome sequencing, X.G. was recently diagnosed "with MED13L Syndrome." Exhibit 45 at 82.

Dr. Mallack's report seems consistent with Dr. Wirrell's opinion that X.G.'s genetic mutation has affected him detrimentally just as Dr. Kearney's May 24, 2013 report about X.G.'s CMV infection is consistent with Dr. Wirrell's opinion. In contrast, Ms. Ellis has not identified any treating doctors — not even the author of the May 17, 2011 note — who linked X.G.'s seizures to the vaccination. See Pet'r's Pre-Hear'g Br. at 15-16.

The pediatricians' actions shed some light on their thinking. The pediatricians often recommended that X.G. receive more vaccinations. On two occasions, doctors gave X.G. another dose of the DTaP vaccine. Exhibit 14 at 8 (June 8, 2012) and exhibit 45 at 48 (Sept. 2, 2014). After encountering the supposedly inciting substance again, X.G. did not have a seizure immediately. Following the June 2012 DTaP vaccination, X.G. had another seizure about three months later. Exhibit 15 at 14. Similarly, after the September 2014 DTaP vaccination, X.G. had another seizure about one month later. Exhibit 45 at 49. Dr. Wirrell commented: "X.G. received a subsequent dose of acellular pertussis vaccine with no exacerbation of seizures or other symptoms." Exhibit AA at 5. Dr. Kinsbourne did not address this point. The lack of adverse response upon rechallenge tends to suggest that the DTaP did not cause the seizures. See McGuire v. Sec'y of Health & Human Servs., No. 10-609V, 2015 WL 6150598, at *24 (Fed. Cl. Spec. Mstr. Sept. 18, 2015) (discussing rechallenge and dechallenge).

Consequently, the medical records are against a finding that the vaccination contributed to X.G.'s seizure disorder. They more support a finding that either the in utero infection or the genetic mutation caused X.G.'s seizure disorder.

D. Ms. Ellis Did Not Persuasively Establish Either that X.G.'s Initial Seizure Caused his Seizure Disorder Or that the DTaP Vaccination Significantly Aggravated X.G.'s Condition

A finding that X.G.'s genetic mutation and his in utero CMV infection are likely causes of his seizure disorder necessarily implies that the vaccination did not cause his seizure disorder. See Bazan, 539 F.3d at 1353 ("It is certainly true that a finding that the administration of a vaccine was not a cause-in-fact of an injury necessarily implies that some other cause resulted in the injury"). However, for sake of completeness, the undersigned addresses two closely related arguments from Ms. Ellis. Ms. Ellis "alleges that the vaccines X.G. received on April 8, 2011 caused his seizure disorder. In the alternative, X.G. [sic] alleges that the vaccines significantly aggravated his preexisting condition." Pet'r's Mot., filed Nov. 22, 2017, at 2. These are taken up in turn.

1. Ms. Ellis Did Not Establish that the DTaP Vaccination Caused His Seizure Disorder

Preliminarily, setting out Ms. Ellis's claim is important. As just explained, she claims that the vaccination contributed to her son's "seizure disorder." "Seizure disorder" is different from the April 9, 2011 seizure. "Seizure disorder," in this context, means the series of seizures that X.G. has experienced intermittently after April 9, 2011.

A claim that the DTaP vaccination caused the April 9, 2011 seizure alone is pointless. If Ms. Ellis's claim the vaccine-induced injury terminated with the conclusion of the April 9, 2011 seizure, then she could not receive compensation. To qualify for compensation, Ms. Ellis must establish that the vaccination-caused injury lasted for more than six months. 42 U.S.C. § 300aa-11(c)(1)(D)(i); Santini v. Sec'y of Health & Human Servs., 122 Fed. Cl. 102, 109 n.12 (2015)(noting, in the context of an SCN1A case, that if petitioners established the vaccine caused only the initial seizure, they would not be entitled to compensation).

To establish the necessary six months of harm, Ms. Ellis attempts to argue that the April 9, 2011 seizure caused lasting consequences. Citing two relatively old articles, Dr. Kinsbourne opines "'seizures beget seizures.'" Exhibit 59 at 2

(citing exhibit 61 (Kang Chen et al., Febrile seizures in the developing brain result in persistent modification of neuronal excitability in limbic circuits, 5 Nature Medicine 888 (1999)) and exhibit 62 (W. Allen Hauser and Ju R. Lee, Do seizures beget seizures?, 135 Progress in Brain Research 215 (2002))). However, Dr. Wirrell effectively refuted this opinion. Exhibit MM at 2; see also Dodd v. Sec'y of Health & Human Servs., No. 09-585V, 2013 WL 3233210 at *14 (Fed. Cl. Spec. Mstr. June 5, 2013) (rejecting Dr. Kinsbourne's opinion that a single seizure permanently lowered a vaccinee's seizure threshold), mot. for rev. denied, 114 Fed. Cl. 43, 54 (2013); Deribeaux v. Sec'y of Health & Human Servs., No. 05-306V, 2011 WL 6935504, at *46 (Fed. Cl. Spec. Mstr. Dec. 9, 2011) (finding that petitioner did not establish that a severe seizure that progressed into status epilepticus caused any lasting damage), mot. for rev. denied, 105 Fed. Cl. 583 (2012), aff'd, 717 F.3d 1363 (Fed. Cir. 2013).

The consequence, if any, of X.G.'s April 9, 2011 seizure is critical to Ms. Ellis's claim that "the vaccines X.G. received on April 8, 2011 caused his seizure disorder." Pet'r's Mot., filed Nov. 22, 2017, at 2. The stronger and more persuasive evidence shows that X.G.'s on-going seizure disorder stems from either his genetic mutation or his in utero CMV infection.

2. Ms. Ellis Did Not Establish that the DTaP Vaccination Significantly Aggravated X.G.'s Preexisting Condition

Alternatively, Ms. Ellis presents the theory that the DTaP vaccination significantly aggravated his preexisting condition. Ms. Ellis elaborates: "the vaccinations triggered any pre-existing latency to become patent. The onset of seizures at such a young age is unquestionably a significant aggravation in X.G.'s condition." Pet'r's Mot., filed Nov. 22, 2017, at 3; accord Pet'r's Pre-Hear'g Br., filed Apr. 23, 2017, at 15.

In evaluating a claim that a vaccine significantly aggravated a preexisting disorder, special masters should consider the natural course of the underlying condition. Locane v. Sec'y of Health & Human Servs., 685 F.3d 1375, 1381 (Fed. Cir. 2013); Loving, 86 Fed. Cl. at 144 (placing burden on respondent after petitioners "successfully put forward such a prima facie case"); Gruber v. Sec'y of Health & Human Servs., 61 Fed. Cl. 674, 684 (2004) (discussing significant aggravation in the context of an on-Table claim).

Preponderant evidence does not support Ms. Ellis's case because Dr. Kinsbourne did not offer a persuasive opinion about how X.G. would have fared in

absence of the vaccination.[38] Dr. Kinsbourne's first report presented the opinion that the acellular pertussis vaccination significantly aggravated X.G.'s pre-existing condition and caused him to suffer a severe refractory seizure disorder. Exhibit 18 at 4. But, Dr. Kinsbourne did not explain how the vaccination made X.G. worse than he would have been. Accordingly, he was ordered to fill this gap. Order, issued May 14, 2014. Dr. Kinsbourne stated: "we cannot know whether X.G. would have joined the minority of affected children who become epileptic had he not receive DTaP vaccination that ushered in his seizure disorder." Exhibit 20 at 1. He was again instructed to present an opinion on this topic. Order, issued June 25, 2014. After this order, Ms. Ellis retained Dr. Harum and sought an opinion from Dr. Barnes, the neuroradiologist. Thereafter, it appears that the closest Dr. Kinsbourne came to comparing the real-world X.G. and the hypothetical X.G. is the statement "X.G.'s seizure onset was far earlier than would have been expected." Exhibit 47 at 2. Dr. Kinsbourne added: "the early onset of seizures induced by vaccinations deprived X.G. of intervening years of unimpeded cognitive development, thus degrading his ultimate cognitive capacities." Id. at 4.

Consistent with Dr. Kinsbourne's report, Ms. Ellis argues that (1) the vaccination caused X.G. to suffer his initial seizure earlier than he would have but for the vaccination, and (2) the earlier onset of seizures means a worse outcome. For the first proposition, Ms. Ellis and Dr. Kinsbourne relied primarily upon a 2008 article by Leventer, which indicated that the onset of seizures is often in the second decade. Pet'r's Br. filed Nov. 22, 2017, at 5; exhibit 47 (Dr. Kinsbourne's report) at 2. However, as explained above, the 2008 Leventer article provides an inapt basis for comparison to X.G. as this article studies children with many types of migration disorders. In contrast, the precise migration disorder that X.G. has (bilateral perisylvian polymicrogyria) was studied in the 2010 Leventer article. Exhibit 54. Thus, the 2010 Leventer article serves as a more accurate basis for comparison and that article indicates that median age of onset of seizures in children with bilateral perisylvian polymicrogyria is 12 months.

Moreover, bilateral perisylvian polymicrogyria is not X.G.'s only problem. He also suffered from microcephaly and a genetic mutation, both of which are

[38] Although Dr. Harum predicted how X.G. would have developed without the vaccination, exhibit 32 at 5 and exhibit 46, she offered this prediction before the discovery of the MED13L mutation. Ms. Ellis has not cited Dr. Harum as a source of information about X.G.'s hypothetical development.

associated with seizures. Consequently, the evidence does not weigh in favor of a finding that X.G. had his first seizure sooner than he would have had absent the vaccination. This finding, in turn, means that evaluating Ms. Ellis's second point — the earlier onset of seizures means a worse outcome — is not required.[39]

In contrast, Dr. Wirrell provided opinions that a natural consequence of an in utero CMV infections is a seizure disorder. She also opined that a MED13L mutation can cause seizures. On both points, Dr. Wirrell cited literature that supported her opinions. See exhibit AA at 3-4 (discussing studies on congenital CMV infections), exhibit KK at 1 (discussing MED13L studies).

It may be the case that the April 8, 2011 DTaP vaccination contributed to X.G.'s April 9, 2011 seizure. In one sense, X.G.'s condition on April 10, 2011, the day after the seizure, was worse than X.G.'s condition on April 7, 2011, the day before the vaccination. X.G. went from a boy who had never experienced a seizure to a boy who had experienced a seizure. However, in another sense, X.G.'s condition did not change. X.G. had been born with microencephaly, a migration disorder, and a genetic mutation. Ms. Ellis has not presented any evidence that the vaccine altered these physical traits. His development is consistent with the outcomes expected from these conditions.

V. Conclusion

The short interval between the vaccination and the onset of X.G.'s seizure disorder, by itself, could suggest that the vaccination caused the seizure disorder. But "temporal association is not sufficient, however, to establish causation in fact." Grant v. Sec'y of Health & Human Servs., 956 F.2d 1144, 1148 (Fed. Cir. 1992). Here, a sophisticated analysis by a knowledgeable and practicing pediatric neurologist has persuasively identified two forces, unrelated to the DTaP vaccination, that were substantial factors in causing X.G.'s seizure disorder: his congenital CMV infection and his genetic mutation. Ms. Ellis's expert could not counter this analysis.

[39] On this point, Dr. Kinsbourne cited supportive evidence. See exhibit 58 (An C. Jansen et al., Cognitive functioning in bilateral perisylvian polymicrogyria (BPP): clinical and radiological correlations, 6 Epilepsy & Behavior 393 (2005)).

Despite Ms. Ellis's sympathetic status as a mother of a disabled child, she is not entitled to compensation through the Vaccine Program. The evidence shows that the DTaP vaccine did not contribute to X.G.'s outcome.

The Clerk's Office is instructed to enter judgment in accord with this decision.

IT IS SO ORDERED.

s/Christian J. Moran
Christian J. Moran
Special Master