In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

* *		
NANCY BARCLAY, as the legal representative of her minor son, MATTHEW RAMIREZ,	*	No. 07-605V
	*	Special Master Christian J. Moran
Petitioner,	*	
	*	Filed: December 15, 2014
v.	*	
	*	Entitlement; significant aggravation;
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	Dravet syndrome; SCN1A mutation; severity (six-month) requirement;
	*	DTaP vaccine.
Respondent.	*	
* *		

Curtis R. Webb, Twin Falls, ID, for petitioner;
Voris E. Johnson, Jr., United States Dep't of Justice, Washington, DC, for respondent.

PUBLISHED DECISION DENYING COMPENSATION[1]

Nancy Barclay is the mother of Matthew Ramirez, a developmentally delayed child, who is 10 years old. When he was born, Matthew had a mutation in a gene, known as the SCN1A gene, that creates a particular type of sodium channel. This sodium channel, which is known as $Na_v1.1$, contributes to preventing seizures. When Matthew was approximately six months old, he received a set of vaccines, including a diphtheria-tetanus-acellular pertussis ("DTaP") vaccine. Later that day, Matthew suffered his first seizure.

[1] The E-Government Act of 2002, Pub. L. No. 107-347, 116 Stat. 2899, 2913 (Dec. 17, 2002), 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.

This first seizure is now recognized as the first manifestation of Dravet syndrome. People suffering from Dravet syndrome typically experience various types of seizures and developmental delay. The developmental delay can vary in severity from mild to severe.

Here, Ms. Barclay alleges that the DTaP vaccine significantly aggravated Matthew's Dravet syndrome. In other words, Ms. Barclay maintains that "but for" the DTaP vaccine, Matthew would have been less delayed. She seeks compensation through the National Childhood Vaccine Injury Compensation Program, 42 U.S.C. § 300aa—10 through 34 (2006). Her primary source of evidence is the opinion of Jean-Ronel Corbier, a pediatric neurologist.

The Secretary disagrees with Ms. Barclay's allegation. The Secretary has presented opinions from Max Wiznitzer, a pediatric neurologist, and Gerald Raymond, a neurologist and geneticist. Both Dr. Wiznitzer and Dr. Raymond maintain that the DTaP vaccination did not affect the degree to which Matthew is delayed. In their view, the SCN1A mutation was sufficient, by itself, to cause Matthew's outcome.

For the reasons discussed in more detail below in sections VI and VII, the Secretary's position is persuasive. Section VI discusses Ms. Barclay's claim that the DTaP vaccine significantly aggravated Matthew's Dravet syndrome. Ms. Barclay has failed to demonstrate that the DTaP vaccination affected Matthew in any meaningful way. Conversely, the Secretary has established that the SCN1A mutation most likely determined Matthew's outcome. Section VII reviews a separate deficit in Ms. Barclay's case: she failed to present preponderant evidence that any harm caused by the DTaP vaccine lasted more than six months as the Vaccine Act requires.

The simplest reason for this case's outcome is that Dr. Wiznitzer's and Dr. Raymond's opinions were more persuasive than the opinion from Dr. Corbier. Dr. Wiznitzer and Dr. Raymond explained the relevant medical concepts and showed how those principles were the foundations for their opinions. Dr. Corbier did not. Dr. Wiznitzer and Dr. Raymond supported their opinions with articles from peer-reviewed medical journals. Dr. Corbier often misinterpreted or misconstrued the most important articles. Finally, the academic and professional backgrounds of the Secretary's experts made them better qualified than Dr. Corbier to discuss the issues in the case.

I. Biographies of Witnesses

The parties rely upon the doctors whom they retained to explain the significance of events in Matthew's life. Thus, the following sections provide some context for the opinions discussed throughout this decision.

A. Dr. Corbier

Dr. Corbier graduated from medical school at Michigan State University. Exhibit 18 at 1. He completed his residency training also through Michigan State University and then went to Cincinnati Children's Hospital, and the University of Cincinnati, to do his neurology fellowship training. Tr. 12. In 2002, Dr. Corbier became board-certified in neurology with a special qualification in child neurology. Exhibit 18 at 2.

Dr. Corbier has been in clinical practice, as a full-time general pediatric neurologist, since 2000. For six years, he practiced in Montgomery, Alabama, before moving to Concord, North Carolina, where he has practiced since 2007. Tr. 12; exhibit 18 at 2-3. Through his practice, Dr. Corbier has "been able to see a lot of kids with a variety of neurological problems including epilepsy, and in severe cases, like Dravet and other conditions." Tr. 13. Dr. Corbier has treated "a handful" of patients with Dravet syndrome, some of whom he diagnosed himself. Tr. 92.

Dr. Corbier has written two self-published books about autism, but has not written any articles published in peer-reviewed journals. Further, because Dr. Corbier's professional work occurs in a clinical practice, his teaching responsibilities are limited to a small number of residents that circulate through a clinic. Tr. 91-92.

B. Dr. Raymond

Dr. Raymond graduated from medical school at the University of Connecticut. Tr. 221. Subsequently, he completed a residency in pediatrics at Johns Hopkins, and then went to Massachusetts General Hospital to study neurology with an emphasis on child neurology. Id. Dr. Raymond spent a year

abroad at the Université catholique de Louvain in Brussels, and then returned to Massachusetts General to complete a fellowship in genetics and teratology.[2] Id.

Dr. Raymond is board-certified in clinical genetics, as well as neurology with a special qualification in child neurology. Tr. 223. According to Dr. Raymond, fewer than ten other individuals hold dual certifications in these areas. Tr. 223. Dr. Raymond has been invited to give lectures in the field of neurogenetics, and has reviewed publications for several medical journals. Tr. 226. Further, Dr. Raymond has several of his own publications in the field of neurogenetics. Id.

Dr. Raymond is currently employed as a Professor of Neurology, and as Director of Pediatric Neurology, at the University of Minnesota. Tr. 220-21. In his position, Dr. Raymond conducts clinical research, focusing predominantly on the interaction between neurology and genetics. Tr. 222. In the clinical side of his practice, Dr. Raymond's patient population is drawn from individuals who have neurogenetic issues, including Dravet syndrome. Tr. 222-24.

C. Dr. Wiznitzer

Dr. Wiznitzer graduated from medical school at Northwestern University. Tr. 335. He completed a pediatrics residency at Cincinnati Children's Hospital, a developmental pediatrics fellowship at the Cincinnati Center for Developmental Disorders, and a child neurology fellowship at the University of Pennsylvania Children's Hospital of Philadelphia. Tr. 336. He then finished his education with a National Institutes of Health-funded fellowship in higher cortical functions in children at the Albert Einstein College of Medicine in New York. Id.

Dr. Wiznitzer is board-certified in pediatrics and neurology with special qualification in child neurology and in neurodevelopmental disabilities. Tr. 339. He has written approximately 60 articles published in peer-reviewed journals, and serves on the editorial boards of the Journal of Child Neurology and Lancet Neurology.

---

[2] Teratology is "the branch of embryology and pathology which deals with abnormal development and the production of congenital anomalies." Dorland's Illustrated Medical Dictionary 1883 (32d ed. 2012).

Since 1986, Dr. Wiznitzer has worked in Cleveland, Ohio, at Rainbow Babies & Children's Hospital as a child neurologist. Id. He currently is responsible for the outpatient practice, and also serves on the hospital's inpatient service. In his clinical practice, Dr. Wiznitzer commonly treats patients with epilepsy, and has treated 6-10 children with Dravet syndrome. Tr. 342-43. Dr. Wiznitzer is also an Associate Professor of Pediatric Neurology and International Health at Case Western Reserve University. Tr. 338.

Collectively, these doctors described the relevant concepts and principles underlying Dravet syndrome.

II. SCN1A Genes and Dravet Syndrome

At conception, the embryo receives a set of genes from its mother and father. Tr. 229. The set of genes may contain spontaneous mutations, meaning that neither the mother nor father carried the particular gene. These spontaneous mutations are said to arise de novo. See Dorland's at 1214; Tr. 169, 240.

Genes contain DNA. DNA is composed of sequences of four nucleotides: adenine, thymine, guanine, and cytosine. Billups-Rothenberg, Inc. v. Assoc. Reg'l and Univ. Pathologists, Inc., 642 F.3d 1031, 1032 (Fed. Cir. 2011). A sequence of nucleotides in a gene is transcribed and translated by a cell to produce a chain of amino acids. Tr. 231-33. In translation, the mRNA translates the amino acid sequence into a protein. Tr. 234. A set of three amino acids determines the type of protein being created. Tr. 233; see also Billups-Rothenberg, at 1032 (discussing genes, amino acids, and proteins).

Genes affect traits of individuals. Tr. 295. For example, eye color is determined by genes. Tr. 154, 296. Genes are expressed at certain times in a person's development. The medical term for how genes are turned on/off is methylation. Tr. 160, 294. For example, Huntington's disease is a genetically caused disease that appears later in life, usually during the fourth decade. Tr. 155, 158-59, 419-20, Dorland's at 536.

Mutations in genes can produce a variety of outcomes. Some mutations are benign, such as when one amino acid is substituted for a similar amino acid. At the other extreme, some genetic combinations may not be consistent with life. Tr. 284. Factors contributing to the extent to which a genetic mutation affects a person's health, if at all, include the type of mutation, the location of the mutation,

whether the mutation arose in a conserved region,[3] and whether the mutation was inherited or arose de novo. Tr. 236-40 (Dr. Raymond); see also Tr. 166-69 (Dr. Corbier).

The brain's development is largely determined by genes. In a child's first six months, neurons are growing rapidly. Tr. 157-58. Within the infant's brain, sodium channels evolve in the first six months of life. Humans contain a variety of sodium channels, which are part of cells that are incorporated into different organs. Tr. 241; Escayg at 1650; Lossin at 114.[4] Sodium channels regulate electrical excitability. Escagy at 1650. The channel is activated by membrane depolarization resulting in increased permeability to sodium ions. Id. Later, the sodium channel closes, decreasing the permeability of sodium ions and the membrane returns to resting level. Id.

As a fetus and shortly after birth, humans and other mammals rely on a sodium channel known as $Na_v1.3$. Tr. 362.[5] At around two-to-three months of age, a different sodium channel, $Na_v1.1$, becomes predominant. Tr. 300; see also Tr. 247-48. The $Na_v1.1$ form is primarily expressed in GABAergic interneurons. Tr. 242, 359. These neurons help maintain balance in the brain and an imbalance can lead to seizures. Tr. 243, 247.

A gene primarily responsible for the body's creation of the $Na_v1.1$ sodium channel is known as the SCN1A gene. Tr. 51, 259. The ensuing protein has more than 2000 amino acids. Lossin at 115. A mutation in an SCN1A gene can have a deleterious effect on a person. Dr. Raymond and Dr. Wiznitzer, as discussed below, opined that the SCN1A mutation in Matthew was the sole cause of his developmental delay because the mutation prevented the creation of a properly functioning sodium channel. Without a properly functioning sodium channel, it was inevitable that Matthew would have seizures. While Dr. Corbier did not

---

[3] A conserved region is an aspect that is preserved through evolution in many species. The repetition of genes suggests that changes are not easily tolerated. Tr. 265, 269.

[4] This decision cites to medical articles by the last name of the first author. A full citation is provided at the end of the decision.

[5] The discussion about sodium channels largely relies upon Dr. Raymond because Dr. Corbier did not know much about sodium channels. Tr. 160.

agree, he still acknowledged that "SCN1A mutation is not good." Tr. 165. Some people with an SCN1A mutation develop Dravet syndrome.[6]

Dravet syndrome is a clinical diagnosis, meaning doctors identify the illness by how the child presents. Tr. 255, 355-57. Typical presentation includes an onset, between four and eight months, of clonic or hemi-clonic seizures. The initial seizure is sometimes an episode of status epilepticus. In the second or third year of life, the seizures evolve into different types of seizures including myoclonic seizures, absence seizures, and complex partial seizures. Although the initial development is normal, by the time the child becomes a toddler, his or her development stagnates. Tr. 350-51, 358. After a doctor suspects a child suffers from Dravet syndrome, the doctor will order genetic testing to confirm. Tr. 255-56 (Dr. Raymond), 357 (Dr. Wiznitzer).

Dravet syndrome encompasses a range of severity. Tr. 357. Particular subtypes have been known as generalized epilepsy with febrile seizures (GEFS), severe myoclonic epilepsy – borderline (SMEB), and severe myoclonic epilepsy in infancy (SMEI) and these have been considered to be conditions occurring on a spectrum. Tr. 278-79.

To understand more about the consequence of an SCN1A mutation, researchers have studied animals with mutations in their SCN1A gene. While animal studies do not always inform a situation involving people, Isaac v. Sec'y of Health & Human Servs., 108 Fed. Cl. 743, 752-53 (2013) (quoting 2011 report from the Institute of Medicine), aff'd, 540 Fed. Appx. 999 (Fed. Cir. 2013), the experts agreed that rodents can model the human condition with regard to an SCN1A mutation. Tr. 110-11 (Dr. Corbier), 184 (discussion of Dr. Corbier's report), 208-09 (Dr. Corbier), 281-87 (Dr. Raymond). One advantage of animal models is that they reduce the influence of any environmental factors. Tr. 318-19 (Dr. Raymond). A group of researchers led by Dr. William Catteral have used rodents with SCN1A mutations in a series of experiments.

---

[6] Some SCN1A mutations are also associated with other conditions such as migraines. Tr. 191. The difference in outcome, as discussed in the text below, depends upon factors such as the location of the mutation and the nature of the mutation.

The mice in these experiments are known as "knock out mice." A portion of the mouse's SCN1A gene has been deleted (or knocked out). This produces a truncated mutation. Tr. 245-46, 282. The mice with this mutation display symptoms analogous to the symptoms of some humans with Dravet syndrome.

According to Dr. Raymond, the development of these mice is consistent with SMEI. In one study, researchers demonstrated that heating mice to replicate a fever provoked a seizure in genetically mutated mice only when the mice were a certain age. Tr. 245-46; Oakley at 4. Dr. Raymond explained that the delay in onset corresponds to the switch from $Na_v1.3$ to $Na_v1.1$. Tr. 247-48. Dr. Corbier agreed. Tr. 182, 532-36.

Another experiment discovered a different consequence of an SCN1A mutation. Unlike the Oakley experiment in which the mice were heated to provoke a seizure, the mice in the second experiment were not heated. They were left alone. Without the introduction of any outside (environmental) factor, the mice with a defective SCN1A gene had seizures spontaneously.[7] Yu at 1144; Tr. 248; see also Tr. 284-88. For the proposition that these knock out mice suffer seizures spontaneously, other researchers have cited the Yu article. See Catarino; Escayg (also citing Oakley), and Martin.

Another group of researchers, who are from Japan, explored the long-term consequence of the genetic mutation in the knock out mice. The researchers found that the defect in the $Na_v1.1$ "causes autistic behaviors and cognitive decline in addition to epileptic seizures" in the knock out mice "as well as in patients with Dravet syndrome." Ito at 29. As discussed by Dr. Raymond, Tr. 318-19, the researchers' conclusion was even stronger in dismissing environmental factors. They stated:

> Although it has been proposed that polytherapy and long-term use of anticonvulsants have potentials to affect the cognitive function and behaviors of Dravet syndrome patients, . . . our present results on mouse models suggest that the $Na_v1.1$ haploinsufficiency is fundamentally responsible for the behavioral and cognitive impairments

---

[7] Mice that had no SCN1A gene ("null mice") died within 15 days of birth. Yu at 1143.

> in Dravet syndrome patients and those impairments should occur in patients even without medications.

Ito at 39. Dr. Wiznitzer interpreted this article as well as an article by Ceulemans as showing the cause of the developmental problems is "not just the seizures themselves. The excitation / inhibition abnormality associated with the sodium channelopathy also impacts cognitive development in an independent manner from the epilepsy." Tr. 411-12.

III. Facts[8]

Matthew was born on November 16, 2004. Exhibit 3 at 3. Although no one knew this in 2004, Matthew was born with an abnormality in his SCN1A gene. Tr. 95 (Dr. Corbier), 263 (Dr. Raymond). The results of testing, which took place in 2009, established the foundation for the disputed issues in this case. The report from Athena Laboratories, Inc. stated: "This individual possesses a DNA sequence variant that is either a previously reported disease-associated mutation or is predicted to be a disease-associated mutation. This test result is consistent with a diagnosis of, or a predisposition to develop, SMEI or SMEB, the severe phenotypes associated with SCN1A mutations." Exhibit 13B at 8.[9] This loss caused a "frameshift" change in the amino acid. Id. at 9;[10] see also Tr. 93 (Dr. Corbier's discussion of results from Athena), 261 (Dr. Raymond's discussion of results from Athena). The frameshift mutation essentially prevents Matthew from producing the expected protein. Tr. 259 (Dr. Raymond), 389 and 426 (Dr. Wiznitzer).

---

[8] The parties generally accept the accuracy of medical records created close in time to the events being memorialized. Resp't's Posthr'g Br., filed Nov. 22, 2013, at 1.

[9] The precise mutation was a deletion of 10 base pairs at nucleotide position 3867-3876 / codon position 1289-1292. This type of mutation is known as a frameshift mutation.

[10] Later testing on Matthew's parents revealed that neither of Matthew's parents possessed this same mutation. Thus, Matthew's mutation is called a "de novo" mutation, meaning he did not inherit it. A de novo mutation "increases the probability that this predicted disease-associated mutation could be causative of a severe phenotype." Exhibit 13B at 8.

The SCN1A mutation did not appear to affect Matthew's initial development. At his first two well-baby visits, which occurred on November 30, 2004, and January 21, 2005, Matthew appeared well. His pediatrician did not note any concerns about his development. Exhibit 4 at 2, 4; see also Tr. 14. During these initial months, Matthew's brain was relying upon a fetal version of a sodium channel, $Na_v1.3$. Tr. 509; see also Escayg at 1650 (describing different types of sodium channels).

On March 25, 2005, Matthew had another well-baby appointment. He, again, appeared to be healthy. He received a set of vaccinations, including a second dose of the DTaP vaccine. Exhibit 4 at 2, 4.

Around 11:00 p.m., Matthew developed a fever. His mother gave him infant Motrin. Exhibit 5A at 12; see also exhibit 1 (Ms. Barclay's affidavit) at 2. Around 6:00 a.m., Ms. Barclay was feeding Matthew again. According to a nurse's report created that day, Matthew felt cool to his mother's touch. Exhibit 5A at 12.[11] At 6:10 a.m., Matthew had a "single isolated seizure. Seizure activity lasted (20 minutes as per mom). He lost consciousness." Id. at 10.

Matthew's parents brought him to a local emergency room. He had a fever on arrival and was still seizing. The doctor gave him Versed and his seizures abated within one minute. Exhibit 5A at 11, 13. The total time of Matthew's seizure was approximately 45 minutes. Id. at 19. The experts testified about Matthew's first seizure. Tr. 14 and 55 (Dr. Corbier), 424 (Dr. Wiznitzer). The doctor admitted him to the hospital.

After admission, doctors ordered a multitude of tests and most were negative. Among the studies that were performed on Matthew were an EEG, a CT scan of his brain, and an MRI. The EEG was normal. Exhibit 5A at 42-44. The CT was normal. Id. at 32. The MRI was essentially normal. Id. at 37-39. Although most were negative, one test with a positive result is arguably significant. An X-ray revealed infiltrates in both lungs. Id. at 36. This test led a doctor to

---

[11] Ms. Barclay's July 26, 2007 affidavit stated that Matthew "was again warm when I fed him at about 6:00 a.m." Exhibit 1 at 2. It is likely that the record created within one hour of the event, the nurse's note, is more accurate than the affidavit, which was created more than two years after the hospitalization. See Cucuras v. Sec'y of Health & Human Servs., 993 F.2d 1525 (Fed. Cir. 1993).

diagnose Matthew as having pneumonia, and his final diagnosis was "[f]ebrile seizures due to pneumonia." Id. at 18.[12]

Matthew remained in the hospital from March 26, 2005, until March 29, 2005. Exhibit 5A at 18 (discharge summary). When he was discharged, Matthew was administered amoxicillin and his final diagnosis stated febrile seizures due to pneumonia. Exhibit 5A at 18.

The testifying experts differed in their assessment of Matthew's health when he was leaving the hospital. Dr. Corbier opined that the March 26, 2005 seizure altered Matthew's brain. Tr. 15, 64-65. He held this opinion despite acknowledging that electroencephalogram and neuroradiological tests were normal. Tr. 97, 216. In Dr. Corbier's view, "an immature brain exposed to prolonged febrile seizure will then not have just an isolated event but will have further seizures." Tr. 99.

In contrast, Dr. Wiznitzer took these same normal test results as evidence that Matthew had returned to baseline. Tr. 423-25. Dr. Wiznitzer also emphasized that Matthew's problem was (and is) in his "wiring." As such, the March 26, 2005 seizure did not affect Matthew's brain. The "wiring" defect happened when Matthew was born with a defective SCN1A gene. Tr. 423.

On April 15, 2005, and April 25, 2005, Matthew had additional seizures. Tr. 15-16. Unlike the March 26, 2005 seizure, the April 15, 2005 seizure was unprovoked.[13] Exhibit 5B at 52-62; Tr. 17. An EEG performed on April 15 to April 16, 2005, indicated that Matthew had some slowing in the background and was interpreted as abnormal. Exhibit 6 at 25-26.

After the April 25, 2005 seizure, Matthew satisfied the criteria for being epileptic, which are two or more unprovoked seizures. Dorland's at 633, accord

---

[12] A pediatric neurologist stated that Matthew had "[f]ocal, prolonged seizures. Complex Febrile Seizure vs. Vaccine Reaction vs. Focal Seizure Disorder." Exhibit 5 at 22 (Mar. 27, 2005). This notation, which was before the discovery of the SCN1A gene, is the closest a doctor saying that Matthew reacted adversely to the vaccine.

[13] An "unprovoked" seizure is one that occurs without an identified trigger, such as a fever or head injury.

Tr. 349 (Dr. Wiznitzer). The doctors discovered the basis for Matthew's epilepsy in June 2009. Athena Diagnostics found that he had a mutation in his SCN1A gene. Exhibit 13B at 16.

Following this discovery, Matthew's treating doctors diagnosed him as suffering from Dravet syndrome. Exhibit 16 at 43-44. The testifying experts all agree that Matthew suffers from Dravet syndrome. Tr. 20 (Dr. Corbier), 227 (Dr. Raymond), 446 (Dr. Wiznitzer). The question in this litigation on which the experts disagree is whether the March 25, 2005 DTaP vaccine affected Matthew's development.

Since he started having seizures, Matthew has not developed normally. Various anticonvulsant medicines have not controlled his seizures. He experiences approximately ten seizures each month. He speaks sentences that are three or four words in length. He can walk but has difficulty catching a ball. Exhibit 40 at 1-2; Tr. 18.

IV. Procedural History

Ms. Barclay began this action when she filed a petition on August 14, 2007, alleging that the DTaP vaccine caused Matthew to suffer a severe seizure disorder and this seizure disorder led to developmental delays. Pet. 1-2. Ms. Barclay supported her allegations by filing some of the pertinent medical records.

In the initial status conference, held on September 20, 2007, the Secretary reported that she had informally requested additional medical records. Ms. Barclay's attorney also represented that he had sent the file to an expert for an opinion.

This expert was Marcel Kinsbourne, a pediatric neurologist. Dr. Kinsbourne summarized Matthew's medical history. Dr. Kinsbourne noted that his presentation "is consistent with the diagnosis of severe myoclonic epilepsy of infancy (SMEI) also known as Dravet's syndrome." Exhibit 9 at 2. Dr. Kinsbourne cited the National Childhood Encephalopathy Study, a study of British children who received the whole-cell diphtheria-pertussis-tetanus ("DPT") vaccine and Dr. Kinsbourne also explained why, a study involving whole-cell DTP provided meaningful information about a vaccine containing acellular pertussis. Id. at 3-5. According to Dr. Kinsbourne, a vaccine containing pertussis --- whether whole cell or acellular --- can cause a seizure disorder via three

mechanisms: (1) blocking G proteins at receptor sites, (2) increasing the production of a cytokine known as interleukin 1beta, and (3) prompting a fever that "may induce neurochemical changes that lower the seizure threshold." Id. at 3-4. Dr. Kinsbourne's opinion was that the DTaP vaccine caused Matthew's problems. Dr. Kinsbourne explained:

> Matthew Ramirez had status epilepticus within 24 hours of his DTaP vaccination. . . . There is no evidence in the medical records for any alternative causation either for the onset seizure or for the residual seizure disorder. . . . [I]t is my opinion, to a reasonable degree of medical probability that Matthew Ramirez's seizure disorder was caused by the DPT [sic] vaccine.

Id. at 5-6.

The parties discussed Dr. Kinsbourne's report in a March 4, 2008 status conference. The Secretary requested medical records about the extent of Matthew's developmental delay and any genetic testing. Ms. Barclay's attorney represented that there had not been any genetic testing for Matthew.

The Secretary filed her report, pursuant to Vaccine Rule 4, on May 5, 2008. The Secretary reviewed the medical records and noted that although a doctor had recommended genetic testing, the exhibits did not contain the results of any genetic testing. Resp't's Rep't at 4 n.2 (citing exhibit 5 at 115, 120). The Secretary also argued that Dr. Kinsbourne's opinion was not reliable. To support her criticism of Dr. Kinsbourne, the Secretary relied upon the report of Dr. Wiznitzer. Id. at 10-11.

Dr. Wiznitzer accepted the diagnosis of SMEI, although he recommended that Matthew be tested. Exhibit A at 3, 6. In Dr. Wiznitzer's view, "SMEI is genetically determined." Id. at 3. He also maintained that "there is no evidence for aggravation of an SCN1A gene mutation by environmental factors." Id.

In addition to the emphasis on genetics, Dr. Wiznitzer challenged the potentially causal mechanisms identified by Dr. Kinsbourne. Dr. Wiznitzer disputed the reliability of the G-protein theory and the interleukin 1beta theory. He asserted that the NCES data did not assist Ms. Barclay because it studied a whole-cell pertussis vaccine, which Matthew did not receive. Id. at 4-5.

Dr. Wiznitzer addressed Matthew's fever after the DTaP vaccine. In Dr. Wiznitzer's view, the cause of this fever was pneumonia. Dr. Wiznitzer opined that, in any event, the initial post-vaccination fever did not affect Matthew's development because "children with SMEI always manifest the disorder" even if they do not have a fever. Id. at 5.

A status conference was held two days after the Secretary filed her Rule 4 report and Dr. Wiznitzer's expert report. The Secretary continued to press for the submission of additional medical records about Matthew and his development, especially the results of any genetic testing. Order, filed May 8, 2008 at 1. Ms. Barclay's counsel aptly condensed the issue: do genes make a person develop epilepsy or do genes make a person vulnerable to developing epilepsy? Id. To answer this question, Ms. Barclay's attorney stated that he would seek a supplemental report from Dr. Kinsbourne, although Dr. Kinsbourne's schedule, which included testifying in the autism omnibus cases, would probably prevent a prompt response. Id.

Approximately 18 months passed during which Ms. Barclay filed successive motions for enlargement of time and status reports. On October 5, 2010, Ms. Barclay filed pediatric neurology records including the Athena Diagnostics Report. Exhibit 13B. As discussed throughout this decision, Athena identified a mutation in Matthew's SCN1A gene. Id. at 16.

At the ensuing status conference, the parties discussed possible next steps. Options included obtaining a supplemental report from Dr. Kinsbourne and waiting for additional developments in other cases involving mutations in an SCN1A gene.[14] In a December 15, 2010 status report, Ms. Barclay stated "[t]he Petitioner would prefer the proceedings in this case be stayed pending the resolution of the appeals in Stone and Hammit."

---

[14] On four occasions, Dr. Kinsbourne has testified that vaccines caused an injury in children with an SCN1A mutation. On May 14-15, 2009, Dr. Kinsbourne testified at a combined hearing for both Stone and Hammitt, and on October 8, and 9, 2009, he testified at a combined hearing for Snyder and Harris. Mr. Webb represented the petitioner in Hammitt. Hammitt v. Sec'y of Health & Human Servs., 07-170V, 2011 WL 1135878, at *1 (Fed. Cl. Spec. Mstr. Mar. 4, 2011), mot. for rev. denied, 98 Fed. Cl. 719 (Fed. Cl. 2011), aff'd sub nom. Stone v. Sec'y of Health & Human Servs., 676 F.3d 1373 (Fed. Cir. 2012).

Again, months passed without much progress. In an August 30, 2011 status conference, the parties explored the status of the case. Ms. Barclay's counsel suggested obtaining an additional expert. To this suggestion, the Secretary's attorney stated that it was petitioner's prerogative to explore. If petitioner obtained a new expert, then the case might be worth pursuing. Ms. Barclay's attorney defined the issue as whether prolonged seizures in a child with an SCN1A mutation damage the child's brain. This issue, according to Ms. Barclay's attorney, was not presented in Hammit or Stone.

Ms. Barclay filed a report from Jean-Ronel Corbier, a pediatric neurologist. In a nutshell, Dr. Corbier's opinion is that a prolonged seizure, especially a prolonged febrile seizure, can change the infant's brain. Dr. Corbier cited articles by McClelland, Dube, and Bender to support the reliability of his opinion. Exhibit 17 at 3-5.

To Dr. Corbier, the presence of a mutation in the SCN1A gene did not automatically determine that a person would suffer Dravet syndrome, as Matthew does. According to Dr. Corbier and the literature he cited, mutations in the SCN1A produce a range of outcomes. For example, some patients develop a more benign condition, generalized epilepsy with febrile seizures plus (GEFS+). Other patients develop familial hemiplegic migraines or familial autism. Dr. Corbier interpreted this spectrum of disorders as meaning that genetics are not a sufficient explanation. He asked: "[N]ow that we have identified a genetic mutation that seems very important in children with Dravet syndrome, given the wide variability in expression, what other factors including environmental ones might be present?" Id. at 10.

The environmental factor at issue here is the DTaP vaccine. Citing McIntosh and Tro-Bauman, Dr. Corbier stated that a vaccination leads to earlier seizures. Exhibit 17 at 11, 14. An earlier seizure links to Dr. Corbier's initial point that prolonged febrile seizures damage the infant's brain.

Dr. Corbier discussed Matthew's case in light of these general principles. Dr. Corbier stated: "The presence of an SCN1A [mutation] undoubtedly represents a strong known risk factor for the development of Matthew's epilepsy and Dravet syndrome. It also made him much more sensitive to the effects of DTaP and fever given his immature brain." Exhibit 17 at 15. He continued: "Like the underlying SCN1A mutation, DTaP made as [sic] significant contribution to the development of Matthew's epilepsy and Dravet syndrome." Id.

In the ensuing status conference, the Secretary aggressively questioned the utility of devoting more resources from the Vaccine Injury Trust Fund to this case. The Secretary stated that the undersigned special master had already determined that a prolonged seizure did not affect the child's outcome. Snyder v. Sec'y of Health & Human Servs., No. 07-59V, 2011 WL 3022544, at *2, *30-31, *35-36 (Fed. Cl. Spec. Mstr. July 21, 2011). The undersigned responded that the Court of Federal Claims did not agree with the analysis and, therefore, the special master's decision could not prevent a hearing in this case. Snyder v. Sec'y of Health & Human Servs., 102 Fed. Cl. 305 (2011). Since a hearing was nearly inevitable, the Secretary planned to obtain more expert reports.[15]

Before the Secretary filed her expert reports, Ms. Barclay submitted a supplemental report from Dr. Corbier. This supplemental report discussed whether pneumonia could have caused Matthew's initial post-vaccination fever. In Dr. Corbier's view, the seizure caused the pneumonia. Exhibit 38.

The Secretary procured two reports --- an initial report from Dr. Raymond, and a supplemental report from Dr. Wiznitzer. Dr. Raymond provided a basic explanation for how SCN1A genes lead to the production of a sodium channel. When a defect in the genes causes an alteration in the normal structure of the sodium channel, the sodium channel does not function properly. Exhibit I at 3-6. Dr. Raymond stated that "it is very clear that based on the present animal investigations, that there is no need to invoke environmental modifiers to explain disease onset or progression." Id. at 6.

In addition, Dr. Raymond disagreed with much of Dr. Corbier's opinion. Most notably, Dr. Raymond questioned the accuracy of Dr. Corbier's assertion that an earlier onset of Dravet syndrome caused a worse outcome. Dr. Raymond's opinion was that the onset did not affect the outcome and he cited articles by McIntosh, Tro-Baumann, and Brunklaus. Id. at 9-11.

---

[15] During the status conference the Secretary noted that Snyder was not yet final. Later, the Secretary filed a notice of appeal, which was docketed as case number 2013-5068 in the Federal Circuit. Later still, on January 28, 2014, in a nonprecedential disposition, the Federal Circuit reversed the Court of Federal Claims and reinstated the (undersigned) special master's findings that the SCN1A gene was the sole cause of the Dravet syndrome. Snyder v. Sec'y of Health & Human Servs., 553 Fed. Appx. 494 (Fed. Cir. 2014).

Dr. Raymond's conclusion supported the Secretary's position that compensation should not be awarded to Ms. Barclay. Dr. Raymond said that: "Matthew is a child with severe myoclonic epilepsy of infancy and developmental delays diagnosed as Dravet syndrome secondary to a mutation in his SCN1A gene. This is the sole cause of his epilepsy condition. It was not caused []or exacerbated by any of the immunizations that he received." Id. at 11.

Dr. Wiznitzer reached the same conclusion. He stated that the finding of a mutation in Matthew's SCN1A gene "leads to the conclusion that Matthew Ramirez's SCN1A mutation by itself explains and caused his clinical neurological disorder – Dravet syndrome." Exhibit K at 2. Like Dr. Raymond, Dr. Wiznitzer stated that the onset of seizures did not affect the outcome. Dr. Wiznitzer relied upon the McIntosh, Brunklaus, and Ragona studies. Id. at 2-4. Dr. Wiznitzer's emphasis on the genetic source of Matthew's neurologic problem led him to describe the question of pneumonia as "irrelevant." Id. at 5.

A status conference followed the submission of these two reports. Ms. Barclay indicated that he did not intend to call Dr. Kinsbourne to testify. Instead, Ms. Barclay wanted to obtain a second supplemental report from Dr. Corbier. In this same status conference, the parties discussed consolidating this case with Santini, No. 06-725V, another case in which the infant-vaccinee (Aydien Omidvar) had an SCN1A mutation and in which the experts were the same.

Ms. Barclay filed the second supplemental report from Dr. Corbier on April 4, 2013, as exhibit 39. The basic thrust of this report was to emphasize the contributions from environmental factors. He stated "the general discovery of an SCN1A mutation and its impact on the sodium channel in epileptic patients can explain why patients with Dravet syndrome can be so vulnerable to certain triggers, among which is the DTaP vaccination." Exhibit 39 at 4.

In conjunction with that report, Ms. Barclay presented her pre-hearing brief. Ms. Barclay's pre-hearing brief was tightly focused. Preliminarily, Ms. Barclay categorized her case as one presenting "an off-Table (cause-in-fact) significant aggravation claim." Pet'r's Prehr'g Br., filed Apr. 22, 2013, at 3. As informed by Dr. Corbier's reports, Ms. Barclay presented the theory on which she was proceeding. He argued that the DTaP vaccine can cause the onset of seizures in children with an SCN1A mutation. He also argued that the outcome for Matthew was worse than it would have been otherwise because Matthew had a prolonged seizure and had status epilepticus. Id. at 10-15.

The Secretary responded in her pre-trial brief. The Secretary agreed that Ms. Barclay presented a claim that the DTaP vaccine significantly aggravated Matthew's condition and, thus, she was required to fulfill the elements set forth in Loving v. Sec'y of Health & Human Servs., 86 Fed. Cl. 135, 144 (2009). The Secretary also agreed that the evidence supported two aspects of Ms. Barclay's proof --- first, "a DTaP vaccine is capable of causing a fever" and, second, "a fever is capable of provoking a seizure in a child with Dravet syndrome." Resp't's Prehr'g Br., filed May 8, 2013, at 4-5.

The Secretary, however, challenged other parts of Ms. Barclay's case. The Secretary maintained that the "petitioner will be unable to produce reliable scientific evidence demonstrating Matthew's initial, prolonged seizure caused any brain damage or caused him to suffer a worse developmental outcome." Id. at 5. The Secretary's arguments focused on three propositions: first, the genetic mutation alone caused Matthew's developmental outcome; second, Matthew's prolonged seizure did not cause his epilepsy; and, third, there is no persuasive evidence that Matthew's initial seizure caused any lasting consequence. Id. at 5-8.

The parties' briefs accurately predicted the experts' testimony at the hearing, which was held on June 5-6, 2013, in Charlotte, North Carolina. Drs. Corbier, Wiznitzer, and Raymond testified in accord with their expert reports. In the course of the hearing, the parties stipulated that all materials should be considered part of the record regardless of whether the particular article or report was in only either Matthew Ramirez's case or Aydien Omidvar's case. Tr. 27.

At the end of the hearing, the parties requested an opportunity to submit briefs.[16] Ms. Barclay filed an initial brief, the Secretary filed one brief, and then Ms. Barclay filed a reply. With the submission of the reply brief, the matter is ready for adjudication.

[16] After the hearing, Ms. Barclay also filed a motion seeking an interim award of attorneys' fees and costs. On February 2, 2014, she was awarded $133,942.46. Interim Fees Decision, 2014 WL 2925245.

V. Elements Required to Establish Entitlement to Compensation and Standards for Adjudication

For petitioners to be awarded compensation, the special master must find that they established the "matters" listed in section 11(c)(1) and "there is not a preponderance of the evidence that the illness . . . is due to factors unrelated to the administration of the vaccine." 42 U.S.C. § 300aa—13(a)(1). Section 11(c)(1), in turn, lists five items in paragraphs (A) through (E). Here, the elements in controversy correspond to paragraphs C (causation / significant aggravation) and D (severity).

Paragraph C requires some showing that the vaccine harmed the person. For certain vaccines and injuries, the Vaccine Act and its associated regulations establish a presumptive causal connection for injuries within a defined time. The injury may be either an initial injury or the significant aggravation of a preexisting injury. 42 U.S.C. § 300aa—11(c)(1)(C); 42 C.F.R. § 100.3. These claims are known as "Table claims." For cases not based upon the Vaccine Injury Table, the petitioners are not entitled to a presumption that a vaccine caused an injury.

Here, Ms. Barclay is pursuing an off-Table claim that the DTaP vaccine significantly aggravated her son's Dravet syndrome. 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 resultant 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.

After Loving, the Federal Circuit has explained that possible alternative causes may be considered in determining whether petitioner has presented a persuasive claim. See Stone v. Secretary of Health & Human Servs., 676 F.3d 1373, 1380 (Fed. Cir. 2012). In context of an SCN1A case, the Federal Circuit held that the special master did not err in finding, after considering the entire record, that the "Secretary proved by preponderant evidence its 'factors unrelated' defense by showing that the gene mutations were the sole cause of the seizure disorders." Snyder v. Sec'y of Health & Human Servs., 553 F. App'x 994, 999 (Fed. Cir. 2014).

If there is preponderant evidence that the vaccine caused some harm as set forth in paragraph C of section 11(c)(1), the petitioner must also establish that the harm was severe pursuant to paragraph D. The Vaccine Act lists three potential avenues, and the one requirement that Ms. Barclay could arguably fulfill is the vaccinee "suffered the residual effects or complications of such illness, disability, injury or condition for more than 6 months after the administration of the vaccine." 42 U.S.C. § 300aa—11(c)(1)(D)(i). Additional guidance about this element is set forth in section VII below.

The burden of proof is preponderance of the evidence. The party bearing the burden of proof need not establish a proposition to the level of scientific certainty. Althen, 418 F.3d at 1278; Knudsen v. Sec'y of Health & Human Servs., 35 F.3d 543, 549 (Fed. Cir. 1994).

VI. Significant Aggravation

A. Parties' Positions

To explain how a vaccine could change the effect of an SCN1A mutation, Dr. Corbier presented three overlapping theories in his testimony. A first idea is that people with an SCN1A mutation are vulnerable or susceptible to developing an adverse reaction to the DTaP vaccine. Tr. 20, 78, 103. A second theory is that vaccines cause Dravet syndrome to manifest earlier by bringing about seizures before they would have occurred otherwise. Tr. 30, 104, 140. For these two

theories, Dr. Corbier relied primarily upon material relating to SCN1A mutations. A third concept from Dr. Corbier is that the vaccines cause a more prolonged seizure and the prolonged seizure inflicts additional damage. Tr. 32, 144. For this theory, Dr. Corbier based much of his opinion upon HCN channels.[17]

Dr. Raymond and Dr. Wiznitzer agreed only with the portion of Dr. Corbier's presentation concerning the onset of the first seizure. Dr. Raymond and Dr. Wiznitzer acknowledged that the vaccination preceded the first seizure and the vaccination, most likely, provoked a fever that triggered the first seizure. Tr. 256 (Dr. Raymond), 353 (Dr. Wiznitzer). Dr. Raymond and Dr. Wiznitzer disagreed with the remaining portions of Dr. Corbier's testimony. In their view, the SCN1A mutation is the sole cause of the developmental delay. Tr. 227, 254 (Dr. Raymond), 359, 416, 446 (Dr. Wiznitzer).

Dr. Raymond and Dr. Wiznitzer stated vaccines did not alter the ultimate outcome for Matthew. Tr. 254 (Dr. Raymond), 302 (Dr. Raymond discussing Matthew Ramirez), 359 (Dr. Wiznitzer), 454 (Dr. Wiznitzer discussing Matthew Ramirez). They provided several reasons for their opinions, including details about genetic mutation, rodent studies, and studies on people.

B. Evidence regarding SCN1A Mutations

1. Genetic Mutation

Dr. Raymond, the board-certified geneticist, stated practitioners look for details about the mutation, including the nature of the mutation, whether the mutation arose de novo, and whether the mutation is in a conserved region. Tr. 317.

Here, Dr. Raymond discussed the details of Matthew's mutation. Matthew has a 10 base pair deletion that arose de novo. Tr. 259. The mutation was in a conserved region. Tr. 317.

Dr. Raymond's opinion is supported by Athena. When Athena detected the genetic mutation, the laboratory correlated the mutation with a disease, not a

[17] In the context of evaluating Dr. Corbier's opinion Section IV.C. provides more information about HCN channels.

normal development. Exhibit 13B. Matthew's gene was defective, creating incorrect wiring in his brain. Tr. 417 (Dr. Wiznitzer).

2. Rodent Studies

As explained above, the rodent studies showed that mammals with a severe SCN1A mutation will have problems. Yu, in particular, showed that even without a fever, the mice will develop seizures. The seizures in the Yu experiment happened spontaneously and not in response to the introduction of an outside force. Yu at 1144.

When Dr. Corbier was asked questions about this study, his answers were vague and confusing. See Tr. 536-41. Dr. Corbier seemingly did not appreciate that the Yu study contradicted his theory that an environmental factor (like a vaccine) affects the consequence of an SCN1A mutation.

These two points provide a strong and reliable foundation for the opinions that genes are the sole cause of the Dravet syndrome and vaccinations do not contribute to developmental delay. But, more evidence buttresses these conclusions. Dr. Raymond and Dr. Wiznitzer also cited various studies on people.

3. People Studies

As more has become known about SCN1A mutations and seizures in mammals, scientists have investigated the connection between the mutation and epilepsy. In that research, the scientists have re-opened the question of whether vaccinations are causing epilepsy. The four important articles are by Berkovic, McIntosh, Tro-Baumann, and Brunklaus.

a) Berkovic

In 2006, Berkovic and colleagues were interested in explaining why pertussis vaccination has been alleged to cause an encephalopathy that involves seizures and intellectual impairment. The researchers postulated that in the cases of so-called vaccine encephalopathy, the individuals could have mutations in the SCN1A gene because of a clinical resemblance to SMEI for which such mutations have been identified. Berkovic et al. retrospectively studied 14 patients with an alleged encephalopathy in whom the first seizure occurred within 72 hours of vaccination. SCN1A mutations were identified in 11 of the 14 patients. Clinical-

molecular correlation showed mutations in eight of eight cases with phenotypes of SMEI, in three of four cases with borderline SMEI, but not in two cases with Lennox-Gastaut syndrome.

The researchers concluded that cases of alleged vaccine encephalopathy could in fact be a genetically determined epileptic encephalopathy that arose de novo. Specifically, the researchers found,

> In the presence of *SCN1A* mutations, vaccination can still be argued to be a trigger for the encephalopathy, perhaps via fever or an immune mechanism. [B]ut the role of vaccination as a significant trigger for encephalopathy is unlikely for several reasons. First, although vaccination might trigger seizures as shown by the increased risk of febrile seizures on the day of triple antigen or MMR vaccination, there is no evidence of long-term adverse outcomes. Second, less than half of our patients had documented fever with their first seizure, which indicates that fever is not essential. Third, our neuroimaging data showed no evidence of an inflammatory or destructive process. Finally, truncation and missense mutations reported in conserved parts of SCN1A have not been found in many hundreds of healthy patients. Thus, individuals with such mutations seem to develop SMEI or SMEB whether or not they are immunized in the first year of life. We do not think that avoiding vaccination, as a potential trigger, would prevent onset of this devastating disorder in patients who already harbour the SCN1A mutation.

Berkovic at 491.

The Berkovic article has been influential. For example, the undersigned special master has previously found Dr. Raymond's opinion that vaccinations do not cause Dravet syndrome persuasive because, in part, it was consistent with the scientific literature, specifically the Berkovic article. Snyder, 2011 WL 3022544, at *5. When the case reached the Federal Circuit, the Federal Circuit ruled that accepting Dr. Raymond's opinion was not arbitrary because "the researchers of the Berkovic article did not believe that 'avoiding vaccination, as a potential

trigger, would prevent onset of this devastating disorder in patients who already harbor the SCN1A mutation.'" Snyder, 553 Fed. Appx. at 1002. Other special masters have also found Berkovic to be a persuasive basis for finding that the child's SCN1A gene mutation was the sole cause of the Dravet Syndrome. Barnette v. Sec'y of Health & Human Servs., No. 06-868V, 2012 WL 5285414, at *11 (Fed. Cl. Spec. Mstr. Sept. 26, 2012), mot. for rev. denied, 110 Fed. Cl. 34 (Fed. Cl. 2013); Deribeaux v. Sec'y of Health & Human Servs., No. 05-306V, 2011 WL 6935504, at *34 (Fed. Cl. Spec. Mstr. Dec. 9, 2011), mot. for rev. denied, 105 Fed. Cl. 583 (2012), aff'd, 717 F.3d 1363 (Fed. Cir. 2013); Stone v. Sec'y of Health & Human Servs., No. 04-1041V, 2010 WL 1848220, at *34 (Fed. Cl. Spec. Mstr. Apr. 15, 2010), mot. for rev. denied, 99 Fed. Cl. 187, 191 (Fed. Cl. 2011), aff'd, 676 F.3d 1373 (Fed. Cir. 2012). In addition to these legal determinations, the Berkovic article has inspired at least three other investigations about the potential link between vaccination and Dravet syndrome.

b) McIntosh

McIntosh and colleagues were interested in explaining why pertussis vaccination has been alleged to cause an encephalopathy that involves seizures and intellectual disability. In 2010, McIntosh and colleagues conducted a study in which they aimed to establish whether the apparent association of Dravet syndrome with vaccination was a result of recall bias and, if not, whether vaccination affected the onset or outcome of the disorder.[18]

The authors retrospectively studied 40 patients with Dravet syndrome, who had mutations in the SCN1A gene, and whose first seizure was a convulsion. McIntosh at 593-94. The authors examined medical and vaccination records to determine whether there was an association between vaccination and onset of seizures in these patients. Patients were separated into a vaccination-proximate group (seizure 0-1 day from vaccination) and vaccination-distant group (seizure 2+ days after vaccination), and the authors compared clinical features, intellectual outcome, and type of SCNIA mutation between the groups. Id. at 594. Twelve

[18] Recall bias is a phenomenon in which people remember events incorrectly. The McIntosh researchers minimized recall bias by relying upon documents. McIntosh at 593. Dorland's at 212.

patients were in the vaccination-proximate group and 28 patients were in the vaccination-distant group. Id.

The authors found "no differences in intellectual outcome, subsequent seizure type, or mutation type between the two groups." Id. at 592. The authors concluded that vaccination might trigger earlier onset of Dravet syndrome in children who, because of an SCN1A mutation, are destined to develop the disease. Id. However, the authors found "no evidence that vaccinations before or after disease onset affect[ed] outcome." Id.

Dr. Corbier interpreted McIntosh as establishing a definitive association between Dravet syndrome and vaccination. He also emphasized that seizures immediately after a vaccine were likely to occur at a younger age than seizures occurring more than two days after the vaccination. Tr. 23. Dr. Corbier explained that McIntosh did not find a recall bias. Further, Dr. Corbier disagreed with the McIntosh conclusion that the vaccinations did not affect outcome. Dr. Corbier contended that because the study was not designed to address outcomes, but rather to determine if there is a relationship at all, several variables were not included, and a proper conclusion cannot be drawn. Tr. 114.

Dr. Raymond maintained that there was no statistically significant effect on outcome between the vaccination-proximate and vaccination-distant groups. Tr. 322.

Dr. Wiznitzer opined that McIntosh suggests that children with Dravet syndrome who have an initial seizure in temporal proximity to a vaccination still have similar clinical outcomes to children whose initial seizures are not temporally related to vaccination. Tr. 404. Further, Dr. Wiznitzer explained that the only significant factor was that the age of onset was earlier for individuals who received vaccinations — but age of onset did not change the outcome. Tr. 407.

c) Tro-Baumann

In 2011, to gain a further understanding of the relationship between Dravet syndrome and vaccination, Blanca Tro-Baumann and colleagues conducted another retrospective analysis of 70 patients with Dravet syndrome and SCN1A mutations. Through examining medical records and conducting parental interviews, Tro-Baumann et al. found that seizures following vaccinations were reported in 27 percent of these patients. Tro-Baumann at 176. In 16 percent of the 70 patients

(that is, 58 percent of all patients with seizures following vaccination) the vaccination-related seizures represented the first clinical manifestation of the Dravet syndrome. Id. Two-thirds of the seizures following vaccination occurred in the context of fever. Id.

The authors suggested that vaccination-related seizures represent a possible presenting feature of Dravet syndrome. Tro-Baumann at 177. Furthermore, the authors characterized an assumed causal connection between vaccine-related seizures and Dravet syndrome as a "misinterpretation." Id.

Dr. Corbier interpreted Tro-Baumann as establishing a "clear connection between Dravet and vaccination with DTP." Tr. 22. When Dr. Corbier was questioned about what whether "connection" meant "causation," his answer revealed the challenges in trying to say whether the vaccine affected the outcome. He stated:

> Well, it depends what we mean by causation. If causation means an inciting factor that in the right condition with the right associated factors can then lead to a disease, then causation fits. If we mean causation whereby the vaccine by itself would have caused the Dravet, then no. So when I use the term causation, what I mean is that the vaccine in a patient who's very vulnerable because of an underlying genetic mutation, there's a whole series of reactions that occur due to that initial vaccine, or it can be a fever or a virus that then changes brain function and circuitry that will result in long-term epilepsy.

Tr. 196.

Moreover, Dr. Corbier contended that the article suggests that vaccines can cause Dravet Syndrome to "occur earlier." Tr. 30. On cross-examination, Dr. Corbier repeated that "vaccine-related seizures . . . represent a possible presenting feature" of Dravet syndrome. Tr. 121. When pressed to explain whether the vaccine-related seizures were the cause of the Dravet syndrome, Dr. Corbier stated the Tro-Baumann article showed "that we cannot ignore the role of vaccine in being a presenting feature in many patients with Dravet syndrome, so vaccination,

with or without fever, plays an important role as a presenting feature in many patients with Dravet." Tr. 122.

When Dr. Wiznitzer was questioned about Tro-Baumann, he opined that vaccination is associated with the onset of Dravet syndrome only so far as the vaccination causes temperature elevation, and temperature elevation, regardless of source, can cause seizures. Tr. 398. Dr. Wiznitzer maintained that the relationship is not a significant aggravation or a causal connection. Tr. 401.

Dr. Raymond did not comment on Tro-Baumann beyond noting that it did not study differences in outcomes. Tr. 333.

d) Brunklaus

In 2012, Brunklaus and colleagues examined a large cohort of patients with SCN1A mutation-positive Dravet syndrome. They intended to identify predictors of developmental outcome and to determine specific clinical and demographic features. During a 5-year study of 355 patients, Brunklaus et al. collected information about several aspects of Dravet syndrome, including epilepsy phenotype, electroencephalography data, imaging studies, and mutation class. Id. at 2329. They also rated each child's developmental status. The developmental status was classified by the referring clinician using a five-point scale. The raters had expertise in the assessment of developmental status including rating of gross and fine motor skills, communication and cognitive abilities, and age appropriate adaptive behavior. Id. at 2330.

The authors found that clinical features predicting a worse developmental outcome included status epilepticus, interictal electroencephalography abnormalities in the first year of life, and motor disorder. Id. at 2329. No significant effect was seen for seizure precipitants, magnetic resonance imaging abnormalities, or mutation class. Id.

Brunklaus also investigated the precipitants of seizures. The authors found that fever or illness had precipitated the majority of seizures, one-third had no precipitant, and vaccination triggered 7 percent of the seizures. Brunklaus at 2333. Moreover, the authors found that vaccination-triggered seizures presented significantly earlier than those without precipitant or with fever/illness. Id. at 2333-34. However, citing McIntosh, the authors concluded that the vaccination itself had no effect on the developmental outcome. Id. at 2334.

Further, the authors contend that "children carrying a SCN1A mutation are destined to develop the disease, which in turn can be precipitated by a series of factors such as fever/illness, vaccination or a bath." Id. However, the nature of the trigger has no effect on overall developmental outcome. Id. The authors acknowledged that their understanding of the functional effect of mutations is still unrefined, and classification models lack accuracy to reflect the true mutation impact. Id. at 2335.

Dr. Corbier interpreted the study as establishing a definitive link between vaccination and the onset of Dravet syndrome and seizures. Tr. 25. Specifically, Dr. Corbier emphasized that the study indicated that children who suffered the onset of seizures associated with a vaccination suffered the onset of seizures at a significantly earlier time. Tr. 26. Moreover, Dr. Corbier explained that the Brunklaus article found that children who had status epilepticus have a worse developmental outcome. Tr. 54.

Dr. Raymond interpreted the Brunklaus study as finding that vaccination itself does not affect developmental outcome. Tr. 331. However, Dr. Raymond acknowledges that the Brunklaus study did not present their data in the published article. Tr. 332.

Dr. Wiznitzer explained that the Brunklaus study clearly states that the authors looked at their data and found that vaccination does not alter developmental outcome, a finding that confirmed the conclusion reached in McIntosh. Tr. 406. Dr. Wiznitzer asserted that this was an independent finding by the Brunklaus authors and was not simply a reiteration of the McIntosh finding. Tr. 405. Furthermore, on cross-examination, Dr. Wiznitzer acknowledged that the Brunklaus study found that the mutation class did not predict a worse outcome, and one of the mutation classes listed was a frame shift mutation. Tr. 450.

4. Assessment

When Dr. Corbier testified in rebuttal, he recognized that Matthew Ramirez's 10 base pair mutation was severe and "explains a lot of things." Tr. 501. But, Dr. Corbier maintained the genetic mutation does not explain everything. The mutation, in Dr. Corbier's view, made Matthew Ramirez "more susceptible to environmental insults." Id.

An opinion that a 10 base pair mutation explains almost everything, leaving room for an environmental factor is not persuasive. As Dr. Raymond and Dr. Wiznitzer thoroughly discussed, the nature of the genetic mutation in these children makes the creation of a normally functioning sodium channel in the brain impossible. Without an effective $Na_v1.1$, controlling the flow of sodium ions in the brain is impaired. The occurrence of seizures is inevitable. Dr. Corbier did not rebut Dr. Raymond's assessment that the genetic mutation was severe. Similarly, Dr. Corbier did not answer Dr. Wiznitzer's assertion that the problem was defective wiring.

Thus, there is no reliable basis for crediting Dr. Corbier's first theory that people with an SCN1A mutation are vulnerable to developing an adverse reaction to the DTaP vaccine. Similarly, there is no reliable basis for crediting Dr. Corbier's second theory that vaccines worsen Dravet syndrome by bringing about seizures before they would have occurred otherwise. Tr. 30, 104, 140. Although there may be an earlier manifestation, Dr. Corbier has not demonstrated how it affects the child's outcome. Dr. Raymond and Dr. Wiznitzer rested their opinion on Berkovic, McIntosh, and Brunklaus. Dr. Corbier, on the other hand, had no support for his opinions that the vaccines change the outcome. These studies showed that children with SCN1A mutations have consistent symptoms, regardless of whether the initial seizure followed a seizure.

C. Analogy to HCN channels

To support the theory that "seizures beget seizures," Dr. Corbier relies upon articles by McClelland, Dube, Bender, Brewster, Chen, and Jung, and also testified about them individually. Tr. 32-48.[19] Some of these articles present results of experiments and some of these articles are review articles that summarize experiments conducted elsewhere. In the articles that reported the results of an experiment, the researchers were generally exploring a hypothesis that febrile seizures lead to long-term epilepsy because the febrile seizures damage an HCN channel. See Tr. 552.

---

[19] Dr. Corbier appeared to know relatively less about HCN channels than the Secretary's experts. For example, Dr. Corbier did not know whether a test could detect defects in HCN channels and he did not know how a defect in an HCN channel would be observable in a clinical setting. Tr. 138.

The HCN channels are located in the hippocampal region. Tr. 132, 382 (Dr. Wiznitzer's discussion of 2001 Chen). HCN channels are ion channels, which allow substances such as sodium and potassium to enter and to exit the cell membrane. Tr. 363. The purpose of HCN channels is to balance and polarize the cell to limit the cell's excitability. Tr. 364.

After a summary about each article, Dr. Corbier was asked about their combined teaching. He stated:

> I think taken collectively, these articles show that we have an explanation for prolonged febrile seizures causing permanent changes, permanent epileptic changes in a brain that may start out normal, for example, Dravet patients. We know that before six months, before they start having seizures, they appear normal. They don't have seizures. They have a prolonged febrile event or a prolonged febrile seizure. Something changes. They develop epilepsy, so this can explain why and how a prolonged febrile seizure vis-a-vis these HCN channels can result in these long-term changes.

Tr. 50. Dr. Corbier also opined about these studies' relevance:

> They're relevant because we have to have a mechanism, we have to have an explanation to show why. Even if you have an important mutation such as SCN1A mutation, the changes from a SCN1A mutation that lead to refractory epilepsy do not occur in a vacuum. There needs to be an explanation from going from no seizures to very refractory seizures unresponsive to medication.

Tr. 51.

Dr. Corbier's logic is flawed in many respects. First, he states that something alters "a brain that may start out normal, for example, Dravet patients." Tr. 50. It is not correct to say that these children's brains "start[ed] out normal." Dr. Corbier recognized that "these kids probably come into the world with that SCN1A mutation." Tr. 41. Although Dr. Corbier qualified his answer by using

the term "probably," he later agreed that Matthew was born with the SCN1A mutation. Tr. 94-95.

The second error in Dr. Corbier's assessment relates to the first. Dr. Corbier asserted that "the changes from a SCN1A mutation that lead to refractory epilepsy do not occur in a vacuum." Tr. 51. There is not a vacuum. The seizures and attendant developmental delays begin after the switch from $Na_v1.3$ to $Na_v1.1$. See Brewster at 4597; Tr. 137.

Third, HCN channels are not sodium channels. Tr. 363 (Dr. Wiznitzer). HCN channels regulate the excitability and inhabitability in the cell. Tr. 364. HCN channels involve not only sodium ions, which cause the cell to be hyperpolarized, but also involve potassium ions. Id. "The HCN channel is not the same thing as an SCN1A channel. It's built differently. It has different components. It has different genes. It probably has different transcriptional regulation." Tr. 470. When Dr. Corbier was asked to comment upon the similarities and differences as part of his rebuttal testimony, he did not address the question very well, beginning his answer "I don't claim to be an expert in channelopathies." Tr. 524. Dr. Corbier's non-answer left unrebutted Dr. Wiznitzer's assertion that "You're dealing with two different creatures here. So I think you can't take the leap from one to the other." Tr. 471.

Fourth, the consequence of a problem in an HCN channel may be temporal lobe epilepsy.[20] But temporal lobe epilepsy is not the same as Dravet syndrome. Tr. 367-68, 372, 385; see also Tr. 498-99 (movement disorders seen in Dravet syndrome do not originate in the hippocampal region).

D. Synopsis

All these reasons contribute to a finding that Dr. Corbier was not persuasive in his opinion that vaccinations affected Matthew's outcome. The flip side of this coin is that Dr. Raymond and Dr. Wiznitzer were persuasive in opining that the SCN1A mutation was the sole cause. Consequently, Ms. Barclay has failed to

---

[20] The text uses the conditional terminology "may be" because the connection between HCN channels and temporal lobe epilepsy is not established. Tr. 516-19 (Dr. Corbier's discussion of Bender), 526-27 (Dr. Corbier's discussion of FEBSTAT study).

establish the first prong of Althen and the Secretary has established an alternative factor.

Although this resolution means that Ms. Barclay cannot be awarded compensation, there is a second aspect to her case. Whether Matthew suffered a severe injury due to the vaccine is discussed below.

VII. Severity of Injury

A. Legal Principles

Another way of evaluating an alleged effect of vaccination on Matthew is to consider how he would be if he had not received a vaccination. In a variety of contexts, the Federal Circuit has held that the person claiming compensation for another's injury must establish a "but for" model. E.g. Nycal Offshore Dev. Corp. v. United States, 743 F.3d 837, 844 (Fed. Cir. 2014) (oil and gas leases); Kellogg Brown & Root Servs., Inc. v. United States, 728 F.3d 1348, 1371 (Fed. Cir. 2013) (government counterclaim pursuant to anti-kick back act), reh'g denied, 2014 WL 1284763 (Fed. Cir. March 28, 2014). Consistent with common law principles, the Federal Circuit has also held that petitioners in the Vaccine Program have the burden to show "but for" the vaccine, they would not have suffered an injury. Shyface v. Sec'y of Health & Human Servs., 165 F.3d 1344, 1352 (Fed. Cir. 1999). Pursuant to the Vaccine Act, the injury suffered must be severe, such as lasting more than six months. 42 U.S.C. § 300aa—11(c)(1)(D).

In the context of a cause of action alleging a vaccine caused a discrete injury, the "but for" world is readily identified. Petitioners maintain that but for a vaccine, they would not have suffered any injury. However, Ms. Barclay in the case at hand is not proceeding on an initial-onset claim. She is instead pursuing a cause of action that the vaccines significantly aggravated Matthew's underlying disorder.

In significant aggravation cases, constructing a hypothetical scenario without the vaccination is more challenging. Because the physiologic basis for the disease existed before vaccination, petitioners must present some persuasive evidence about the natural or expected course of the disease. From this benchmark, petitioners should show their outcome is worse than what would normally occur. Locane v. Sec'y of Health & Human Servs., 99 Fed. Cl. 715, 731-32 (2011), aff'd, 685 F.3d 1375 (Fed. Cir. 2012); Loving v. Sec'y of Health & Human

Servs., No. 02-469V, 2009 WL 3094883, at *11-12 (Fed. Cl. Spec. Mstr. July 30, 2009), clarified on denial of reconsideration, 2010 WL 1076124 (Fed. Cl. Spec. Mstr. March 2, 2010).

In the cases involving an SCN1A mutation, the petitioners' inability to explain how the children would have fared without the vaccination was one reason the petitioners were not compensated. Harris, 2011 WL 2446321 at *33; Snyder, 2011 WL 3022544, at *34. The Federal Circuit specifically ruled that these findings were not arbitrary and capricious. Snyder, 553 Fed. Appx. at 999, 1003; cf. Deribeaux, 717 F.3d at 1369 (ruling the special master was not arbitrary in finding the SCN1A mutation to be the sole cause of the child's injuries).

B. Assessment of Evidence

For the case at hand, Ms. Barclay's proof again falters. She has failed to establish Matthew would be different today if he had not received the DTaP vaccination. She has not demonstrated any sequela to his initial seizure after which he returned to his baseline. Ms. Barclay also has not established any change in outcome.

All experts agree that there is a causal relationship between the vaccinations and the initial seizure. More specifically, the DTaP vaccine prompted a fever and fever, in children with an SCN1A mutation, can prompt a seizure. The Secretary's experts conceded this point without dispute. Tr. 320 (Dr. Raymond), 448 (Dr. Wiznitzer).[21]

A fever and an associated seizure, however, do not meet the Vaccine Act's severity requirement. Following the seizures, Matthew remained in the hospital for less than four days. Exhibit 5 at 13. He underwent various tests including an EEG and an MRI. The results of these tests were normal. Exhibit 5 at 21-22, exhibit 6 at 23. Upon discharge, Matthew was said to be in good condition. Exhibit 5 at 18; see also Tr. 144, 423, 427, 437. Consequently, Ms. Barclay cannot receive compensation for just the initial fever and initial seizure. Therefore, Ms. Barclay must look to Matthew's outcome after the initial presentation.

[21] It is possible that Matthew Ramirez was suffering from pneumonia before his vaccination and the pneumonia caused the fever that led to the seizure. For simplicity, this decision is assuming that he did not have pneumonia before the vaccination.

Ms. Barclay has not demonstrated Matthew would have been worse. Dr. Corbier, on cross-examination, was asked if Matthew Ramirez did not have his initial seizure, how would he be today? Dr. Corbier responded: "the simple answer is I don't know." He elaborated: "I can take an educated guess that if he did have seizures, it would have occurred later on." Tr. 104. In the subsequent discussion, Dr. Corbier suggested that Matthew Ramirez may not have had any seizures. When questioned about the basis for this possibility, Dr. Corbier answered:

> Is it possible that he could go without seizure despite the fact that he has an SCN1A mutation disease producing type of mutation? The answer is maybe.
>
> I can't say for sure. I don't have any evidence to back me up, but I don't see why not. . . .
>
> [B]ut if we're able to control all of the potential triggers, could we be left without a seizure disorder? Perhaps.

Tr. 107-08. Because Dr. Corbier's answer suggested that triggers were not needed, he was asked more questions about this point. Dr. Corbier stated "this is a question, the answer of which I don't know based on not seeing any particular study designed to address that particular question. [B]ut at least hypothetically, you know, I don't see why not." Tr. 109.

Later, Dr. Corbier was again asked to differentiate Matthew from what happens in Dravet syndrome generally. But, Dr. Corbier did not provide any meaningful information. Tr. 142-43. Because Dr. Corbier did not explain his opinion regarding the difference between a hypothetical Matthew Ramirez (who did not receive the vaccination) and the real Matthew Ramirez (who did receive the vaccination), Dr. Corbier was asked about this topic again. But, once more, he could say only that the seizures occurred earlier. He could not say that the earlier onset affected his longer term outcome. Tr. 185-91.

These vague responses largely undermined the value of Dr. Corbier's earlier testimony, on direct examination, that the children at issue in the consolidated cases were worse after the vaccination. Tr. 19-20 (Matthew Ramirez), 77 (Aydien). In the sense that the children had seizures, they were worse. But this

conclusion is too facile. It ignores the role the mutation plays and the natural course of Dravet syndrome.

The opinions from Dr. Raymond and Dr. Wiznitzer that the mutation determined the children's outcome were much more persuasive. In their view, the vaccinations did not affect the Dravet syndrome. Tr. 263 (Dr. Raymond on Matthew Ramirez), 270 (Dr. Raymond on Aydien), 319 (Dr. Raymond on Aydien), 423 (Dr. Wiznitzer on Matthew), 454 (Dr. Wiznitzer on both). Dr. Raymond and Dr. Wiznitzer based their opinions that the gene caused the developmental delay on biology. As explained above, neither child can produce a normally functioning $Na_v1.1$.

The medical literature also supports the opinion that vaccinations did not affect the outcome. Tr. 302-06 (Dr. Raymond citing McIntosh), 439 (Dr. Wiznitzer citing McIntosh, Brunklaus, and Ragona). For example, Brunklaus and colleagues studied more than 300 cases with an SCN1A mutation. They attempted to determine whether different variables accounted for the range of developmental outcomes in patients with Dravet syndrome. The authors concluded that their finding "supports the argument that children carrying a SCN1A mutation are destined to develop the disease, which in turn can be precipitated by a series of factors such as fever/illness, vaccination or a bath. However, the nature of the trigger has no effect on overall developmental outcome and thus does not seem to be responsible for the subsequent encephalopathy." Brunklaus at 2334. In addition to their own data, Brunklaus and colleagues cited the articles by Tro-Baumann, Berkovic and McIntosh. When asked about this passage from the Brunklaus article, Dr. Corbier said "I don't see proof." Dr. Corbier's assessment of Brunklaus is not credible.

Overall, the evidence overwhelmingly demonstrated that Matthew Ramirez would be the same even if he did not receive the vaccine. The vaccination did not affect or contribute to his developmental delay. Ms. Barclay has failed to meet her burden of establishing, by preponderant evidence, that he suffered an injury for more than six months.

VIII. Additional Comments

The results in the case at bar match the results in previous cases involving an SCN1A mutation. The identical outcome is not surprising because human biology has not changed. The SCN1A genes still largely control the creation of $Na_v1.1$.

Furthermore, the evidence is largely the same. Dr. Raymond and Dr. Wiznitzer testified in previous cases. They cited to the same articles, such as Oakley and Yu. The newer articles such as Brunklaus reinforce the opinions of Dr. Raymond and Dr. Wiznitzer.

Potential petitioners who intend to claim a vaccine injured a child with an SCN1A mutation should consider carefully whether there is a reasonable basis for their claims. Special masters have consistently credited evidence that the gene is the sole cause of developmental problems.[22] An expert's opinion that a vaccine can trigger an initial seizure in a child with an SCN1A mutation has been insufficient to demonstrate that the vaccine caused a subsequent seizure disorder in such a child, at least in the absence of evidence regarding a difference in the ultimate outcome. Against this backdrop, future claims involving an SCN1A mutation may lack a reasonable basis.

IX. Conclusion

Dravet syndrome has interfered with Matthew's development since its manifestation following the March 25, 2005 DTaP vaccination. The timing of events (in that Matthew experienced his first seizure within one day of the vaccination) understandably led to a hypothesis that the vaccination contributed to the Dravet syndrome.

However, scientific research, as Dr. Raymond and Dr. Wiznitzer ably explained, has shown that a genetic mutation caused Matthew's Dravet syndrome. It is more likely than not that Matthew would be the same today whether he received the vaccination or not. Ms. Barclay has failed to demonstrate that she is entitled to compensation from the Vaccine Program. Consequently, the Clerk's Office is instructed to enter judgment in accord with this decision.

---

[22] The list of final opinions in other SCN1A cases includes: Snyder, 553 Fed. Appx. 994; Deribeaux, 717 F.3d 1363; Stone, 676 F.3d 1373; Barnette v. Sec'y of Health & Human Servs., 110 Fed. Cl. 34 (2013); and Waters v. Sec'y of Health & Human Servs., No. 08-76V, 2014 WL 300936 (Fed. Cl. Spec. Mstr. Jan. 7, 2014).

IT IS SO ORDERED.

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