In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: January 7, 2014

* *	**PUBLISHED**
MICHAEL B. WATERS and * KIM K. WATERS, as Parents and Legal * Representatives of their Minor Son, * KARSEN STEELE WATERS, * * Petitioners, * * v. * * SECRETARY OF HEALTH * AND HUMAN SERVICES, * * Respondent. *	No. 08-76V Special Master Dorsey Entitlement; SCN1A gene mutation; Severe Myoclonic Epilepsy of Infancy ("SMEI"); Dravet syndrome; seizure disorder; encephalopathy; Diphtheria Tetanus acellular Pertussis ("DTaP") vaccine; inactive polio virus ("IPV") vaccine; haemophilus influenza type B ("HiB") vaccine; pneumococcal conjugate vaccine ("Prevnar"); significant aggravation; alternative causation.

David L. Terzian, Rawls, McNelis & Mitchell, P.C., Richmond, VA, for petitioners.
Heather Lynn Pearlman, U.S. Department of Justice, Washington, DC, for respondent.

DECISION DENYING ENTITLEMENT[1]

I. Introduction

On February 6, 2008, Michael B. Waters and Kim K. Waters ("petitioners") filed a petition for compensation under the National Vaccine Injury Compensation Program ("the Program")[2] as the parents and legal representatives of their son, Karsen Steele Waters

[1] Because this published decision contains a reasoned explanation for the action in this case, the undersigned intends to post this decision on the website of the United States Court of Federal Claims, in accordance with the E-Government Act of 2002 § 205, 44 U.S.C. § 3501 (2006). In accordance with the Vaccine Rules, each party has 14 days within which to request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). Further, consistent with the rule requirement, a motion for redaction must include a proposed redacted decision. If, upon review, the undersigned agrees that the identified material fits within the requirements of that provision, such material will be deleted from public access.

[2] The Program comprises Part 2 of the National Childhood Vaccine Injury Act of 1986, 42 U.S.C. §§ 300aa-10 et seq. (hereinafter "Vaccine Act" or "the Act"). Hereafter, individual section references will be to 42 U.S.C. § 300aa of the Act.

("Karsen"), in which they allege that the Diphtheria Tetanus acellular Pertussis ("DTaP"), inactive polio virus ("IPV"), haemophilus influenza type B ("HiB"), and pneumococcal conjugate ("Prevnar") vaccines that Karsen received on February 19, 2005, caused him to develop severe neurological complications. Petition ("Pet.") at 1. Respondent recommended against compensation. Respondent's Report ("Resp't's Rep't"), filed Aug. 15, 2012, at 2.

During the course of the proceedings, the parties discovered and do not dispute that Karsen was born with a mutation of his SCN1A gene and that he has Dravet syndrome.[3] Petitioners allege that "Karsen suffers from Severe Myoclonic Epilepsy of Infancy ('SMEI'), also known as Dravet syndrome, as a result of [his February 19, 2005 vaccinations], or alternatively, suffers from a significant aggravation of his Dravet syndrome as a result of the administration of the aforesaid immunizations." Petitioners' Pre-Hearing Brief ("Pet'rs' Pre-Hearing Brief"), filed April 9, 2013, at 2. Petitioners also claim that Karsen now suffers from "a severe encephalopathy with debilitating seizures and global developmental delays, including significant cognitive impairment, all of which have persisted to the present time." Id.

Respondent asserts that petitioners cannot establish a prima facie case as they fail to prove either the elements for an off-Table causation claim or the elements required for a significant aggravation claim. Resp't's Pre-Hearing Brief, filed July 12, 2013, at 4. Respondent asserts that Karsen's SCN1A mutation is the sole cause of his neurological condition (Dravet syndrome) and that his vaccinations did not affect his clinical course. Id. at 6-8. Although respondent indicates that Karsen's vaccinations may have triggered an earlier onset of his Dravet syndrome, as manifested by his first seizure, respondent maintains that his vaccinations did not have any material effect on his neurological condition, prognosis, or outcome. Id. at 7-10.

The parties agree and stipulate that the issue for the undersigned to decide is "whether Karsen's February 19, 2005 vaccinations can and did cause and/or significantly aggravate[] his injury." Stipulation of Facts ("Stip. of Facts"), filed August 15, 2012, at 1.

The undersigned finds that there is not a preponderance of the evidence showing that Karsen's injuries were caused or significantly aggravated by his February 19, 2005 vaccinations. Although Karsen's vaccinations may have caused a low grade fever or otherwise triggered his first seizure on February 20, 2005, neither that initial seizure nor his vaccinations caused or significantly aggravated his Dravet syndrome and resulting neurological complications. Rather, his SCN1A genetic mutation is the sole cause of his injuries. For that reason, the undersigned finds by a preponderance of the evidence that respondent has provided an alternative cause of Karsen's injuries, and, therefore, petitioners are not entitled to compensation.

In the discussion below, the undersigned describes the pertinent factual background as stipulated to by the parties, a description of the genetic mutation and background information on Dravet syndrome (the seizure disorder from which Karsen suffers), and a history of the procedural developments in this case. In the discussion section, the undersigned separately reviews the applicable standards of proof for causation and significant aggravation and then

[3] Dravet syndrome is a severe epilepsy of infancy. See Section V, infra, for a more complete description.

analyzes the arguments and evidence as presented by the parties. Finally, the undersigned discusses whether respondent presented sufficient evidence to prove alternative causation.

II. Factual Background

While the undersigned has considered all the evidence in this case and has considered the record as a whole, the parties have stipulated to the facts set forth in respondent's Rule 4 report. See Resp't's Rep't, at 1; see also § 300aa-13(a) (stating that the special master should consider the "record as a whole"). Thus, the following facts are taken verbatim from respondent's Rule 4 report without modification.

a. Facts Stipulated to by the Parties

Karsen was born on October 21, 2004, at Kapiolani Medical Center in Honolulu, Hawaii ("Kapiolani"). See Petitioner's Exhibit ("Pet. Ex.") 6 at 507; Pet. Ex. 3 at 23. He was delivered vaginally at thirty-eight and three-sevenths weeks gestation. Pet. Ex. 3 at 23. The birth weight was 7 lbs., 12 oz. Id. His Apgar scores were seven (7) and nine (9). Id. Karsen's neonatal course was unremarkable and he was discharged in good health on October 22, 2004. See Pet. Ex. 4 at 8-20.

Of note, Karsen's mother was forty years old at the time of delivery, gravita four, para two, and abortus zero. Id. She was noted to be of advanced maternal age, with a triple test that showed increased Down syndrome risk, and GBS positive serology non-reactive. Pet. Ex. 3 at 7. See also id. at 83. She was diagnosed with gestational diabetes and started on insulin on July 28, 2004, at approximately twenty-six weeks gestation. Pet. Ex. 3 at 38, 41. One month before Karsen's delivery, Dr. Greigh L. Hirata, M.D., Medical Director of Maternal Fetal Medicine at Kapiolani, concluded: "Impression at this time is intrauterine pregnancy at 34-1/2 weeks with gestational diabetes class A 2, poorly controlled." Pet. Ex. 4 at 2 (emphasis added). As a result, Dr. Hirata enrolled her in the Sweeter Choice outpatient program ("Sweeter Choice") for dietary counseling and blood sugar monitoring. Id. Sweeter Choice continued to monitor her glucose levels through October 21, 2004, conducting routine adjustments of insulin dosages, and the remainder of her prenatal care was uncomplicated. See Pet. Ex. 21-23.

Karsen initially received his pediatric care from the Kwajalein Hospital in the Marshall Islands, where the Waters resided. He exhibited normal development at his one-month well child visit ("WCV") on November 23, 2004. Pet. Ex. 5 at 2. On December 29, 2005, during his two-month WCV, Karsen received the first administration of the DTaP, IPV, HiB, and Prevnar vaccination. Id. at 4, 6. He was noted to be both developmentally and physically normal. Id. at 6. His head circumference placed him in the 5th percentile of the American Academy of Pediatrics growth chart. Id. at 3. His weight was normal at 8 lbs., 2 oz. Id.

On February 19, 2005, more than seven weeks after the first series of vaccination, Karsen returned to Kwajalein Hospital for his four-month WCV. Pet. Ex. 5 at 7. Dr. Jillian Homer, M.D., observed normal physical and neurological development. Id.

Karsen weighed 12 lbs., 13 oz. Id. He received the second administration of the DTaP, IPV, HiB, and Prevnar vaccination. Id. at 4, 7.

On February 20, 2005, Karsen arrived to the Kwajalein Hospital emergency room ("ER") with "seizure activity." Pet. Ex. 5 at 8. Karsen's symptoms were reported to have started when his mother, holding him, noticed his leg twitching and then his whole body shaking. Id. According to a nurse's notation, Karsen's father "was able to give child swallows of water during [the] event [and, thereafter the] child quit shaking." Id. The Waters further stated that Karsen was "fussy" the night before with a low grade fever. Id. He was reportedly nursing well and did not have any nausea and vomiting or change in diapers. Id. The nurse recorded a temperature of 99.2º F axillary at 9:30 p.m. and 99.9º F rectally at 9:50 p.m. Id. At 9:40 p.m., medical personnel observed him to be nursing and hungry. Pet. Ex. 5 at 8. Dr. Edward T. Paget, M.D., admitted Karsen overnight for observation. Id.

The initial admission note indicates that Karsen's seizure lasted approximately five minutes in duration, beginning with jerking of his right leg and arm. Pet. Ex. 5 at 10. Karsen was able to swallow water according to his father even though he was flaccid. Id. The note also states that Karsen's mother "noticed some fever," which she treated with Tylenol in the morning. Id. According to the Waters, Karsen "seemed to be OK" before leaving for the ER. Id.

Karsen's physical examination, which Dr. Paget conducted, was normal, including with respect to Karsen's neurological status. See Pet. Ex. 5 at 9-15. His complete blood count ("CBC") was 13.4 for white blood cells with 37 neutrophils and 55 lymphocytes. Id. at 15. At 10:30 p.m., a nurse observed, "the baby interacts well with both parents and was awake, voided, breastfeeding by mother." Id. at 27. Dr. Paget's assessment was seizure activity secondary to immunization, id. at 9, 10, and "possible immunization reaction." Id. at 22. After twelve hours of observation, Dr. Paget discharged Karsen on February 21, 2005, with a recommendation for a follow up at his six-month WCV. Id. at 10, 18, 19.

According to an undated seizure record, Karsen experienced an approximately five minute seizure involving his left leg on February 28, 2005. Pet. Ex. 5 at 16. This same record indicates that Karsen suffered two other "small" seizures within one hour of each other on March 6, 2005. Id. The first seizure episode reportedly affected the left forearm and the second, three minute seizure episode affected the left arm. Id.

On March 17, 2005, Karsen underwent an electroencephalography ("EEG") and magnetic resonance imaging ("MRI"). Pet. Ex. 5 at 42-46. The MRI of the brain was normal. Id. at 44. The interpreting physician, Dr. Mitchell A. Moy, M.D., at Kapiolani, observed: "No mass, hemorrhage, or encephalomalacia. No evidence of schizencephaly. No cortical dysplasia is encountered. The degree of myelination is normal for age. Normal size and position of the ventricles. There are normal flow voids in the major arteries at the base of the brain." Pet. Ex. 5 at 44. The EEG was also normal. Id. at 42.

On March 28, 2005, Karsen and his mother presented to neurologist Dr. Richard D. Bart, M.D., in Honolulu, Hawaii. See Pet. Ex. 6 at 613. Dr. Bart recorded Karsen's first three episodes of seizures:

> [H]e had three seizures, with the first having occurred roughly 25 days ago. It occurred approximately 24 hours after immunization, was right sided, involving arm and leg, with loss of consciousness, or loss of awareness, and lasting for approximately 8 minutes. He was lethargic, and was not moving the right side for a period of time thereafter. The second occurred roughly a week later, and involved his left side, las[t]ing for about 5 minutes, and again, with a postictal period, with a transient Todd's paralysis. The third occurred roughly a week after that, and was roughly a week ago, involving his left arm, lasting for 3 minutes, with him much more alert and interactive during the event.

Id. at 613. Dr. Bart stated that all of the seizures were afebrile. Id. He observed that "[Karsen's] development seems to have been perfectly normal, if not precocious." Id. Karsen's physical, including neurological examination, was normal. Id. Dr. Bart opined:

> One has to wonder whether or not the seizures are related to the immunization. On the other hand, a child who's in the first six months of life who has a seizure will have it within a month or two of an immunization just by chance. On the other hand [sic] he fulfills the criteria for the National Immunization Act; [sic] having a seizure within 24 hours of an immunization.

Pet. Ex. 6 at 614. The doctor's impression was multifocal seizure disorder, right- and left-sided, of unknown etiology but temporally related to immunization. Id. Dr. Bart recommended an additional MRI and EEG. Id.

Two days later, on March 30, 2005, Karsen returned to Dr. Bart with his mother. Pet. Ex. 6 at 615. Dr. Bart reported to Karsen's mother that the MRI and EEG were again normal. Id. He confirmed no additional seizures since February 28, 2005. Id. He decided to defer the start of medication, but advised Dr. Homer at Kwaijalein Hospital to start Karsen on Phenobarbital, 5 mg/kg a day, if Karsen suffers another seizure. Dr. Bart further noted:

> when it comes time for his next immunization, I would not give him the pertussis portion of the DPaT [sic], recognizing that this could have been an allergic reaction or other reaction to the immunization, and while we don't know that for sure, if it was, the next time around may be an even more serious reaction.

Id. at 615. Records reflect that Karsen was not again vaccinated. See, e.g., Pet. Ex. 5 at 4.

Later on March 30, at 7:00 p.m., Karsen was seen by the ER at Kapiolani for a seizure episode. His temperature was 99.2º F rectally.

Having returned to the Marshall Islands, Karsen had his six-month WCV at Kwaijalein Hospital on May 20, 2005. See Pet. Ex. 5 at 58. With the exception of atopic

dermatitis affecting Karsen's skin, his physical examination was normal. Id. Immunizations were deferred secondary to parental request. Id.

Shortly after his WCV, at 2:30 p.m., EMS transported Karsen to the Kwaijalein Hospital ER as a consequence of a petit mal seizure lasting ten minutes. Pet. Ex. 5 at 59-64. His temperature was 97.2º F. Id. at 59. His physical was benign. Id. at 63. Dr. John Janikowski, D.O., M.D., discharged Karsen with an instruction to follow-up as needed. Id. at 60, 69.

At 7:40 p.m., Karsen returned to the ER with a chief complaint of seizure activity. Pet. Ex. 5 at 61. His temperature was 100.2º F. Id. at 70. His mother provided a history of congestion and vomiting. Id. at 69. A chest x-ray revealed signs of possible pneumonia. Id. at 57. Dr. Janikowski observed a seizure in progress. See id. He stated, "[Seizure …] was in progress. Eyes were rolled back [and] there was tonic clonic movements in 4 extremities and facial twitching." Pet. Ex. 5 at 69. Dr. Janikowski wrote on the inpatient story/assessment note: "?? onset of seizure disorder related to 2nd set of immunizations." Id. Dr. Janikowski controlled Karsen's seizures with Valium. Id. at 78-79. Karsen was not intubated. See id. He was discharged on March 22, 2005, with a diagnosis of status epilepticus, seizure disorder, bronchitis, and atopic dermatitis. Id. at 83.

On May 29, 2005, Karsen once again presented to the Kwaijalein Hospital ER for seizure activity of approximately one hour in duration. See Pet. Ex. 6 at 570. Reportedly, he had three seizures in succession during that hour. Id. Karsen was afebrile. Pet. Ex. 5 at 126. He was given Valium by EMS and then Ativan 0.8 mg IV, which calmed the seizure activity. Pet. Ex. 6 at 570.

Karsen was transferred from the Marshall Islands to Kapiolani on the same day for further observation and treatment, and he was admitted. Id. There, Karsen's mother reported that Karsen "started to have rash and fever and had break-through seizures the day after the immunizations." Pet. Ex. 6 at 570. She also related that one week ago Karsen had a breakthrough seizure because of poor sleep. Id. On examination, Dr. New Sang, M.D., observed Karsen to be resting comfortably, moving all four extremities equally, and no focal deficits. Id. He prescribed Ativan at bedside of 0.1 mg/kg and Tegretol 30 mg/kg per day and recommended, inter alia, a neurology consultation and EEG. Id. In his assessment, Dr. Sang wrote:

> Although mom attributes seizures to a reaction to four-month immunizations, the origin of the seizures are dubious at this time. In addition, the patient has a sleep disorder with only being able to sleep 2-3 hours at a time and when the patient does not get any sleep, the mom notes that the patient has break-through seizures. This may also may [sic] contribute to the patient's seizure disorder although it is difficult to tell given the lack of evidence for the etiology of these seizures.

Id.

On May 30, 2005, neurologist Dr. Bart examined Karsen. See Pet. Ex. 6 at 394. Dr. Bart noted a history of recent seizures about once every seven to ten days, predominately right-sided and accompanied occasionally by transient post-seizure weakness. Id. He noted that Karsen had gone two to two and half days without a seizure. Id. His neurological examination continued to be "normal." Id. Dr. Bart diagnosed Karsen with "[p]artial seizures with secondary generalization, at least involving the left motor strip." Id. He recommended an EEG and continuation of Tegretol. Id.

On May 31, 2005, Dr. Sang observed a ten minute seizure. Pet. Ex. 6 at 396. Karsen had twitching of the right extremities and eyelid. Id. His left-side was normal. Id. Dr. Sang treated Karsen with a dose of Diastat rectally at approximately four to five minutes after the start of the seizure. Id. Karsen's EEG was normal on June 1, 2005. Pet. Ex. 5 at 160. Karsen again, however, suffered a seizure, which lasted approximately twenty minutes starting with an absence followed by clonic movements generalized. Pet. Ex. 6 at 366.

Dr. Bart again examined Karsen on June 4, 2006. See Pet. Ex. 6 at 406. Dr. Bart noted that Karsen "continued to have nearly daily morning or afternoon partial seizures with secondary generalization which, for the most part, have required either Diastat or Ativan to break." Id. As a result of Karsen becoming "fussy and irritable" on Tegretol, Dr. Bart, in consultation with other doctors at Kapiolani, switched Karsen to Dilantin. Id.

On June 7, 2006, more than a week into Karsen's hospital admission, Dr. Bart reported that Karsen had "now gone a little more than 48 hours without any seizures. That is the longest he has gone since admission." Pet. Ex. 6 at 580. Physicians had decreased the Tegretol by fifty percent on June 5, 2005. Id. Dr. Bart indicated that Tegretol would finally be stopped completely on this date. Id. He noted, "[the Waters] are convinced that the Tegretol was causing the seizures." Id. It appears Karsen was discharged on or about June 14, 2008. See Pet. Ex. 6 at 588.

On June 20, 2005, Karsen was admitted to the ER as a result of another seizure episode. Pet. Ex. 6 at 310. His mother witnessed a seizure of three to four minutes in duration before beginning to administer rectal Diastat without any effect. Id. at 322. Dr. Bart examined Karsen on June 21, 2005. Id. at 314. Dr. Bart noted that Karsen was admitted to the pediatric intensive care unit after a forty-five minute seizure. Id. Karsen was intubated. Id. Although Karsen did not respond to 5 mg of Diastat, he did respond to 10 mg/kg load of Fosphenytoin. Id. Dr. Bart recommended that Karsen's Dilantin prescription be increased from 25 to 50 mg. Pet. Ex. 6 at 314.

As the summer continued and into fall 2005, Karsen's partial seizures perpetuated, occurring approximately one time per week and included the variety of different types of seizures including the left or right partial complex-sided seizures, grand mal seizures, and absence seizures. Pet. Ex. 8 at 1.

At some point that summer or early fall, the Waters moved to Grover Beach, California. See Pet. Ex. 7 at 3. On September 27, 2005, Karsen was admitted to UCLA

Westwood campus because of seizure activity. See Pet. Ex. 8 at 19-21. The September 30, 2005 discharge diagnosis by Dr. Barbara Changizi, M.D., was "[l]ikely idiopathic generalized epilepsy with generalized clonic tonic seizures and myoclonic jerks." Id. at 18. An addendum notes that Karsen's development was normal and consistent with primary generalized seizure. Id. at 21.

From September 28, 2005, to September 30, 2005, Karsen had a video telemetry performed. Pet. Ex. 7 at 39. This was noted to be abnormal. Id. There were three episodes of subtle myoclonic jerks. Id. In addition, occipital intermittent rhythmic delta activity was noted. Id.

On November 2, 2005, Dr. Debra Balke, M.D, a pediatric neurologist in Templeton, California, examined Karsen. See Pet. Ex. 7 at 2-4. At the time, he was taking Phenobarbital 30 mg and Topamax 30 mg twice a day ("b.i.d.") to control his seizures. Id. at 2. Dr. Balke observed that Karsen was experiencing medically intractable epilepsy of unknown etiology. Id. at 4. She noted, "He did have a past normal EEG but this is surprising given the abnormalities seen at UCLA." Id. at 2. Dr. Balke ordered blood work for chromosomes analysis and metabolic work up, which resulted in normal findings. See Pet. Ex. 7 at 28-35. On examination, Dr. Balke observed some developmental delay:

> He can pull to stand, get into a sitting position, but cannot stand alone. He cannot say Mama or Dada specifically yet. He did seem to regress in his development after the long seizure in August 2005. He tends to hold his hands more fisted now. He is not yet pointing. He can indicate desires somewhat. He is not yet waving bye bye."

Id. at 3. Dr. Balke recommended that Karsen be gradually tapered off from Phenobarbital, "for fear that this is worsening his seizure activity," and rely entirely on Topamax 30 mg b.i.d instead. Id. at 4.

More recently, Dr. Steffane Battle, M.D., an Alabama pediatric neurologist examined Karsen on June 7, 2007. Pet. Ex. 10 at 3. Karsen's prescriptions included Topamax 150 mg per day, Ativan 2.5 mg a day, Diastat 2.5 mg when necessary, and Keppra 21 ml per day. Id. at 4. He was also started on the ketogenic diet in February 2007 on a 3:1 ratio. Pet. Ex. 10 at 3. Dr. Battle noted Karsen's history of seizure activity beginning "on February 24, 2004, within 24 hours after his DTAP immunization. His initial seizure was approximately 35 minutes." Id. He further reported that, "[c]urrently, [Karsen's] primary seizure types are tonic seizures and, by parents' report, he is having over 100 per day. He has generalized tonic clonic seizures every other month. He has occasional absence seizures and about two complex seizures per month." Id. Despite the severity of his seizures, Dr. Battle observed continued developmental gains: He sat at six to seven months, stood at eight to nine months, walked at fourteen to fifteen months of age. Id. at 4. Dr. Battle attributed the cognitive side effects to Karsen's medication. Id. His overall impression was "generalized mixed seizure disorder, which is refractory to multiple medications." Id.

On November 28, 2007, Karsen presented to Dr. Martina Bebin, M.D., a pediatric neurologist in the North Alabama Children's Health System. See Pet. Ex. 10 at 12-13. Dr. Bebin noted that Karsen was scheduled to have a vagus nerve stimulation ("VNS") implant the first week of December to possibly improve his seizure control. Id. at 12. She also reported that, from October 18, 2007, to November 28, Karsen had not had any hospitalizations. Id. His medications included Lamictal 25 mg b.i.d., Keppra 1000 mg in the morning and 1250 mg at night, Klonopin 0.25 mg b.i.d., Dilantin 30 mg in the morning and 60 mg at night, Topamax 100 mg b.i.d., and Diastat 7.5 mg for seizure clusters. Id. Karsen was on the 4:1 ratio of the ketogenic diet. Id. On exam, Karsen was alert and interactive, but had some brief clusters of atonic seizures. Id. Dr. Bebin did not observe focal deficits on his neurological examination. Pet. Ex. 10 at 12. Her impression was "three year old with a history of mixed generalized seizures consistent with Lennox-Gastaut syndrome."[4] Id. at 13. The VNS implant was inserted in Karsen on December 6, 2007. Pet. Ex. 10 at 14.

b. Genetic Testing, SCN1A Mutation, and Dravet syndrome

In addition to the facts set forth above, the following facts relate to Karsen's SCN1A gene mutation and Dravet syndrome.

(1) Genetic Testing/SCN1A Mutation

On December 12, 2008, Karsen presented to Dr. Bebin for a follow-up of his seizure disorder. Petitioners' Exhibit ("Pet'rs' Ex.") 38 at 14. Dr. Bebin noted that Karsen was continuing to have tonic-clonic seizures approximately every 7-10 days. Id. Karsen remained on Dilantin and other anti-seizure medication. Id. He was also on a ketogenic diet. Id. At this visit, Dr. Bebin recommended that Karsen be tested for the SCN1A genetic mutation and for Dravet syndrome. Id. Dr. Bebin reviewed the diagnostic criteria, clinical course, and prognosis of Dravet syndrome with Karsen's family. The family agreed to the genetic testing. Id.

On December 29, 2008, Karsen's genetic testing results detected a missense[5] gene mutation in "exon 5 of the patient sample: C.680T>G P.Ile 227 Ser (Heterozygous)." Pet'rs' Ex. 38 at 64. Warren Sanger, Ph.D., FACMG, provided the following interpretation: "this missense mutation has been reported in other SMEI patients in the medical literature and seen in the spectrum of SCN1A mutations in severe myoclonic epilepsy in infancy ('SMEI')." Id. The lab report also provided the following general information about Karsen's SCN1A missense mutation:

[4] Lennox-Gastaut syndrome is "an atypical form of absence epilepsy characterized by diffuse slow spike waves, often with atonic, tonic, and clonic seizures and mental retardation; there may also be other neurological abnormalities or multiple seizure types. Unlike typical absence epilepsy, it may persist into adulthood." Dorland's Illustrated Medical Dictionary ("Dorland's") 1837 (32[d] ed. (2012)).

[5] Missense, in genetics, pertains to a "mutation in which a codon is altered so that it encodes a different amino acid from that found in the wild type." Dorland's at 1169.

> The sodium channel is a voltage-gated ion channel essential for the generation and propagation of action potentials in nerve and muscles. Mutations in the . . . (SCN1A) gene have been reported in patients with severe myoclonic epilepsy in infancy (SMEI) …

Id.

On January 8, 2009, Dr. Bebin diagnosed Karsen with "SCN1A-myoclonic astatic epilepsy," based upon the results of his genetic testing. Id. at 16. Based on this diagnosis, Dr. Bebin recommended a new medication, stiripentel, for Karsen's seizures. Id.

(2) Dravet Syndrome

Dravet syndrome is a rare syndrome with an incidence of 1:40,000 children. Pet'rs' Ex. 92.[6] Seventy to 80% of Dravet syndrome cases are caused by SCN1A mutations. Id. Ninety percent of these mutations are de novo.[7] Id. The gene which is affected by the mutation is in the alpha subunit of the SCN1A gene, which "encodes the voltage-dependent sodium channel (Nav 1.1)." Pet'rs' Ex. 95 at 79.[8] The SCN1A gene is "an important epilepsy-related sodium channel gene." Pet'rs' Ex. 107at 9.[9] Research has shown that there is a "powerful network hyperexcitability underlying Dravet syndrome, a severe epilepsy of infancy." Id.

Dravet syndrome is also referred to as Severe Myoclonic Epilepsy of Infancy (SMEI) and is an epilepsy syndrome that starts at about six months of age. Respondent's Exhibit ("Resp't's Ex.") Y2 at 1.[10] Initial seizures may be accompanied by fever. Id. Development is generally normal at the onset of the disease, but then there is a subsequent and progressive decline in intellectual function. Id. The time frame in which the disease first presents "overlaps" with the schedule of routine childhood vaccinations. Id. Children with Dravet syndrome usually have clonic[11] seizures in the first year of life, followed by myoclonic[12] seizures. In addition to

[6] Claudia B. Catarino et al., "Dravet syndrome as epileptic encephalopathy: evidence from long-term course and neuropathology," 134 Brain 2982, 2983 (2011).
[7] De novo is a Latin expression meaning "from the beginning." Merriam-Webster, available at http://www.merriam-webster.com/dictionary/denovo. In this context, a "de novo mutation " is used to mean "an alteration in a gene that is present for the first time in one family member as a result of a mutation in a germ cell (egg or sperm) of one of the parents or in the fertilized egg itself." Genetics Home Reference – NIH, http://ghr.nlm.nih.gov/glossary=denovomutation
[8] Akihisa Okumura et al., "Acute encephalopathy in children with Dravet syndrome," 53(1) Epilepsia 79, 79 (2012).
[9] Tara Klassen et al., "Exome Sequencing of Ion Channel Genes Reveals Complex Profiles Confounding Personal Risk Assessment in Epilepsy," 145 Cell 1036, 1043 (2011).
[10] Blanca Tro-Baumann et al., "A retrospective study of the relation between vaccination and occurrence of seizures in Dravet syndrome," 52(1) Epilepsia 175, 175 (2011).
[11] Clonic is an adjective of the word "clonus" which is defined as "alternate muscular contraction and relaxation in rapid succession." Dorland's at 373.

developmental delay, the children may have an ataxic[13] gait. Pet'rs' Ex. 60 at 1.[14] The seizures are refractory to treatment. Id.

The clinical course of Dravet syndrome is "characterized by onset of recurrent febrile and/or afebrile hemiclonic or generalized seizures…. in a previously healthy infant." Pet'rs. Ex. 92 at 2.[15] The seizures usually evolve into multiple types of seizures which are drug resistant. Id. By the second year of life, children usually have an encephalopathy with cognitive, behavioral and developmental delays. Id.; Resp't's Ex. Z9 at 2.[16] Even children with Dravet syndrome who have well controlled epilepsy experience developmental problems. Id. at 4.

c. Chronology of Developmental Delay

In addition to the parties' stipulated facts and the summary of the facts surrounding Karsen's genetic testing for the SCN1A gene mutation, the following facts provide a chronology of Karsen's developmental delay.

On March 17, 2005, approximately one month after the vaccinations at issue and Karsen's initial seizure, Karsen had a normal EEG. Pet'rs' Ex. 5 at 42; Pet'rs' Ex. 6 at 540-41. An MRI performed on March 17, 2005, was also normal. Pet'rs' Ex. 5 at 44; Pet'rs' Ex. 6 at 540-41. On March 28, 2005, Dr. Bart documented that Karsen's development was normal. Dr. Bart described Karsen as "alert, interactive, and precocious." Pet'rs' Ex. 5 at 47-48.

On May 29, 2005, Karsen was diagnosed with status epilepticus. Pet'rs' Ex. 5 at 126. Karsen's treating physician, Dr. Jeremy Lam, stated that Karsen had a history of "2 seizures within the last 10 d[ays] . . . classified as status epilepticus (>30 minutes). Today's seizure [May 29, 2005] lasted >1 [hour] in spite of oral tegretol on board." Id. Even after having status epilepticus, Karsen's neurological examination remained normal. On May 30, 2005, Dr. Bart wrote that Karsen's neurological examination "continues to be normal." Id. at 162. An EEG performed on June 1, 2005, was also normal. Id. at 160.

On June 21, 2005, at eight months of age, and four months after the subject vaccinations, Karsen was again noted to be neurologically normal. He was "moving all extremities, tracks across midline, rolls over, good head control." Pet'rs' Ex. 6 at 296.

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[12] Myoclonic seizures are characterized by "shocklike contractions of a portion of a muscle, an entire muscle, or a group of muscles, restricted to one area of the body or appearing synchronously or asynchronously in several areas." Dorland's at 1222.

[13] Ataxia is the "failure of muscular coordination; irregularity of muscular action." Dorland's at 170.

[14] Renzo Guerrini & Hirokazu Oguni, "Borderline Dravet syndrome: A useful diagnostic category?," 52(2) Epilepsia 10, 10 (2011).

[15] Catarino, see supra footnote 6.

[16] A. Brunklaus, et al., "Prognostic, clinical and demographic features in SCN1A mutation-positive Dravet syndrome,"135 Brain 2329, 2330 (2012).

On June 26, 2005, Karsen's mother expressed concerns regarding his floppiness and unsteadiness after he had received Dilantin. Pet'rs' Ex. 6 at 295. Two weeks later, however, on July 13, 2005, Karsen was described by Dr. Bart as being "back to usual self." Pet'rs' Ex. 5 at 167. On July 27, 2005, Dr. Bart documented that Karsen, now age nine months, was "back to usual self, and continues to show progress developmentally. He can now pull to a stand and cruise . . . is socially very interactive." Id. at 168. An MRI performed on August 31, 2005, was normal, as was an EEG performed on September 1, 2005. Pet'rs' Ex. 6 at 768, 772-73.

On September 15, 2005, Karsen was described as having mild developmental delays and loss of some developmental milestones. Pet'rs' Ex 6 at 19, 20, 24. On November 2, 2005, Karsen's behavior was described as "younger than stated age." Pet'rs' Ex. 7 at 2-4. By January 4, 2006, Karsen was having "50 small myoclonic seizures per day" and he was diagnosed with "catastrophic epilepsy." Id. at 5. By March 3, 2007, he had a six-month developmental delay. Id. at 14. "The development has been delayed. The child did walk at 14 months but at present says only 10 words. He is repeating words. He can feed himself with a spoon only sloppily." Pet'rs' Ex. 39 at 81-82. Karsen's developmental delay continued along with his intractable seizures. See Pet'rs' Ex. 38 at 8, 9, 12.

d. Procedural History

Petitioners filed their petition on February 6, 2008. Respondent filed her report pursuant to Vaccine Rule 4(c) on May 2, 2008. Petitioners filed four expert reports from Dr. Yuval Shafrir and one from Dr. Frances Kendall. Respondent filed four expert reports from Dr. Max Wiznitzer and three from Dr. Gerald Raymond. In total, the parties filed 120 medical texts and articles. The parties also filed pre-hearing briefs.

A two-day hearing was held on July 23-24, 2013. Mrs. Waters and Karsen were present for the first day of the hearing. On the first day of the hearing, Drs. Shafrir and Kendall testified on behalf of petitioners and Dr. Raymond testified on behalf of respondent. On the second day of the hearing, Dr. Wiznitzer testified on behalf of respondent and Drs. Shafrir and Kendall again testified on behalf of petitioners. The parties did not request to file post-hearing briefs. The matter is now ripe for adjudication.

III. Discussion

The Vaccine Act established the Program to compensate vaccine-related injuries and deaths. § 300aa-10(a). "Congress designed the Vaccine Program to supplement the state law civil tort system as a simple, fair and expeditious means for compensating vaccine-related injured persons. The Program was established to award 'vaccine-injured persons quickly, easily, and with certainty and generosity.'" Rooks v. Sec'y of Health & Human Servs., 35 Fed. Cl. 1, 7 (1996) (quoting H.R. Rep. No. 908 at 3, reprinted in 1986 U.S.C.C.A.N. at 6287, 6344).

A. Standards for Adjudication – Causation

To establish causation in fact, a petitioner must show by a preponderance of the evidence that but for the vaccination, the petitioner would not have been injured, and that the vaccination was a substantial factor in bringing about the injury. Cedillo v. Sec'y of Health & Human

Servs., 617 F.3d 1328, 1338 (Fed. Cir. 2010); Shyface v. Sec'y of Health & Human Servs., 165 F.3d 1344, 1352 (Fed. Cir. 1999). Proof of actual causation must be supported by a sound and reliable "medical or scientific explanation that pertains specifically to the petitioner's case, although the explanation need only be 'legally probable, not medically or scientifically certain.'" Moberly v. Sec'y of Health & Human Servs., 592 F.3d 1315, 1322 (Fed. Cir. 2010) (quoting Knudsen v. Sec'y of Health & Human Servs., 35 F.3d 543, 548-49 (Fed. Cir. 1994)); see also Grant v. Sec'y of Health & Human Servs., 956 F.2d 1144, 1148 (Fed. Cir. 1992) (medical theory must support actual cause). "[A] petitioner must demonstrate the reliability of any scientific or other expert evidence put forth to carry this burden . . . . Expert testimony, in particular, must have some objective scientific basis in order to be credited by the Special Master." Jarvis v. Sec'y of Health & Human Servs., 99 Fed. Cl. 47, 54-55 (2011) (citing Moberly, 592 F.3d at 1322; Cedillo, 617 F.3d at 1339; Terran v. Sec'y of Health & Human Servs., 195 F.3d 1302, 1316 (Fed. Cir. 1999)).

Causation is determined on a case-by-case basis, with "no hard and fast per se scientific or medical rules." Knudsen, 35 F.3d at 548. A petitioner may use circumstantial evidence to prove the case, and "close calls" regarding causation must be resolved in favor of the petitioner. Althen v. Sec'y of Health & Human Servs., 418 F.3d 1274, 1280 (Fed. Cir. 2005).

To receive compensation under the Program, petitioners must prove either: (1) that Karsen suffered a "Table Injury"—i.e., an injury listed on the Vaccine Injury Table—corresponding to a vaccine that he received, or (2) that Karsen suffered an injury that was actually caused by the vaccine (or vaccines) he received. See §§ 300aa-13(a)(1)(A) and 11(c)(1); Capizzano v. Sec'y of Health & Human Servs., 440 F.3d 1317, 1319-20 (Fed. Cir. 2006). Petitioners must show that a vaccine was "not only a but-for cause of the injury but also a substantial factor in bringing about the injury." Moberly, 592 F.3d at 1321 (quoting Shyface, 165 F.3d at 1352-53).

Because petitioners do not allege that Karsen suffered a Table injury, they must prove that a vaccine Karsen received caused his injury. To do so, they must establish, by preponderant evidence: (1) a medical theory causally connecting a vaccine and Karsen's injury ("Althen Prong One"); (2) a logical sequence of cause and effect showing that a vaccine was the reason for his injury ("Althen Prong Two"); and (3) a showing of a proximate temporal relationship between a vaccinee and his injury ("Althen Prong Three"). Althen, 418 F.3d at 1278; § 300aa–13(a)(1) (requiring proof by a preponderance of the evidence).

B. Causation Theory

The first issue presented to the undersigned is whether Karsen's February 19, 2005 vaccinations can and did cause his injury. Stip. of Facts, at 1. As an initial matter, it must be clarified that the parties do not dispute that Karsen was born with a mutation of his SCN1A gene and that the vaccinations at issue in this case did not cause this gene mutation. Id. The parties dispute whether the vaccinations at issue caused Karsen to develop a seizure disorder, i.e., Dravet syndrome, and the resulting complications. The undersigned finds that it did not.

(1) **Althen Prong One: Petitioners' Medical Theory**

Under Althen Prong One, petitioners must set forth a medical theory explaining how the received vaccine could have caused the sustained injury. Andreu v. Sec'y of Health & Human Servs., 569 F.3d 1367, 1375 (Fed. Cir. 2009). Under this prong, petitioners must make a showing that the received vaccine "can" cause the alleged injury. Pafford v. Sec'y of Health & Human Servs., 451 F.3d 1352, 1355-56 (Fed. Cir. 2006).

Petitioners' theory of causation need not be medically or scientifically certain, Knudsen, 35 F.3d at 548-49, but it must be informed by "sound and reliable medical or scientific explanation." Id. at 548; see also Veryzer v. Sec'y of Health & Human Servs., 98 Fed. Cl. 214, 223 (2011) (noting that special masters are bound by both § 300aa-13(b)(1) and Vaccine Rule 8(b)(1) to consider only evidence that is both "relevant" and "reliable"). If petitioners rely upon a medical opinion to support their theory, the basis for the opinion and the reliability of that basis must be considered in the determination of how much weight to afford the offered opinion. See Broekelschen v. Sec'y of Health & Human Servs., 618 F. 3d 1339, 1347 (Fed. Cir. 2010) ("The special master's decision often times is based on the credibility of the experts and the relative persuasiveness of their competing theories."); Perreira v. Sec'y of Health & Human Servs., 33 F.3d 1375, 1377 n.6 (Fed. Cir. 1994) ("An expert opinion is no better than the soundness of the reasons supporting it.") (citing Fehrs v. United States, 620 F.2d 255, 265 (Ct. Cl. 1980)).

a. Petitioners' Expert, Dr. Shafrir

Dr. Shafrir is a pediatric neurologist at Sinai Hospital in Baltimore. Tr. 9. He attended medical school in Israel, and then completed his pediatric internship in Israel. Id. After moving to the United States, he did a pediatric residency at Cornell University and completed his pediatric neurology training at Washington University in St. Louis. Id. Dr. Shafrir then trained in pediatric epilepsy at Miami Children's Hospital. Id. After completing his training, he entered practice in pediatric neurology. Id. Dr. Shafrir is board-certified in neurology with a specialty in pediatric neurology, clinical neurophysiology and epilepsy. Tr. 10. He has a pediatric neurology clinical practice where he sees and treats patients for "most of the day." Tr. 9.

Although Dr. Shafrir testified that the exact mechanism by which vaccinations may trigger Dravet syndrome is unknown, he proposes two possible theories. The first proposed theory is that Karsen's vaccinations may be a "second hit." Dr. Shafrir described the "second hit" mechanism as an "abnormal gene that make[s] the child . . . at high risk to develop a certain condition, but it's not enough." Tr. 45-46. "And in order to develop the condition, you have to have one more thing happen," which is the "second hit." Id. In essence, Dr. Shafrir's proposed "second hit" mechanism is simply that the child first has an abnormal gene which is essentially the first "hit". Id. The "second hit" is the DTaP[17] vaccination which becomes a trigger for the first seizure in a susceptible child. Tr. 46. The first seizure created an "equivalent second hit by changing in the brain [the] different ways [of] gene expression … and in chang[ing] the

[17] While petitioners allege that all of the vaccines Karsen received on February 19, 2005, caused his injuries, Dr. Shafrir's report focuses mainly on the DTaP vaccine. For purposes of the analysis of this decision, the undersigned will consider all vaccinations given to Karsen on February 19, 2005, as alleged in the petition.

excitatory and inhibitory cells." Id. "[W]e can make the assumption that the vaccination and the onset of the initial seizure is the same second hit that le[a]ds a child to have the full-blown Dravet syndrome." Id.

Dr. Shafrir's second proposed mechanism is based on an immune-mediated response to the DTaP vaccination. Tr. 98-99. Dr. Shafrir asserts that the immune-mediated hypothesis has been raised by the authors of the Catarino (Pet'rs' Ex. 92),[18] and McIntosh (Pet'rs' Ex. 59),[19] studies. Tr. 99-101. These authors and others have noted that immune-inflammatory mediators have received attention for the role that they may play in the genesis of epilepsy, febrile seizures, and some chronic epilepsies. The authors are hopeful that "Dravet syndrome may provide a model to advance understanding of inflammation in epileptogenesis and fever as a seizure provoking factor. The influence in Dravet syndrome of additional environmental factors such as vaccination may provide another window into investigation of immune factors in epileptogenesis." Pet'rs' Ex. 92 at 2.[20] These authors, however, have not established that such an immune-mediated mechanism exists. They are hopeful that through study of Dravet syndrome, further insight may be gained as to the cause of Dravet as well as other forms of epilepsy.

In addition to his two proposed causation theories, Dr. Shafrir also set forth several arguments to support his position that children with the SCN1A mutation are not destined to have severe Dravet syndrome and that vaccination may exacerbate the underlying disease. The first of these arguments deals with the issue of gene expression. According to Dr. Shafrir, gene expression is the phenotypic variation among those who have the same genetic mutation. Pet'rs' Ex. 112 at 14.[21] Dr. Shafrir argued that children with SCN1A-related seizure disorders could have variable expressivity. Id. at 15. Dr. Shafrir cited the Klassen (Pet'rs' Ex. 107)[22] study for support of his position that the same genetic mutation can have different clinical manifestations. Simply stated, a child with the SCN1A genetic mutation is not always destined to develop severe Dravet syndrome and the "full expression of the disease." Id. at 23, 26. Dr. Shafrir argued that the Klassen article also stressed the complexity of the neuronal circuits of the brain. Even if some of the circuits do not function due to genetic mutations, a patient can appear and function normally because there are compensating mechanisms. Tr. 39.

In the Klassen study, the authors studied 152 patients with epilepsy and 139 control patients who were "neurologically unaffected." Pet'rs' Ex. 107 at 2.[23] A missense mutation in a gene known to cause epilepsy was found in 96.1% of the epilepsy group and 66.9% of the control group. Id. at 3.[24] One individual in the control group had a variation of the SCN1A

[18] Catarino, see supra footnote 6.
[19] Anne M. McIntosh et al., "Effects of vaccination on onset and outcome of Dravet syndrome: a retrospective study," 9 Lancet Neurology 592 (2010).
[20] Catarino, see supra footnote 6.
[21] Petitioners' exhibit 112 is a PowerPoint presentation that Dr. Shafrir prepared and discussed during the hearing.
[22] Klassen, see supra footnote 9.
[23] Klassen, see supra footnote 9 at 1037.
[24] Klassen, see supra footnote 9 at 1038.

gene. The parties' experts disagreed about the significance of the presence of an SCN1A gene mutation in that individual. Dr. Shafrir argued that the fact that this individual with the SCN1A mutation was asymptomatic was proof that patients with the mutation are not destined to have severe Dravet syndrome. Tr. 72-73. Dr. Raymond cautioned against placing too much weight on the finding since "we know very little about this control individual." Tr. 201. Dr. Raymond thought additional evaluation of the control individual was necessary and that without more information, it was not possible to draw conclusions. Tr. 202.

Dr. Shafrir does not believe that the association of seizures following vaccination is due to fever.[25] Pet'rs' Ex. 112 at 5; Tr. 52. He cited the Verbeek article (Pet'rs' Ex. 94)[26] for the proposition that children with the SCN1A mutation have more afebrile seizures than children without the genetic mutation (64.3% vs. 25.4%). Pet'rs' Ex. 83 at 5; Pet'rs' Ex. 112 at 12; see also tr. 53. Dr. Shafrir interpreted the McIntosh article to state "in [an] unequivocal manner . . . that fever was not . . . the cause of the trigger of the seizures, because only a third of the patients had fever." Tr. 16.

The timing of the onset of seizures was also important to Dr. Shafrir. Dr. Shafrir agreed that "[i]n theory, and according to the rationale of the authors of the McIntosh article . . . the timing of one seizure should not make any difference in the prognosis of a lifelong genetic syndrome which is already present at birth." Pet'rs' Ex. 83 at 8. But Dr. Shafrir argued that the Jozwiak study "shows that even one seizure can change the physiological landscape in the child's brain, make subsequent seizures more difficult to control, and aggravate mental retardation…. in a child who carries a genetic disease that makes him susceptible to severe epilepsy and mental retardation." Id. at 9; Pet'rs' Ex. 102.[27]

Dr. Shafrir also based his opinions on the "close relationship between DTP and DTaP[28] and the onset of the epileptic encephalopathy in patients who carry certain mutations in the SCN1A gene." Pet'rs' Ex. 112 at 1.[29] He believed the issue "in this case is the effect of the vaccine on the clinical picture and prognosis of children who carry certain SCN1A mutations." Id. Dr. Shafrir acknowledged that individuals with the SCN1A mutation, like Karsen, are

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[25] See also section III(C)(3)(a) regarding Dr. Shafrir's opinions regarding fever.

[26] N.E. Verbeek et al., "Prevalence of Dravet syndrome among children reported with a convulsion after vaccination, in a nationwide ten-year cohort," 8(6) PLoS One (2013). Petitioners submitted an abstract of this article on April 19, 2013. See ECF Doc. No. 51 at 4. The article was subsequently published on June 6, 2013, with the title "Prevalence of SCN1A-Related Dravet Syndrome among Children Reported with Seizures following Vaccination: A Population-Based Ten-Year Cohort Study," and respondent filed it as Respondent's Exhibit DD.

[27] Sergiusz Jozwiak et al., "Poor Mental Development in Patients With Tuberous Sclerosis Complex – Clinical Risk Factors," 55(3) Arch Neurology 379 (1998).

[28] Dr. Shafrir made references to both DTP and DTaP. Based on the medical records, Karsen received only the DTaP vaccination, so for purposes of this opinion, that acronym is used throughout, unless the reference is a quotation. The difference between the DTP and DTaP vaccines, for purposes of this opinion, is not determinative of the outcome.

[24] Pet'rs Ex. 112 (citing Pet'rs' Ex. 54, M. Nieto-Barrera et al., "Severe Myoclonic Epilepsy in Infancy. Analytical Epidemiological Study," 30 Rev. Neurology 620 (2000)).

generally predisposed to suffering seizures, but he disputed respondent's position that individuals with the SCN1A mutation are "destined" to develop "full-blown, severe Dravet syndrome." Tr. 16-17, 21, 72-73.

As evidence of the "close relationship" between the vaccines at issue and the onset of Dravet syndrome, Dr. Shafrir cites medical literature in which the authors studied the onset of seizures following vaccination. See, e.g., Pet'rs' Ex. 112[30] at 3. According to Dr. Shafrir, the medical literature establishes that some "patients with Dravet syndrome will have the onset of their condition within 48 hours after the DPT vaccination." Tr. 11. Dr. Shafrir contends that this relationship "is [a] proven, undisputed clinical fact." Id. He acknowledges that there is disagreement as to the percentage of patients whose Dravet syndrome manifests within 48 hours of DTaP vaccination, but stated that 30% "would be accepted [by] most people." Id.

Although Dr. Shafrir proposes two mechanisms of causation and argues that the relationship between the DTaP vaccine and Dravet syndrome is undisputed, he is unable to explain the association. Tr. 103. Dr. Shafrir testified as follows: "I don't have any—and nobody else has any—explanation for the relationship between Dravet syndrome and the DPT vaccination." Id. And he testified that he has no evidence that links a change in outcome of Dravet syndrome to vaccination. Tr. 73.

In his initial expert report, Dr. Shafrir did not set forth any proposed mechanism of causation. Pet'rs' Ex. 14. Dr. Shafrir filed a first supplemental expert report on April 14, 2009, responding to the expert report of Dr. Max Wiznitzer, in which Dr. Shafrir stated that he did not see "much point in trying to speculate on the mechanism by which the vaccination triggers the onset of the [Dravet] syndrome." Pet'rs' Ex. 40 at 11. Dr. Shafrir further stated that "[o]ne may speculate, but there is simply no data." Id. Dr. Shafrir filed a second supplemental expert report on March 28, 2013, in which he addressed specific questions asked by the special master previously assigned to this case. See Pet'rs' Ex. 83 at 1. In that report, Dr. Shafrir explained why he had not previously provided an opinion as to the mechanism by which the DTaP vaccine triggered seizures in children with the SCN1A mutation. Id. Dr. Shafrir stated that he had not provided an opinion as to the mechanism "for the simple reason that the mechanism is completely unknown." Id. at 4; see also tr. 25.

Dr. Shafrir explicitly stated during the hearing that his proposed medical theories of causation are not known by the medical community and that there is a need to investigate the theories. Below is the pertinent portion of Dr. Shafrir's testimony:

> (Special Master): Are these theories that you have applied in this case thought to be reliable by the medical community?
> Dr. Shafrir: Well, the evidence for them.
> (Special Master): No. Specifically, these two theories as applies to Dravet syndrome and the relationship of vaccines, as you have testified here today, those specific theories, are they thought to be reliable by the medical community?

[30] Pet'rs' Ex. 112 (citing Pet'rs' Ex. 54, M. Nieto-Barrera et al., "Severe Myoclonic Epilepsy in Infancy. Analytical Epidemiological Study," 30 Rev. Neurology 620 (2000)).

> Dr. Shafrir: They are not judged by the medical community. As I saw in the Catarino article, they say that these need to be investigated. It's a possibility. I don't have any strong evidence to support it, other than some peripheral evidence.

Tr. 99.

And although medical literature is not required to prove petitioners' theories, the undersigned notes that Dr. Shafrir acknowledged that his theories have not been published in peer-reviewed medical literature. Tr. 100. Dr. Shafrir was unable to identify anyone else who has expressed the same theories, although he did testify that some authors have questioned the relationship between the vaccines at issue and seizures. Tr. 100-01.

b. Petitioners' Expert, Dr. Kendall

Dr. Frances D. Kendall is a biochemical geneticist and mitochondrial disease specialist. Pet'rs' Ex. 67 (Dr. Kendall's curriculum vitae) at 1; tr. 107. She earned her B.A. from Temple University and her M.D. from the University of Medicine and Dentistry of New Jersey. Pet'rs' Ex. 67 at 1. She completed a pediatric residency after medical school. Id.; tr. 107. After her residency, she completed research fellowships in genetics and metabolism at Harvard Medical School. Pet'rs' Ex. 67 at 1. Dr. Kendall has extensive experience in clinical, instructional, and research positions. Id. at 1-3. She has also published and served as a peer reviewer for numerous articles in the fields of pediatrics, genetics, and mitochondrial diseases. Id. at 6-8. She is board-certified in biochemical genetics and pediatrics. Id. at 1.

Dr. Kendall defined a "missense mutation" as one that alters the genetic code such that the new code creates a mistake; the gene is no longer translated into the appropriate protein. Tr. 125. She testified that an SCN1A mutation here is a severe mutation reported in children with Dravet syndrome. Tr. 126. An alteration in the SCN1A gene results in "an alteration in the protein that [is] part of the sodium channel that ultimately results in cortical network problems and epileptic encephalopathy." Id.

Like Dr. Shafrir, Dr. Kendall testified that individuals with the same genetic disorder may have different expressions of that disorder. Tr. 111. Dr. Kendall testified that an example of this variability can be seen in the genetic disorder glutaric acidemia type I, found in the Amish population. Tr. 110. Some individuals with this genetic disorder have minimal symptoms while others are devastated. Tr. 111. Dr. Kendall testified that the expression of a genetic mutation in any given individual is due in part to environmental factors as well as genetic factors. Tr. 111. Examples of environmental factors include illness and surgery, and these factors may play a role in the expression of a genetic disorder. Tr. 128. Although Dr. Kendall testified that vaccination may also be an environmental factor, she was unable to cite any medical study or literature to support the proposition that expression of a genetic mutation may be affected by vaccination. Tr. 116, 128-29.

Lastly, Dr. Kendall agreed with the conclusion reached in the Brunklaus study (Pet'rs' Ex. 77,)[31] that vaccination had no impact on developmental outcome in individuals with Dravet syndrome due to an SCN1A mutation. See tr. 124-25. However, she cautioned against trying to predict the outcome of individuals with the SCN1A mutation without knowing the incidence of the genetic defect in the general population. Tr. 114-15. Currently, this information is not available because such studies have not been conducted. Id.

c. Respondent's Expert, Dr. Wiznitzer

Dr. Max Wiznitzer attended medical school at Northwestern University and completed his pediatrics residency at Cincinnati Children's Hospital in Cincinnati, Ohio. Resp't's Ex. B at 1; tr. 226-27. He then completed a fellowship in developmental disabilities. Tr. 227. Dr. Wiznitzer also trained in child neurology at Children's Hospital in Philadelphia. Id. Dr. Wiznitzer is board-certified in pediatrics, psychiatry and neurology with special qualification in child neurology, and neurodevelopmental disabilities. Resp't's Ex. B at 5; tr. 227. He has had extensive clinical, instructional, and research experience in, among other areas, the fields of neurology and pediatrics. Resp't's Ex. B at 1-3, 10-12. He has served as a peer reviewer and has published numerous articles in these fields as well. Id. at 5-6, 12-22.

Dr. Wiznitzer described Dravet syndrome as "an epilepsy that has a characteristic clinical evolution." Tr. 240. The syndrome starts with seizures at approximately four months of age to one year. Id. The initial seizures may be associated with temperature elevation. Id. By age two, the seizures usually become more frequent. Tr. 241. There is a "stagnation in development," which occurs along with the manifestation of epileptic encephalopathy. Id. Seventy to 90% of cases of Dravet syndrome are associated with a mutation of the SCN1A gene. Id. Generally, Dr. Wiznitzer holds the opinion that the onset of seizures which occur after vaccination in a child with Dravet syndrome does not affect the child's developmental outcome. Tr. 238-39.

Dr. Wiznitzer considered Dr. Shafrir's two theories of causation to be implausible and unreliable because they have "no biologic basis." Tr. 254. Dr. Wiznitzer testified that the proposed theories ignore the known evolution of Dravet syndrome. Id. Dr. Wiznitzer explained this evolution as follows: when infants are born, "they do not have the sodium channel 1.1, which is the SCN1A gene product . . . as the major sodium channel in the brain." Tr. 258. Instead, they have the NAV sodium voltage-gated channel 1.3. Id. Sometime between three to six months of age, infants begin substituting "the mature sodium channel, which is sodium channel 1.1, the one that's made by the SCN1A gene." Id. At that point, the infant with a SCN1A mutation will begin having seizures and become symptomatic. Id. Dr. Wiznitzer emphasized that the theories proposed by Dr. Shafrir ignore this process. Dr. Wiznitzer testified that there is no need to postulate a theory to explain why seizures occur in light of current knowledge about the evolution of sodium voltage-gated channel changes that occur as an infant ages. Tr. 259.

[31] A. Brunklaus et al., "Prognostic, clinical and demographic features in SCN1A mutation-positive Dravet syndrome," 135(8) Brain 2329 (2012).

Dr. Wiznitzer also relied on the Catarino article,[32] which found that there was "no evidence of any ongoing neuro-inflammatory or immune-mediated problem" of the individuals with Dravet syndrome that the authors studied. Tr. 256. In Catarino, the authors reported on a systematic neuropathology study of post-mortem adult and pediatric Dravet syndrome cases, four pediatric specimens from children with Dravet syndrome, and post-mortem controls with no neurological disease. Pet'rs' Ex. 92. Detailed histological and immunohistochemical studies were performed. Id. at 27.[33] The authors found no evidence of abnormal neuroinflammatory pathology or any "histopathology hallmark" in the brain tissue of the subjects who had Dravet syndrome. Id.

Moreover, Dr. Wiznitzer rejects Dr. Shafrir's second hit theory. Tr. 283-284. Dr. Wiznitzer testified that there is no medical literature or other support for this theory. Id.

Dr. Wiznitzer testified that there are no children with Karsen's specific SCN1A mutation who do not develop Dravet syndrome. Tr. 289. According to Dr. Wiznitzer, the genetic mutation at issue is not benign. Id. Dr. Wiznitzer also relied on the Ohmori article (Resp't's Ex. Z5),[34] which described SCN1A mutation as "a loss of function mutation, which means the gene product doesn't work." Tr. 289. In other words, the SCN1A gene channel is not functional. Tr. 290.

d. Respondent's Expert, Dr. Raymond

Dr. Gerald Raymond attended medical school at the University of Connecticut. Resp't's Ex. I at 1 (Dr. Raymond's curriculum vitae). After medical school, Dr. Raymond completed a residency in pediatrics and neurology. Id. He then completed a fellowship in developmental neuropathology and another in genetics and teratology. Id. Dr. Raymond is board-certified in pediatrics, clinical genetics, and neurology, with special competency in child neurology. Id. at 10. He has had extensive clinical, instructional, and research experience in the fields of neurology, pediatrics, and genetics. See id. at 1-2, 9-10. He has served as a peer reviewer and published numerous articles in these fields as well. See id. at 2-9.

Dr. Raymond described Karsen's genetic mutation as "an alteration in the SCN1A gene at – in the CDA at position 680 from thymine, guanine, and this results in a missense in exon 5 that results in changing what should have been an isoleucine to serine." Tr. 144. This change in the amino acids builds a different protein in the DNA, the protein which is the "building blocks of our cells." Tr. at 142-44. The SCN1A gene is "a voltage-gated sodium channel," which is a complex protein in the cell membrane. Tr. 145. Channels are like doors that open and close; they "open and actually reset the cell." Tr. 146. SCN1A defects are seen in a variety of seizure disorders, and approximately 70-80% of children with Dravet syndrome have SCN1A mutations. Tr. 147-48.

[32] Catarino, see supra footnote 6.
[33] Catarino, see supra footnote 6 at 3007.
[34] Iori Ohmori et al., "Nonfunctional SCN1A Is Common in Severe Myoclonic Epilepsy of Infancy," 47(10) Epilepsia 1636 (2006).

According to Dr. Raymond, animal models play an important role in contributing to the understanding of the pathogenesis of Dravet syndrome. Tr. 151. During his testimony, Dr. Raymond discussed the Oakley article (Resp't's Ex. Q), [35] which describes a study of animals with the SCN1A mutation. Tr. 151. In that study, animal models were created with an abnormal SCN1A gene. Id. The animals were normal at birth. Tr. 152. One group of animals was subjected to hyperthermia, or increased temperature, until seizures were provoked. Tr. 152. The other group of animals was not exposed to temperature elevations. Id. Even those animals not exposed to hyperthermia subsequently developed seizures. Id. Of particular interest to Dr. Raymond was the fact that the animals had features typically seen in Dravet syndrome, including gait problems and behavioral abnormalities. Id. Dr. Raymond testified the Oakley study showed that the animals that did not have seizures initially "spontaneously developed a seizure disorder based upon their genetics." Tr. 153. Dr. Raymond emphasized that the seizure disorder developed without immunization or any other trigger. Id.

Dr. Raymond addressed Dr. Shafrir's argument that individuals with SCN1A mutations are not destined to develop Dravet syndrome and that they can exhibit a wide variability in the severity of their symptoms, namely, their seizures and resulting neurological complications. Dr. Raymond disagreed that Dravet syndrome has wide variability in genetic expression. Tr. 166. To the extent that there is variability in expression of the genetic mutation, Dr. Raymond explained that such variability is due to the nature of the mutation; for example, whether the mutation is de novo. Tr. 173.

Dr. Raymond also disagreed with Dr. Shafrir's proposed theories of second hit and immune-mediation. Dr. Raymond testified that it is sufficient to have the SCN1A genetic alteration to explain Dravet syndrome and its outcomes. Tr. 182. Dr. Raymond also refuted the notion of gene-environmental factor, as testified to by Dr. Kendall. Dr. Raymond testified that "in this specific genetic alteration . . . . there is significant environmental modifiers." Tr. 160.

e. Evaluation of the Evidence

Petitioners' expert, Dr. Shafrir, testified that there is no known medical theory to explain how the vaccination at issue causes Dravet syndrome. While Dr. Shafrir proposed two theories of causation, he testified that the mechanisms by which the vaccine causes the seizures is "completely unknown" and still needed to be investigated by the medical community. In addressing respondent's statement that Karsen would have developed the same neurological injuries, even if he did not receive the vaccinations at issue, Dr. Shafrir stated that respondent's statement was too speculative. Pet'rs' Ex. 83 at 4; see also tr. 35, 99. Petitioners' second expert, Dr. Kendall, suggested that the vaccination was an environmental factor which could serve to alter the genetic expression of the SCN1A mutation, but she was unable to cite any evidence to support her suggested theory. Therefore, petitioners failed to provide a theory "informed by sound and reliable medical or scientific explanation" as required by Althen Prong One.

[35] John C. Oakley et al., "Temperature- and age-dependent seizures in a mouse model of severe myoclonic epilepsy in infancy," 106(10) PNAS 3994(2009).

(2) Althen Prong Two: Logical Sequence of Cause and Effect

Under Althen Prong Two, petitioners must prove "a logical sequence of cause and effect showing that the vaccination was the reason for [Karsen's] injury." Althen, 418 F.3d at 1278. This requires petitioners to show that the vaccines Karsen received actually caused the alleged injury. Pafford, 451 F.3d at 1354. Petitioners need not make a specific type of evidentiary showing. That is, petitioners are not required to offer "epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect." Capizzano, 440 F.3d at 1325. Instead, petitioners may satisfy their burden by presenting circumstantial evidence and reliable medical opinions. See id. at 1325-26.

a. Petitioners' Expert, Dr. Shafrir

Dr. Shafrir agreed that Karsen has the SCN1A mutation and that this mutation is a "risk factor" that can lead to Dravet syndrome. Tr. 64. Dr. Shafrir also agreed that Karsen's clinical course is consistent with Dravet syndrome. Pet'rs' Ex. 83 at 24. Dr. Shafrir argued, however, that the vaccines Karsen received on February 19, 2005, "either caused or significantly aggravated the devastating, lifelong epileptic encephalopathy from which he currently suffers." Id. at 25. According to Dr. Shafrir, Karsen's seizures may not have occurred when they did and that there is a "high likelihood" that Karsen's resulting neurological injuries may not have been as severe had he not received his DTaP vaccination. Tr. 23, 62, 64, 78. Dr. Shafrir argues that "Karsen started to exhibit the symptoms of Dravet syndrome within 24 hours after his DPT vaccination. It is certainly possible that without this . . . vaccination, Karsen may have . . . develop[ed] Dravet syndrome at a significantly later date; or he could have developed a milder epileptic encephalopathy . . . or he [may not] have developed an encephalopathy at all." Pet'rs' Ex. 83 at 24; see also tr. 64. But Dr. Shafrir conceded that there is no data to make a prediction one way or the other as to Karsen's outcome. Tr. 63-64.

Karsen's injury has been described as an encephalopathy. Dr. Shafrir opines that Karsen's encephalopathy started 48 hours after vaccination. Tr. 74. Dr. Shafrir defined encephalopathy as "abnormality in brain function." Tr. 14. Dr. Shafrir also defined "epileptic encephalopathy" as a condition in which the patient has seizures and severe "impairment of brain function that cannot be explained by the seizure alone." Tr. 15. The authors of the Okumura study[36] define acute encephalopathy as a "sudden onset of severe central nervous system (CNS) symptoms such as convulsions followed by prolonged consciousness disturbance." Pet'rs' Ex. 95 at 79. In the Berkovic study (Resp't's Ex. C),[37] epileptic encephalopathy is defined as "refractory seizures and developmental slowing." Resp't's Ex. C at 489. And in the Brunklaus article,[38] the authors state that children with Dravet syndrome may develop epileptic encephalopathy after their first birthday. Pet'rs' Ex. 77 at 2.

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[36] Okumura, see supra footnote 8.

[37] Samuel F. Berkovic et al., "De-novo mutations of the sodium channel gene SCN1A in alleged vaccine encephalopathy: a retrospective study," 5 Lancet Neurology 488, 489 (2006).

[38] Brunkalas, see supra footnote 16 at 2329.

b. Petitioners' Expert, Dr. Kendall

Other than stating the fact that there is a "temporal association between [Karsen's] immunization and the onset of his seizure disorder," tr. 125-26, Dr. Kendall offered no further support on petitioners' theory of causation as to Karsen's Dravet syndrome and/or neurological injury. See tr. 125. Dr. Kendall had no opinion as to whether Karsen's clinical outcome was worse due to the vaccines. Id. at 126. Dr. Kendall agreed that Karsen had a severe SCN1A mutation, and that, like other children with this mutation, he has Dravet syndrome. Id.

c. Respondent's Expert, Dr. Raymond

Dr. Raymond testified that Karsen has the SCN1A mutation, which is the "sole cause" of his seizure disorder, his developmental delay, and the other features of his Dravet syndrome. Tr. 141, 159. Dr. Raymond explained that Karsen developed Dravet syndrome at the "moment of conception" and that the vaccine did not cause or aggravate his Dravet syndrome. Tr. 141, 158. Dr. Raymond opined that the vaccines given to Karsen may have caused a mild elevation in his temperature (99.2ºF), which was a sufficient enough elevation to result in a seizure. Tr. 158-59, 204. The elevation in temperature probably altered the cell membrane, resulting in dysfunction of the sodium channels, and "an imbalance between excitatory and inhibitory neurons, and you get a seizure disorder." Tr. 204-05. Dr. Raymond has seen low-grade temperature elevations, like Karsen's temperatures of 99.2º F and 99.9º F, result in seizures. Tr. 204, 212.

In support of his position that a mild temperature elevation may have triggered Karsen's seizure following vaccination, Dr. Raymond cited the McIntosh article (previously discussed) and the Guerrini article. Resp't's Ex. Y-3.[39] In the Guerrini article, the authors explain that seizures in patients with SCN1A mutations are often triggered by fever. Id. at 1.

d. Respondent's Expert, Dr. Wiznitzer

Dr. Wiznitzer testified that there is no clinical evidence that the onset of Karsen's seizures caused or altered the course of his Dravet syndrome. Tr. 260. Karsen would have had the same clinical course with or without the vaccine. Tr. 263.

Moreover, Dr. Wiznitzer saw no indication of an immune-mediated injury (Dr. Shafrir's second proposed theory) on Karsen's MRIs or EEGs, which would have been present had an immune-mediated process occurred. Tr. 256. Likewise, Dr. Wiznitzer opined that Karsen would have demonstrated "some change in [his] acute clinical picture" if he had suffered an immune-mediated injury, but he found no evidence in Karsen's medical records to suggest that such a process occurred. Tr. 256-57. He also disagreed with Dr. Shafrir's opinion that Karsen suffered an encephalopathy within 72 hours of his February 19, 2005 vaccination. Rather, Dr. Wiznitzer pointed out that Karsen appeared normal and healthy 72 hours after his initial seizure. Tr. 257, 259. Dr. Wiznitzer testified that after Karsen's seizure on February 20, 2005, Karsen may have experienced fatigue but he had had no permanent effects or injury from the seizure. Tr. 292.

[39] Guerrini, see supra footnote 14.

e. Evaluation of Evidence

There are no facts in the medical record which suggest that Karsen suffered from an encephalopathy after his first seizure; nor was Karsen diagnosed with encephalopathy by his treating physicians after his first seizure. In fact, there is no evidence to suggest that Karsen suffered any abnormality or impairment of function after his vaccinations or initial seizure. Karsen's initial seizure on February 20, 2005, lasted approximately five minutes. Pet'rs' Ex. 5 at 10. After the seizure, Karsen was taken to the emergency room where his physical examination, including his neurological examination, was noted to be normal. Id. at 9-15. A nurse documented that Karsen was interacting with his parents and that he was awake and breastfeeding. Id. at 27. After being observed in the hospital for 12 hours, Karsen was discharged from the hospital. Id. at 10, 18, 19. Results from Karsen's MRI and EEG studies performed in March 2005, were both normal. Id. at 42, 44.

Once Karsen's treating physician, Dr. Bebin, received the result of Karsen's genetic test confirming the presence of an SCN1A mutation, she diagnosed Karsen with "SCN1A-myoclonic astatic epilepsy." Pet'rs' Ex. 38 at 16. Once the genetic cause of Karsen's illness was known, his diagnosis was clear. There is no evidence that Dr. Bebin, or any other of his treating physicians, diagnosed Karsen with a vaccine-related injury after the results of his genetic tests were reported.

Dr. Shafrir conceded that there is no data to make a prediction one way or the other as to whether Karsen's outcome would have been different if he had not had the vaccinations. Tr. 98. Dr. Shafrir also agreed that Karsen did not show any developmental delay or have epileptic encephalopathy until months after the vaccinations.

Dr. Kendall also agreed that Karsen has a severe SCN1A mutation and that, like other children with this mutation, he has Dravet syndrome. She had no opinion as to whether Karsen's clinical outcome was worsened by the vaccinations. Other than Dr. Shafrir, none of the treating doctors or experts has suggested that Karsen suffered any permanent brain injury as a result of his initial seizure. Dr. Wiznitzer testified that the only effect of the initial seizure was perhaps a bit of fatigue. Tr. 292. There is no evidence that the initial seizure had any permanent effect. Id.

Neither of petitioners' experts offered any evidence that Karsen suffered any injury as a result of his seizure on February 20, 2005. Therefore, petitioners failed to prove Althen Prong Two, a logical sequence of cause and effect, showing that the vaccination caused Karsen's injuries.

(3) Althen Prong Three: Timing

Under Althen Prong Three, petitioners must establish that Karsen's injury occurred within a time frame that is medically acceptable for the alleged mechanism of harm. See Pafford, 451 F.3d at 1358 ("Evidence demonstrating petitioner's injury occurred within a medically acceptable time frame bolsters a link between the injury alleged and the vaccination at issue under the 'but-for' prong of the causation analysis.") Petitioners may satisfy this prong by producing "preponderant proof that the onset of symptoms occurred within a timeframe for

which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." de Bazan v. Sec'y of Health & Human Servs., 539 F.3d, 1347, 1352 (Fed. Cir. 2008).

Petitioners may meet their burden by showing: (1) when the condition for which they seek compensation first appeared after vaccination, and (2) whether the period of symptom onset is "medically acceptable to infer causation." Shapiro v. Sec'y of Health & Human Servs., No. 99-552V, 2011 WL 1897650, at *13 (Fed. Cl. Spec. Mstr. Apr. 27, 2011), aff'd in relevant part and vacated on other grounds, 101 Fed. Cl. 532, 536 (2011), aff'd, 503 Fed. App'x 953 (2013) (per curiam). The appropriate temporal association will vary according to the particular medical theory advanced in the case. See Pafford, 451 F.3d at 1358.

a. Petitioners' Expert, Dr. Shafrir

Dr. Shafrir opined that the vaccinations given to Karsen at 3 p.m. on February 19, 2005, caused his seizure the following day. Pet'rs' Ex. 112 at 41. Dr. Shafrir believed that Karsen's vaccines triggered the onset of his Dravet syndrome because he had his initial seizure within 48 hours of receiving the vaccine. Id. at 10.

Dr. Shafrir cited several articles where the authors have studied the temporal relationship between vaccination and onset of the initial seizure in patients with Dravet syndrome. In the Nieto-Barrera article,[40] 16 out of 28 children had their first seizure after DTP vaccine (the whole cell pertussis vaccine as opposed to the acellular form), and 10 of the patients had a seizure within 24 hours of vaccination. Pet'rs' Ex. 54 at 7. In the Berkovic study,[41] 14 out of the 96 children had their initial seizure within 48 hours of vaccination. Resp't's Ex. C at 489. In the McIntosh study,[42] 12 out of 40 children with Dravet syndrome and SCN1A mutation had seizure onset within 48 hours. Pet'rs' Ex. 59 at 594. And in the Tro-Baumann study,[43] the authors reviewed information about 70 children diagnosed with Dravet syndrome and found that seizures occurred after vaccination in 19 of the children (27%). Pet'rs' Ex. 76 at 175.

Dr. Shafrir explained that in the McIntosh study, there were 12 out of 40 children who had the onset of seizures 48 hours after vaccination. Tr. 15. Only a third of these children had a fever, defined as 38ºC.[44] Tr. 16. Dr. Shafrir disagreed with the notion that fever triggers seizures in children with the SCN1A mutation. Tr. 57. Instead, he believes that vaccination triggers the onset of seizures. Tr. 13, 52-53. Dr. Shafrir does not believe that Karsen's seizure was triggered by fever. Tr. 53. Although Dr. Shafrir does not believe that fever triggered Karsen's initial seizure, he does not have any other explanation for the relationship between Dravet syndrome and the DTaP vaccination. Tr. 103.

[40] Nieto-Barrera, see supra footnote 24.
[41] Berkovic, see supra footnote 37.
[42] McIntosh, see supra footnote 19.
[43] Tro-Baumann , see supra footnote 10.
[44] 38°C is 100.4ºF.

b. Petitioners' expert, Dr. Kendall

The medical literature cited by Dr. Kendall, as set forth above, including the McIntosh study which found that 30% of patients with Dravet syndrome had "disease onset [initial seizure] less than two days after vaccination," was also relied on by Dr. Shafrir. Pet'rs' Ex. 66 at 5. The mean age of the children who had seizures within two days of vaccination was lower than those children whose seizures did not occur immediately after vaccinations. Id. Other than the finding of a younger mean age for the children who had seizures after vaccinations, Dr. Kendall noted that the McIntosh study found no other significant differences with regard to clinical course or prognosis of children with Dravet syndrome. Id. Dr. Kendall also cited Tro-Baumann (27% had seizures after vaccinations) and Brunklaus. Id. at 5-6. In Brunklaus, the authors stated, "despite the earlier onset of seizure activity in the vaccine group, it was determined that different seizures precipitants, to include fever, illness, vaccine, or bath, had no effect on overall developmental outcome." Pet'rs' Ex. 66 at 6.

Other than testifying that there is a "temporal association" between Karsen's vaccination and the "onset of his seizure disorder," Dr. Kendall did not have any opinion as to whether Karsen's outcome was worse due to the vaccination. Tr. 125-26. Dr. Kendall also had no opinion about whether Karsen's earlier onset of his disease made any difference in his clinical course or outcome. Tr. 130.

c. Respondent's Expert, Dr. Raymond

Dr. Raymond agreed that there is a temporal proximity between vaccination and the onset of seizures in children with SCN1A mutations due to the sensitivity in these children of a rise in temperature. Tr. 171. Dr. Raymond explained that Karsen's vaccination on February 19, 2005, probably led to a mild elevation in his temperature, resulting in a brief seizure. Tr. 158-59, 171. Dr. Raymond explained that mild infections and hot baths may also trigger seizures in children with Dravet syndrome. Tr. 172. Dr. Raymond testified that these trigger events do not cause Dravet syndrome. Id. Dravet syndrome is caused by a genetic mutation. Id. The first seizure following vaccination may simply be the first manifestation of Dravet syndrome. Tr. 171. Dr. Raymond opined that, "while children with SCN1A mutations are vulnerable to seizures caused by slight rises in temperature from whatever cause there is no evidence that timing of their first seizure alters their subsequent course." Resp't's Ex. Y at 4-5.

Dr. Raymond also cited the McIntosh study, which found that "disease onset was 7.8 weeks earlier" in those children who had seizures within 24 hours of vaccination, but this did not affect the clinical course or outcome of Dravet syndrome. Id. at 2. Dr. Raymond cited additional literature including the Tro-Baumann article for the same proposition. Id.

d. Respondent's expert, Dr. Wiznitzer

Dr. Wiznitzer testified that there was abundant support in the medical literature for the proposition that a mild elevation in an individual's body temperature can trigger the onset of Dravet syndrome and thus there was a temporal association between vaccination and the onset of the first seizure. He further acknowledged that Karsen had "a temperature elevation after the

vaccines he received on [February 19, 2005], and that temperature elevation was related to his vaccines." Tr. 253. While Dr. Wiznitzer agreed that Karsen's temperature was elevated after his February 19, 2005 vaccinations, he disagreed that the temperature elevation that may have triggered his first seizure caused Karsen's encephalopathy or any of the injuries from which Karsen ultimately suffered. Tr. 253-54, 262.

e. Evaluation of the Evidence

The medical records show, and all of the experts agree, that Karsen's initial seizure, or seizure onset, was within 24 hours after vaccination. This proximity between vaccination and seizure onset suggests a causal relationship between the two events. But without evidence of a causal mechanism or evidence of injury, the temporal relationship is not enough. See Grant v. Sec'y of Health & Human Servs., 956 F.2d 1144 (Fed. Cir. 1992) (holding "a proximate temporal association alone does not suffice to show a causal link between the vaccination and the injury").

Moreover, the McIntosh study shows that in children with Dravet syndrome, the seizures that occur following vaccination do not change the clinical course or outcome of these children. Even assuming that the petitioners had proven a causal mechanism, petitioners are unable to show that any injury resulted due to the vaccinations.

C. Standards of Adjudication - Significant Aggravation

The second issue presented by the parties for the undersigned to decide is whether Karsen's February 19, 2005 vaccinations significantly aggravated his injury. Stip. of Facts at 1. The undersigned holds that it did not.

The elements of an off-Table significant aggravation case are set forth in Loving v. Sec'y of Health & Human Servs., 86 Fed. Cl. 135 (2009). There, the court combined the Althen test, which defines off-Table causation cases, with a test from Whitecotton v. Sec'y of Health & Human Servs., 17 F.3d 374 (Fed. Cir. 1994), rev'd on other grounds sub nom.; Shalala v. Whitecotton, 514 U.S. 268 (1995), which concerns on-Table significant aggravation cases. The resultant test has six components, which 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 significant 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.

D. Significant Aggravation Theory

(1) Loving Prong 1: What was Karsen's Condition Prior to Administration of the Vaccine?

The first step in the Loving test is to define Karsen's condition before he received the vaccinations at issue. Karsen was born with a mutation of his SCN1A gene. See Stip. of Facts at 1. The specific mutation was a "missense mutation" of the sodium channel, "a voltage-gated ion channel essential for the generation and propagation of action potentials in nerve and muscle." Pet'rs' Ex. 38 at 64. Mutations in this gene are seen in infants with severe epilepsy, referred to as Dravet syndrome, and also SMEI. Resp't's Ex. Y2.

Although Karsen had the SCN1A gene mutation prior to the administration of the vaccines, his physical and neurological examinations were all normal up until the date of his vaccinations. See Pet'rs' Ex. 5 at 3, 7. He appeared healthy and did not have any seizures prior to the vaccinations.

(2) Loving Prong 2: What is Karsen's Current Condition (or His Condition Following the Vaccination, if Also Pertinent)?

The second part of the Loving test is to discuss "the person's current condition (or condition following the vaccination if that is also pertinent)." 86 Fed. Cl. at 144. Here, the condition following his vaccination is most pertinent.

On the day following his vaccinations, February 20, 2005, Karsen had an initial seizure. Pet'rs' Ex. 5 at 8. Karsen's initial seizure lasted about five minutes, and he had jerking of his right leg and arm. Id. at 10. Afterwards, Karsen was able to swallow water although he was noted to be flaccid. Id. Prior to the seizure, Karsen's mother noted that he had a fever, and she had given him Tylenol earlier that morning. Id. After the seizure, Karsen's parents noted that he "seemed to be OK." Id. Karsen's physical examination after the seizure, including his neurological exam, was normal. Id. at 9-15. Karsen was noted to be awake, interacting with his parents, breastfeeding and voiding. Id. at 27. After observation at a hospital for 12 hours, he was discharged home to follow up with his pediatrician. Id. at 10, 18-19.

Karsen had another five-minute seizure involving his left leg on February 28, 2005, and two other small seizures on March 6, 2005. Pet'rs' Ex. 5 at 16. The results from an EEG and MRI performed on March 17, 2005, were both normal. Id. at 42-46. On March 30, 2005, Dr. Bart documented that Karsen had a normal neurological exam. Tr. 95. On June 16, 2005, Dr. Bart documented that Karsen continued "to be alert and develop normally." Tr. 95-96. Likewise, on June 21, 2005, a neurologist documented that Karsen was "[m]oving all extremities, tracks across midline, rolls over, and [had] good head control." Tr. 96. Dr. Shafrir agreed that on July 27, 2005, Karsen was described as showing developmental progress and had normal development for his age at that time. Id. An MRI done on August 31, 2005 was normal, and an EEG done on September 1, 2005 was also normal. Tr. 96-97. Karsen's development delay did not become manifest until August/September 2005. Tr. 98. Karsen continued to have seizures as set forth in the summary of stipulated facts, supra, at 2-8.

In December 2008, genetic testing revealed that Karsen had the SCN1A genetic mutation. "With respect to Karsen's current condition, the parties…stipulate that Karsen has [SMEI/DS] with a mutation in his SCN1A gene." Stip. of Facts at 1.

The evidence in the record indicates that Karsen's current condition is consistent with that of a child who has the SCN1A gene mutation and Dravet syndrome. Likewise, Dr. Shafrir testified and does not dispute that Karsen's clinical course is consistent with Dravet syndrome. Pet'rs' Ex. 83 at 24.

(3) Loving Prong 3: Does Karsen's Current Condition (or Condition after Vaccination) Constitute a "Significant Aggravation" of his Condition Prior to Vaccination?

The next prong of the Loving test is to determine whether there is a "significant aggravation" of his condition by comparing Karsen's condition before vaccination to his current condition. The statute defines "significant aggravation" as "any change for the worse in a preexisting condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration in health." § 300aa-33(4).

Based upon the facts as set forth earlier in this decision, Karsen's condition immediately after vaccination did not change, except that he had a brief seizure. Over time, however, Karsen's condition deteriorated and he developed severe epilepsy and developmental delay. The question relevant to this prong of the Loving analysis is whether Karsen's vaccination significantly aggravated his Dravet syndrome. In other words, is Karsen's clinical course and outcome any different than it would have been if he had not been vaccinated? See Locane v. Sec'y of Health & Human Servs., No. 99-599V, 2011 WL 3855486, *10-11 (Fed. Cl. Spec. Mstr. Feb. 17, 2011), aff'd, 99 Fed. Cl. 715 (Fed. Cl. 2011), aff'd, 685 F.3d 1375 (Fed. Cir. 2012) (special master's holding affirmed finding that petitioner's condition was not inconsistent with the disease generally and not affected by the vaccinations).

All of the experts, including Dr. Shafrir, agree that Karsen's clinical course is consistent with Dravet syndrome. See e.g., Pet'rs' Ex. 83 at 24. Dr. Shafrir stated, however, that Karsen developed seizures, a symptom of Dravet syndrome, within 24 hours of vaccination. Id. Dr. Shafrir also opined that it was possible that if Karsen had not received the vaccinations on February 19, 2005, the onset of his Dravet syndrome would have been later. Id. Dr. Shafrir further argued that it was possible that if Karsen had not been vaccinated, he might not have developed an encephalopathy. Id.; see also tr. 64. All of these arguments fail, however, because Dr. Shafrir conceded that there is no way to predict what Karsen's outcome would have been if he had not received the vaccines. Tr. 63-64, 98.

According to Dr. Shafrir, vaccination does not change the course or outcome of the Dravet syndrome. Dr. Shafrir testified as follows:

> Once you develop Dravet syndrome, you have Dravet syndrome. This is a clinical course of the condition. Whenever the patient have the first seizure, the seizure is over, they look perfectly normal. Nothing changed. Then they have a second seizure, then they

have a second seizure. By age two, they still talk and walk, and at age five, they don't. So, this is a way that they – that their condition progresses with and without vaccination.

Tr. 93.

Alternatively, Dr. Shafrir argued that the McIntosh study provided a basis upon which to find significant aggravation. In that study, patients with seizure onset within two days of vaccination were referred to as the vaccination-proximate group. Resp't's Ex. Y1 at 1.[45] Those patients who had seizures two days or more following vaccinations were the vaccination-distant group. Id. In the vaccination-proximate group, seizure onset occurred on average around 18.4 weeks of age. Id. In the vaccination-distant group, seizure onset occurred on average at 26.2 weeks of age. Id. There were no other statistically significant differences between the two groups as to subsequent seizure types, intellectual function , or outcome. Id. at 4. Dr. Shafrir testified that the "earlier onset of seizure…. is a significant aggravation of the condition." Pet'rs' Ex. 112 at 44. Thus, Dr. Shafrir suggested that earlier seizure onset of approximately eight weeks constituted a significant aggravation. Dr. Shafrir's conclusion, however, contradicts the conclusion of the authors of the study, who found that although vaccination might appear to trigger the onset of Dravet syndrome, there was no difference in clinical and outcome measures in patients with vaccination-proximate seizures.

Petitioners have failed to show by a preponderance of the evidence that Karsen's current condition constitutes a significant aggravation of his condition prior to vaccination. He had the SCN1A mutation before his vaccinations, his clinical course developed consistent with that condition, and his current condition is a result of his genetic mutation.

(4) Loving Prong 4: Is there a Medical Theory Causally Connecting Such a Significant Worsened Condition to the Vaccination?

As set forth in section III(B)(1) above, petitioners failed to establish by a preponderance of the evidence, a medical theory causally connecting Karsen's condition, or any significant aggravation. Dr. Shafrir did not set forth any additional mechanistic theory for his argument based on significant aggravation, apart from the theories addressed above, in section III(B)(1), supra. Therefore, petitioners failed to prove causation as to significant aggravation.

(5) Loving Prong 5: Is there a Logical Sequence of Cause and Effect Showing that the Vaccination Significantly Aggravated Karsen's Condition?

For the same reasons set forth in section III(B)(2) above, petitioners failed to prove by preponderant evidence a logical sequence of cause and effect showing that the vaccination significantly aggravated Karsen's condition.

[45] McIntosh, see supra footnote 19.

(6) Loving Prong 6: What is a Proximate Temporal Relationship Between the Vaccination and the Significant Aggravation?

The last element in the six-part Loving test has origins in Althen Prong 3. As stated in Loving, this element is "a showing of a proximate temporal relationship between vaccination and the significant aggravation." 86 Fed. Cl. at 144. To satisfy this requirement, petitioners must provide "preponderant proof that the onset of symptoms occurred within a timeframe for which, given the understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." de Bazan, 539 F.3d at 1352 (citing Pafford, 451 F.3d at 1358 (Fed. Cir. 2006)).

Again, for the same reasons set forth in section III(B)(3), petitioners failed to prove the third prong of Althen, which is the last element of the Loving test.

E. Alternative Causation

Because petitioners did not meet their burden of proof on causation or significant aggravation, respondent does not have the burden of establishing a factor unrelated to the vaccination caused Karsen's injuries. See Doe v. Sec'y of Health & Human Servs., 601 F.3d 1349, 1358 (Fed. Cir. 2010) ("[petitioner] Doe never established a prima facie case, so the burden (and attendant restrictions on what 'factors unrelated' the government could argue) never shifted"). Nevertheless, respondent has identified an alternative cause of Karsen's injuries – the SCN1A gene mutation.

Pursuant to the Vaccine Act, compensation shall be awarded where the petitioner demonstrates the requirements set forth under the Act by a preponderance of the evidence, and "there is not a preponderance of the evidence that the . . . injury . . . is due to factors unrelated to the administration of the vaccine." § 300aa-13(a)(1)(A)-(B). The Act provides that "factors unrelated to the administration of the vaccine" are those "which are shown to have been the agent . . . principally responsible for causing the petitioner's illness, disability, injury, condition or death." Id. § 13(a)(2)(B).

In this case, even if petitioners had established their case by a preponderance of the evidence, their arguments fail because respondent has proven that the SCN1A mutation—a factor unrelated to the administration of the vaccines—is the agent solely responsible for causing Karsen's Dravet syndrome and resultant neurological injuries.

Compensation has been denied in a case factually similar to this case based upon a finding that the SCN1A mutation was a "factor unrelated to the administration of the vaccine" and the agent solely responsible for causing Dravet syndrome in a child. Deribeaux v. Sec'y of Health & Human Servs., 717 F.3d 1363 (Fed. Cir. 2013).

In Deribeaux, the infant Madison Deribeaux received the DTaP vaccine at about six months of age, on March 28, 2002. Id. at 1364. The next day Madison had a prolonged seizure. She was ultimately diagnosed with a seizure disorder. Id. A case was filed on her behalf by her parents in the Vaccine Program, in which her parents alleged that the DTaP vaccine triggered Madison's initial seizure and subsequent neurological condition. Id. The case proceeded to hearing and the special master found entitlement to compensation. See Deribeaux v. Sec'y of

Health & Human Servs., No. 05-306V, 2007 WL 4623461, at *1 (Fed. Cl. Spec. Mstr. Dec. 17, 2007) ("Deribeaux I").

Madison subsequently underwent genetic testing which revealed that she had a SCN1A mutation. Deribeaux, 717 F.3d at 1363. She was then diagnosed with Dravet syndrome. Id. Based on this evidence, respondent filed a motion to set aside the prior ruling in favor of petitioners. The case was assigned to a different special master who held that the evidence presented at the first hearing established a prima facie case in favor of petitioners, but that a second hearing would be held on the issue of alternative causation. Deribeaux v. Sec'y of Health & Human Servs., No. 05-306V, 2011 WL 6935504, at *3 (Fed. Cl. Spec. Mstr. Dec. 9, 2011) ("Deribeaux II"). Respondent was allowed to present evidence to prove that Madison's Dravet syndrome was caused by the SCN1A mutation, an etiology unrelated to the vaccine, pursuant to § 300aa-13(a)(1)(A)-(B). Id. At the hearing, respondent put on evidence that the vaccine caused a fever, which triggered Madison's initial seizure, but that the cause of the seizure disorder and resulting neurological injuries was the SCN1A mutation and that the vaccine did not cause or aggravate her condition. Id.

In Deribeaux II, the special master specifically addressed the Althen elements of causation and found that the SCN1A mutation was the "sole substantial factor" which caused Madison's Dravet syndrome. Id. at *33. The special master's decision was affirmed by the Court of Federal Claims and the Court of Appeals for the Federal Circuit, which held that the special master applied the "correct legal standards" for proving alternative causation, as well as the three-pronged Althen analysis. See Deribeaux, 717 F.3d 1363.

Similarly, special masters have denied compensation in other SCN1A cases. The Federal Circuit's decision in Stone v. Sec'y of Health & Human Servs., 690 F.3d 1380 (Fed. Cir. 2012),[46] cert denied, 133 S.Ct. 2022 (Apr. 29, 2013), affirmed the special master's finding that the SCN1A gene mutation was solely responsible for the vaccinee's SMEI and not the administered DTaP vaccine which caused only a "single, isolated initial febrile seizure." See also Snyder v. Sec'y of Health & Human Servs., No. 07-60V, 2011 WL 2446321 (Fed. Cl. Spec. Mstr. May 27, 2011); Harris v. Sec'y of Health & Human Servs., No. 07-59V, 2011 WL 3022544 (Fed. Cl. Spec. Mstr. May 27, 2011). The Court of Federal Claims reversed the special master in Snyder, 102 Fed. Cl. 282 (2011), and in Harris, 102 Fed. Cl. 305 (2011), and damages were awarded to petitioners by the special master on remand. Snyder v. Sec'y of Health & Human Servs., No. 07-60V, 2013 WL 391169 (Fed. Cl. Spec. Mstr. Jan. 8, 2013); Harris v. Sec'y of Health & Human Servs., No. 07-59V, 2013 WL 599976 (Fed. Cl. Spec. Mstr. Jan. 18, 2013). Petitioners elected to accept judgment, but respondent has appealed to the Federal Circuit. Snyder, 102 Fed. Cl. 282, appeal docketed, No. 13-5068 (Mar. 14, 2013); Harris, 102 Fed. Cl. 305, appeal docketed, No. 13-5073 (Mar. 22, 2013).

In Barnette v. Sec'y of Health & Human Servs., 110 Fed. Cl. 34, 26 (2013), however, the special master's finding that the child's SCN1A mutation was the sole cause of her Dravet

[46] The Federal Circuit's decision in Stone resolved two cases where the petitioners alleged that the DTaP vaccines their children received caused their children's Dravet syndrome. See Stone, 676 F.3d 1373, 1374-75. In both cases, the special master denied compensation and his decisions were affirmed on review to the court. Id. The decisions were jointly appealed to the Federal Circuit. Id.

syndrome and related injuries was affirmed.[47] The Court of Federal Claims also affirmed the special master's finding that the child's vaccinations did not significantly aggravate her Dravet syndrome or any other injury. Id. Petitioners did not appeal to the Federal Circuit.

In this case, like Deribeaux II and Barnette, respondent has put forth preponderant evidence establishing that Karsen's SCN1A mutation, a factor unrelated to the administration of the vaccines, is the agent solely responsible for causing his Dravet syndrome and neurological injuries.

a. Althen Prong One: Respondent's Medical Theory

To prove Althen Prong One in order to establish alternative causation, respondent is required to set forth a medical theory explaining how a factor unrelated to the vaccine caused the injury at issue. Here, respondent set forth ample evidence that the SCN1A mutation is the sole cause of Karsen's Dravet syndrome and its complications.

Respondent's expert, Dr. Raymond, explained the pathophysiology of Dravet syndrome.[48] Dr. Raymond's expert report, in pertinent part, states as follows:

> The gene SCN1A encodes a portion of a channel that controls the transport of sodium molecules across cell membranes in the neurons . . . . [This is] a highly complex chemical environment that allows the net passage of sodium from one side to another . . . .
>
> Mutations in the SCN1A gene have been associated with . . . [SMEI] or Dravet syndrome . . . a rare condition . . . [and] . . . an animal model has been an extremely important development in our understanding of the pathogenesis of the disease[]. The model deletes one copy of the SCN1A gene and results in an animal that has spontaneous seizures, ataxia, and premature death.

Resp't's Ex. H at 3-4.

Respondent's expert, Dr. Wiznitzer, explained that the medical community is not aware of any children with the specific SCN1A mutation that Karsen has who do not develop Dravet syndrome. Tr. 289. "[T]his is not listed as one of the benign changes [on the gene] . . . . [but is] a loss of function mutation, which means the gene product doesn't work." Tr. 289.

Petitioners' expert, Dr. Kendall, testified that in children with Dravet syndrome, the SCN1A mutation is severe, resulting in "an alteration in the protein that's part of the sodium channel that ultimately results in cortical network problems and epileptic encephalopathy." Tr. at 126.

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[47] The petitioners in Barnette acknowledged that the child was born with an SCN1A gene mutation that predisposed her to developing seizures and cognitive problems. They maintained, however, that the DTaP vaccination acted as an environmental trigger effected an earlier onset of her Dravet Syndrome. 110 Fed. Cl. at 38.

[48] For a complete discussion of the pathophysiology and cell abnormalities that result due to the SCN1A mutation, see Dr. Raymond's first expert report, Resp't's Ex. H at 3-5; see also the Brunklaus study, Pet'rs' Ex. 77 at 6.

Both parties filed medical articles and studies which establish that the international medical community generally agrees that vaccinations are not the cause of Dravet syndrome and that the SCN1A mutation is responsible for causing the disease. For example, the authors of the Brunklaus study, reporting on a five year study of data collected in the United Kingdom on patients with Dravet syndrome, describe the mutation as the "primary genetic cause" of the disease. Pet'rs' Ex. 77 at 1.[49] In fact, the authors state that "children carrying the SCN1A mutation are destined to develop the disease." Id. at 6. The authors explain that while the onset may be precipitated by "fever/illness, vaccination or a bath . . . . the nature of the trigger has no effect on overall developmental outcome and does not seem to be responsible for the subsequent encephalopathy." Id.

Likewise, Professor Dr. Berten Ceulemans from the Department of Child Neurology at the University of Antwerp, Belgium, and his colleagues conducted a clinical study[50] on 60 patients with Dravet syndrome. Dr. Ceulemans concluded that there "is a strong argument favouring the genetic disorder itself as probably being the most important factor for developmental problems in these [Dravet syndrome] patients." Resp't's Ex. Z8 at 4.

In the McIntosh study, the authors corrected their previous misunderstanding as to "presumed vaccine encephalopathy" as follows:

> We previously reported a retrospective analysis in which 12 of 14 patients with presumed vaccine encephalopathy in fact had previously unrecognized Dravet syndrome, 11 of whom had mutations in SCN1A. This showed that vaccination was wrongly blamed as an acquired cause of a genetic disorder, and the hypothesis that vaccination was the causal factor in our cohort could be rejected.

Pet'rs' Ex. 59 at 5.

And in the Verbeek article reporting on a Dutch study of patients with SCN1A and Dravet syndrome, the authors concluded that "an early diagnosis will prevent parents and professionals from assuming that vaccination is the cause of the epilepsy, and will thereby promote faith and participation in immunization programs." Resp't's Ex. DD at 8.

Dr. Shafrir testified about his personal experience. He testified that he has only one patient with the SCN1A condition, and that patient did not have his initial seizure as a result of a vaccine. Dr. Shafrir conceded that he did not have "the clinical experience to [say] that I've seen patients whose course is changed by the DTP vaccination." Tr. 315.

Like Deribeaux, respondent in this case has established by a preponderance of the evidence that the SCN1A mutation is the sole cause of Dravet syndrome and the resulting neurological condition.

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[49] Brunkalas, see supra footnote 16.

[50] Resp't's Ex. Z8, Berten Ceulemans et al., "Overall management of patients with Dravet syndrome," 53 Developmental Med. & Child Neurology 19-23 (2011).

b. Althen Prong Two: A Logical Sequence of Cause and Effect

The second prong of Althen requires proof of a "logical sequence of cause and effect" showing that factors unrelated to the administration of the vaccine are responsible for causing Karsen's Dravet syndrome/SMEI and neurological injury.

As Dr. Raymond explained, Karsen did not develop the SCN1A mutation and resulting Dravet syndrome as a result of receiving the vaccination at issue in this case. Dr. Raymond testified that Karsen developed Dravet syndrome "[a]t the moment of conception." Tr. 158. In his expert report, Dr. Raymond stated that individuals with the type of SCN1A mutation Karsen has, a missense mutation as previously discussed, have been reported to have SMEI or Dravet syndrome. Resp't's Ex. H at 2. Dr. Raymond stated that mutations in the SCN1A gene can result in a number of different variations including familial hemiplegic migraines and several epilepsy syndromes—Generalized epilepsy with Febrile Seizures (GEFS+) and SMEI. Id. at 4. "The reason for this variation in diseases resulting from alternations in SCN1A rests on the structure of the channel and how the genetic mutation affects function." Id. When examining the specific mutation in the SCN1A gene that does not result in early termination, but amino acid substitution, the next step is the examination of the situation. i.e., whether the gene mutation is carried by the parents or a de novo mutation. Id. at 5. A de novo or spontaneous mutation is a "powerful indicator that it is disease causing." Id. The specific gene alternation, as seen in Karsen, results in a missense mutation and other individuals with this identical type of mutation "have been shown to have SMEI." Id.

During the hearing, Dr. Raymond testified that Karsen's specific SCN1A mutation has been examined as described in the Ohmori[51] article. Pet'rs' Ex. 96. Dr. Raymond explained that this type of mutation "resulted in a nonfunctioning protein" and that based on previously reported experience, a family with a child with this specific mutation would have to be counseled because the child would have "a most significant form of this [Dravet syndrome or SMEI] condition." Tr. 157-58.

According to Dr. Raymond, even assuming that children who have initial seizures after vaccination may have an earlier onset, this does not alter the ultimate developmental outcome. Tr. 261. As explained by Dr. Wiznitzer, "Karsen . . . would have followed the same clinical course if he had not received any vaccines." Tr. 263. Dr. Raymond and Dr. Wiznitzer rely on the McIntosh and Brunklaus articles, respectively, in support of this proposition. See Resp't's Ex. Y at 1 (citing Resp't's Ex. Y1 (McIntosh)); Resp't's Ex. Z at 2 (citing Resp't's Ex. Z9 (Brunklaus)).

Dr. Raymond also testified that Karsen's SCN1A mutation is the "sole cause" of his seizure disorder (Dravet syndrome), his developmental delay, and all of the other features of Dravet syndrome. Tr. 159. Both Dr. Raymond and Dr. Wiznitzer testified that it is not necessary to invoke an environmental factor, like the vaccination, to explain Karsen's condition. Tr. 161. Dr. Wiznitzer testified that Karsen would have followed the same clinical course even if he had not received any vaccine. Tr. 263. Petitioners' expert, Dr. Kendall, testified that she is not aware of any healthy children with the exact mutation which Karsen has, although she

[51] Ohmori, see supra footnote 34.

qualified her statement by explaining that children are not typically screened for this mutation unless they present with symptoms. Tr. 114, 117-18.

c. Althen Prong Three: Timing

The last element of causation is proof of a proximate temporal relationship between the vaccination and the injury. Althen, 418 F. 3d at 1278. Karsen's alleged injury is his Dravet syndrome and his resulting neurological complications. See Pet'rs' Prehearing Submission at 2.

Petitioners frame the injury here as vaccine-caused and/or vaccine-aggravated Dravet syndrome. In reality, the only temporal relationship is between the vaccination and Karsen's first seizure. Karsen did not manifest the criteria for Dravet syndrome for months after his first seizure, and so there is no temporal relationship between his vaccinations and the onset of his Dravet syndrome. Moreover, Karsen had no brain damage after the vaccination at issue. Therefore, while Karsen did not have an injury that was temporally associated with the vaccination at issue, his initial seizure was, in hindsight, a suspicious sign that he might develop Dravet syndrome, or the initial manifestation of his genetic mutation. That fact alone does not establish a vaccine-related injury.

Respondent's experts, on the other hand, stated that Karsen's clinical course, timing of the onset of his initial seizure and overall outcome were consistent with Dravet syndrome. Dr. Raymond testified that Dravet syndrome usually presents in the first year of life. Resp't's Ex. H at 2. "Infants have normal development in the first months of life, but then develop seizures in a characteristic fashion . . . . Individuals subsequently manifest a variety of seizure types not associated with fever, including absence, myoclonic, and partial seizures which are refractory therapy." Id. In addition, Dr. Raymond stated that while development in the first year is often normal, after the first year "delays become evident and most children will have mental retardation and significant speech and language delays." Id. Karsen's clinical course and the timing of the manifestation of his Dravet syndrome are consistent with what is expected in children with his specific SCN1A gene mutation. Id. at 2-3. Therefore, the undersigned finds by a preponderance of the evidence that respondent has satisfied Althen Prong Three.

IV. Conclusion

For the reasons discussed above, the undersigned finds that petitioners have not established entitlement to compensation and their petition must be dismissed. In the absence of a timely filed motion for review filed pursuant to Vaccine Rule 23, the clerk is directed to enter judgment consistent with this decision.

IT IS SO ORDERED.

s/Nora Beth Dorsey
Nora Beth Dorsey
Special Master