In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Case No. 10-704V
January 29, 2016
PUBLISHED

* *	Chief Special Master Dorsey
KIMBERLY FAORO and TYSON FAORO, as parents and natural guardians of H.E.F.,	Entitlement; SCN1A Gene Mutation; Severe Myoclonic Epilepsy of Infancy ("SMEI"); Dravet Syndrome; Seizure Disorder; Diphtheria Tetanus acellular Pertussis ("DTaP") Vaccine; Inactive Polio Virus ("IPV") Vaccine; Haemophilus Influenza Type B ("Hib") Vaccine; Pneumococcal Conjugate Vaccine ("Prevnar"); Rotavirus Vaccine; Significant Aggravation; Alternative Causation
Petitioners,	
v.	
SECRETARY OF HEALTH AND HUMAN SERVICES,	
Respondent.	
* *	

Martin A. Diaz, Martin Diaz Law Firm, Iowa City, IA, for petitioners.
Jennifer Leigh Raynaud, U.S. Department of Justice, Washington, DC, for respondent.

DECISION DENYING ENTITLEMENT[1]

I. Introduction

On October 15, 2010, Kimberly Faoro and Tyson Faoro ("petitioners") filed a petition for compensation under the National Vaccine Injury Compensation Program (the "Vaccine Act" or

[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.

"Program")[2] as the parents and natural guardians of their minor daughter, H.E.F., in which they allege that the diphtheria-tetanus-acellular-pertussis ("DTaP"), hepatitis B ("Hep B"), polio ("IPV"), haemophilus influenza type B ("Hib"), pneumococcal ("PCV") and rotavirus vaccines that H.E.F. received on December 28, 2007, caused her to develop seizures, brain damage, and developmental delay, or in the alternative, "significantly aggravated . . . an underlying genetic pre-disposition." Petition ("Pet.") at 1, 7. Respondent recommended against awarding compensation. Respondent's Report ("Resp't Rep't"), filed March 28, 2011, at 2.

During the course of the proceedings, the parties discovered and do not dispute that H.E.F. was born with a mutation of her SCN1A gene and that she has a seizure disorder known as Dravet syndrome.[3] Petitioners allege that "H.E.F. suffered her seizures as a result of the administration of one or more of the vaccines she received on December 28, 2007" which led to "intractable seizures . . . and brain damage with developmental delay." Petitioners' Pretrial Submission ("Pet. Pretrial Sub.") at 7. While there have been a number of SCNIA cases in the Program,[4] entitlement to compensation has not been awarded in any of those cases. The difference in this case, as compared to the other SCN1A cases, is that H.E.F. and her mother share the exact same SCN1A genetic mutation. H.E.F. has Dravet syndrome, but her mother does not and shows no signs or symptoms of neurological problems. The parties disagree as to why the genetic mutation causes illness in H.E.F. but not her mother. Petitioners argue that the SCN1A mutation made H.E.F. susceptible to developing a seizure disorder (i.e., Dravet syndrome) but that a gene-environmental interaction is at play, and that the vaccinations triggered that interaction. Respondent disagrees and asserts that the phenomenon of mosaicism explains why H.E.F. has Dravet syndrome but her mother is asymptomatic. Respondent asserts that H.E.F's SCN1A mutation is the sole cause of her Dravet syndrome and neurological condition.

The parties agree and stipulate that the only issue to be resolved is "whether any of the vaccines, alone or in combination, that H.E.F received on December 28, 2007, caused or significantly aggravated H.E.F.'s condition." Joint Prehearing Submission ("Jt. Sub.") at 1.

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[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.

[3] Dravet syndrome is a severe epilepsy of infancy also known as Severe Myoclonic Epilepsy of Infancy ("SMEI"). See Section V, infra, for a more complete description.

[4] The list of final opinions in other SCN1A cases includes: Stone v. Sec'y of Health & Human Servs., 676 F.3d 1373 (Fed. Cir. 2012); Barnette v. Sec'y of Health & Human Servs., 110 Fed. Cl. 34 (2013); Deribeaux v. Sec'y of Health & Human Servs., 717 F.3d 1363 (Fed. Cir. 2013); Snyder v. Sec'y of Health & Human Servs., 553 Fed. Appx. 994 (Fed. Cir. 2014); Waters v. Sec'y of Health & Human Servs., No. 08-76V, 2014 WL 300936 (Fed. Cl. Spec. Mstr. Jan. 7, 2014); Barclay v. Sec'y of Health & Human Servs., 122 Fed. Cl. 189 (2015); and Santini v. Sec'y of Health & Human Servs., 122 Fed. Cl. 102 (2015).

The undersigned agrees with respondent that H.E.F.'s SCN1A gene mutation is the reason she has Dravet syndrome and associated neurological symptoms, and finds that petitioners have failed to show by a preponderance of the evidence that H.E.F.'s injuries were caused or significantly aggravated by her December 28, 2007 vaccinations. Although H.E.F.'s vaccinations may have caused a low-grade fever or otherwise triggered her first seizure, neither that initial seizure nor her vaccinations caused or significantly aggravated her Dravet syndrome and resulting neurological complications. Rather, her SCN1A genetic mutation is more likely than not the sole cause of her injuries. For that reason, the undersigned also finds by a preponderance of the evidence that respondent has provided an alternative cause of H.E.F.'s injuries, and, therefore, petitioners are not entitled to compensation.

In the discussion below, the undersigned describes the pertinent factual background, a description of the genetic mutation and information on Dravet syndrome, and a history of the procedural developments in this case. This is followed by a discussion of the applicable standards of proof for causation and significant aggravation, and an analysis of the expert testimony, 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 the record as a whole, the following is a brief summary of the medical records, testimony, and discussion of Dravet syndrome taken from the record in the case. This is by no means a complete recitation of all the relevant facts and evidence considered. See § 300aa-13(a) (stating that the special master should consider the "record as a whole").

a. Summary of medical records

H.E.F. was born on August 28, 2007. Jt. Sub. at 1. She was delivered at 40 weeks gestation. Pet. Ex. 4 at 9. Her birth weight was 7 pounds 3½ ounces and her Apgar scores were nine (9) and ten (10) at one and five minutes, respectively. Pet. Ex. 4 at 9, 24. She passed her newborn hearing test and her newborn screening tests were all normal. Pet. Ex. 7 at 20, 27. H.E.F.'s neonatal course was unremarkable and she was discharged in good health on August 30, 2007. Pet. Ex. 4 at 8.

Of note, H.E.F.'s mother ("Ms. Faoro") was 27 years old at the time of delivery and H.E.F. was her fifth child. Pet. Ex. 3 at 250; Pet. Ex. 4 at 8. Ms. Faoro's past medical history was significant for migraines, hypothyroidism, and mild obesity. Pet. Ex. 3 at 246-47. During her pregnancy with H.E.F., Ms. Faoro received antibiotics for a urinary tract infection and bronchitis, and she was also treated for viral gastritis. Id. at 72, 79, 83, 246-47. Ms. Faoro smoked up to one-half pack of cigarettes daily. Id. at 92, 246-47; Pet. Ex. 19 at 7.

H.E.F. received her early pediatric care from Dr. Rebecca White at Mahaska Health Partnership. Pet. Ex. 5. On September 4, 2007, H.E.F. was treated for diarrhea and a diaper rash. Id. at 3. On September 6, 2007, H.E.F. again presented to Dr. White for constipation and a continuing diaper rash. Id. at 5. A few days later, on September 11, 2007, H.E.F. had a mild upper respiratory infection. She was noted to have normal growth and development. Id. 6.

On October 2, 2007, H.E.F. was seen and treated for thrush and dermatitis. Pet. Ex. 5 at 7. On October 9, 2007, H.E.F. presented to Dr. White's office again with greenish-yellow matter in her eyes and persistent diaper rash. Id. at 8.

On October 22, 2007, H.E.F. received her two-month vaccines – Pediarix[5], Hib, Prevnar[6] and RotaTeq.[7] Pet. Ex. 5 at 11. The next day, October 23, 2007, H.E.F. had a temperature of 102 degrees, with vomiting and a poor appetite. Pet. Ex. 7 at 39. She was taken to the Emergency Department ("ED") at Mahaska Hospital in Oskaloosa, Iowa, where she was seen by Dr. White, who diagnosed H.E.F. with "vomiting and fever status post immunization." Id.

Approximately one week later on October 31, 2007, H.E.F. was taken again to the ED for fever and diarrhea and was diagnosed with an ear infection. Pet. Ex. 7 at 48-49. She returned to the ED the next day, November 1, 2007, with fever. Id. at 51-53. She was admitted overnight, and treated with antibiotics. Id.

The next week, on November 6, 2007, H.E.F. was seen by Dr. White for vomiting, coughing, congestion and diarrhea. Pet. Ex. 5 at 12. H.E.F. was diagnosed with gastroenteritis and an upper respiratory infection. Id.

On December 20, 2007, H.E.F. was seen by Dr. White for complaints of diarrhea for the past three days and vomiting. Pet. Ex. 5 at 13. She was diagnosed with gastroenteritis and thrush. Id. Approximately one week later, on December 28, 2007, H.E.F. returned to Dr. White for her four-month well-child visit at which time she received her four-month vaccinations - Pediarix, Hib, Prevnar, and RotaTeq. Id. at 14; Pet. Ex. 6 at 4.

Approximately six to seven hours after receiving her vaccinations, H.E.F. began to have "shaking of her right side involving both her arm and leg" and had temporarily lost the use of her right arm. Pet. Ex. 7 at 92. H.E.F. was taken to the ED where she was seen by her pediatrician, Dr. White. Id. The shaking movements were noted to have lasted about two minutes. Id. Dr. White's physical examination revealed that H.E.F. had a temperature of 99.4 degrees and decreased strength and tone of her right arm. Id. at 94-95. The results of H.E.F.'s CT scan of her head, a complete blood count, and electrolytes were all normal. Id. Dr. White's diagnosis was "seizure most likely [secondary] to DTaP vaccine." Id. at 95. H.E.F. improved and was discharged home at approximately 9:30 p.m. that same day. Id. at 94-101.

Around 2:00 a.m. on December 29, 2007, H.E.F. was taken to the ED after she had a second episode of seizure activity. Pet. Ex. 7 at 104-05. This seizure caused her left arm to curl

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[5] Pediarix is the "trademark for a combination preparation of hepatitis B vaccine (recombinant), diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine, and poliovirus vaccine inactivated." Dorland's Illustrated Medical Dictionary 1400 (32 ed. 2012).

[6] Prevnar is the "trademark for a preparation of pneumococcal 7-valent conjugate vaccine." Dorland's at 1514.

[7] RotaTeq is the "trademark for a preparation of rotavirus vaccine, live, oral, pentavalent." Dorland's at 1655.

up and shake for approximately two minutes and then go flaccid. Id. at 109. After this episode, H.E.F.'s left arm and leg were flaccid for approximately two hours. Id. at 105-07; Pet. Ex. 5 at 19. Her temperature was 99.5 degrees. Pet. Ex. 7 at 105. H.E.F. was transferred to Blank Children's Hospital ("BCH") in Des Moines, Iowa, for further treatment. Id. at 104-11. At BCH, the physician who documented the admitting history noted that H.E.F. had two "episodes of seizure-like activity" following receipt of her vaccinations the day prior. Pet. Ex. 8 at 4. The physician also noted that H.E.F. had a fever of 101 prior to her transfer to BCH. Id. Pediatric neurologist, Dr. Duangchai Narawong, attended H.E.F. and diagnosed her with complex febrile seizures. Pet. Ex. 9 at 1-2. H.E.F. was given phenobarbital and Diastat and was discharged home on December 30, 2007. Id.

H.E.F.'s next seizure was associated with an illness. On January 17, 2008, H.E.F. had a seizure affecting her left extremities due to a respiratory syncytial virus ("RSV") and she was taken to the ED at Mahaska Hospital. Pet. Ex. 7 at 115. The EMS report stated that H.E.F.'s parents called EMS because H.E.F. was experiencing "involuntary muscle tremors and jerking in her left-side extremities" after which her left upper extremity was immobile. Id. at 141. EMS gave H.E.F. Ativan, which stopped her seizures. H.E.F.'s temperature during this episode was 101 degrees. Pet. Ex. 7 at 137, 141. Dr. Narwong admitted H.E.F. to the hospital for observation due to the lack of mobility in her left extremities. During the admission process, H.E.F. experienced another seizure, which included "twitching of the right side which affected both the arms and legs." Pet. Ex. 7 at 115. After her second seizure, H.E.F.'s temperature increased to 103 degrees. It was noted that H.E.F. had a previous "reaction to DTaP shot." Id. at 122. At this point, H.E.F. was airlifted to BCH. She had no further seizure activity and her condition improved. Id. at 55, 115; Pet. Ex. 9 at 3-4. On January 19, 2008, H.E.F. was discharged home. Pet. Ex. 9 at 3-4.

On February 6, 2008, H.E.F. returned to Mahaska Hospital because she experienced a left-sided seizure lasting at least seven minutes. Pet. Ex. 7 at 159. She then suffered another seizure, this time a "right sided partial complex seizure, which lasted approximately eight minutes." Id. at 152. She was given phenobarbital, valium, and Tylenol. Id. at 155. H.E.F. was discharged the following day, on February 7, 2008. At that time, her physical exam "was within normal limits except for plaque on tongue and buccal mucosa." Id. at 152.

H.E.F. improved and did not experience another seizure until April 8, 2008, when she was taken to Mahaska Hospital by ambulance because of generalized twitching of her left extremities for 45-50 minutes. Pet. Ex. 7 at 219. H.E.F. had a fever of 102 degrees. She was treated with Valium and phenobarbital. Id. at 215. H.E.F. was again airlifted to BCH. She required intubation due to hypoxemia. Id. at 214-15. Dr. Narawong's diagnosis was complex febrile seizures. Pet. Ex. 5 at 6. From May 10-12, 2008, H.E.F. was admitted to Mercy Medical Center in Des Moines, Iowa, for increased seizure activity. Pet. Ex. 10 at 26.

During the spring of 2008, H.E.F.'s parents moved from Oskaloosa, Iowa, to Ottumwa. Pet. Ex. 1 at 10. H.E.F. received continuing pediatric care from Ottumwa Pediatrics and later from All-Ages Pediatric Clinic. Pet. Ex. 1; Pet. Ex. 12; Pet. Ex. 19. On June 12, 2008, Dr. Eric L. Dodson of Ottumwa Pediatrics referred H.E.F. to the Mayo Clinic for repeated episodes of

"status epilepticus." Pet. Ex. 16 at 7. She was diagnosed with "epilepsy with tendency for recurrent prolonged seizures." Pet. Ex. 16 at 9.

On June 21, 2008, Dr. Narawong contacted the Mayo Clinic and explained that H.E.F. was experiencing "unprovoked recurrent status epilepticus." Pet. Ex. 16 at 14. One month later, on July 22, 2008, H.E.F. had a seizure and was taken to Dr. Dodson who prescribed Diastat and Midazolam. Pet. Ex. 16 at 16. The next day, July 23, 2008, H.E.F. presented to the Mayo Clinic for an appointment regarding her seizures. Dr. K.C. Nickels diagnosed H.E.F. with intractable recurrent status epilepticus and noted she may have Dravet syndrome. Id. at 18.

On November 26, 2008, H.E.F. experienced another seizure and was taken to BCH. Pet. Ex. 8 at 380, 495, 573. On January 16, 2009, H.E.F. experienced a seizure associated with a fever and an upper respiratory tract infection. Pet. Ex. 16 at 35. Her seizure was treated with Valium. Id.

A few months later, on April 17, 2009, H.E.F. experienced a seizure during a visit to the Mayo Pediatric Neurology Clinic. Pet. Ex. 16 at 44, 52. After arriving in the ED, she had another left-sided seizure lasting approximately 20 minutes. Id. at 45, 51. H.E.F.'s status epilepticus resolved, but she had a fever, possible pneumonia, and recent influenza exposure. Id. at 45. Dr. Nickels diagnosed H.E.F. with Dravet syndrome. Id. at 57.

From summer through the winter of 2009-2010, H.E.F. continued to experience seizure activity associated with high fevers of 104 to 105 degrees. Pet. Ex. 16 at 91-92, 102. On January 7, 2010, H.E.F. suffered another seizure associated with a high fever. Id. at 106. She suffered another seizure on May 7, 2010. Id. at 108.

A few years later, on June 2, 2012, during a visit to the Mayo Clinic, neurologist Dr. Amy M. Martyanov documented that H.E.F. was being seen in follow-up for her "Dravet's syndrome." Pet. Ex. 16 at 120. Dr. Martyanov noted that H.E.F. "has very classic Dravet's phenotype with prolonged seizures that are temperature sensitive," although at the time of her examination, H.E.F. was noted as doing well regarding her seizure control. Id.

In April 2013, H.E.F. experienced breakthrough seizures after having no seizures since November of 2011. Pet. Ex. 16b at 3. These seizures occurred over several days and were accompanied by a fever of 104 degrees. Id.

b. Summary of the Testimony by Kimberly Faoro

Kimberly Faoro is one of the petitioners and H.E.F's mother. She has seven children, and H.E.F. is the only one who has a seizure disorder. Tr. 8. Ms. Faoro's other children all have had DTaP vaccines during their first year of life and did not experience seizures after vaccination. Tr. 38. Ms. Faoro does not have Dravet syndrome or any other seizure disorder. Tr. 8-9. She did not receive her childhood vaccinations until age four. Tr. 35.

H.E.F. received her first vaccinations when she was two months old, on October 22, 2007. After the vaccinations, she vomited and had diarrhea but did not experience any seizures.

Tr. 14-15. H.E.F. received her four month vaccinations on December 28, 2007. That same afternoon, H.E.F. experienced jerking of her left arm and leg. Tr. 16-18. She did not have a fever at this time. Tr. 35. H.E.F. was taken to the ED, where she did have fever. Tr. 36. She was treated and discharged. Tr. 19. The next day, December 29, 2007, H.E.F. had jerking on the opposite side of her body. Tr. 20. She was ultimately taken to BCH in Des Moines by ambulance. Tr. 21. H.E.F was noted to have esotropia,[8] and her left eye turned inward. Tr. 22. She was also unable to use the side of her body where the seizure activity occurred. Tr. 37.

Ms. Faoro testified that H.E.F. experienced developmental delay. As a child, H.E.F. did not roll over, crawl, or climb up furniture like her siblings. Tr. 23. At nine and one-half months, H.E.F. was referred to early childhood intervention. Tr. 25. On August 11, 2008, an evaluation was performed that showed H.E.F. had a 25% delay in her cognitive skills. Tr. 26.

Currently, H.E.F. is eight years old and is able to walk but she has problems with her balance. Tr. 27. She is able to speak in two-to three-word sentences and can eat with a fork and spoon. Tr. 28. H.E.F. still has seizures, but less frequently. She has had two seizures in the last six months. Tr. 31. She takes Depakote for her seizure disorder. Tr. 33. H.E.F. had no seizures prior to the vaccines she received at her four-month well-child visit. Tr. 14-15.

c. Genetic Testing, SCN1A Mutation, and Dravet syndrome

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

(1) Genetic Testing/SCN1A Mutation

On June 12, 2008, physicians from the Mayo Clinic recommended that H.E.F. undergo genetic testing. Pet. Ex. 16 at 9. On September 5, 2008, Transgenomic Clinical Reference Laboratory reported the results of H.E.F.'s genetic tests, which revealed that she has a novel SCN1A mutation (a "variant C.2531T>G in exon 14 that encodes a stop (TGA) at codon 844"). Id. at 28; Jt. Sub. at 1. To understand the significance of this mutation, some background information is warranted.

A gene is a molecular unit of heredity. It contains DNA which is a molecule that carries most of the genetic instructions used in the development, functioning, and reproduction of all known living organisms and many viruses. Resp't Ex. C. at 5. DNA encodes a functional RNA (or protein product) through a process known as translation. Tr. 302; Resp't Ex. C. at 5. Resp't Ex. G at 6-7, 11. This process of translation from the DNA to RNA produces a specific amino acid chain which becomes an active protein and performs specific functions in the cell. Id. A "stop codon" is a truncation mutation. Resp't Ex. C. at 7. The SCN1A gene encodes the $Na_v1.1$ protein subunit – a voltage-gated sodium channel responsible for transporting positively charged

[8] Esotropia is defined as "strabismus in which there is manifest deviation of the visual axis of an eye toward that of the other eye, resulting in diplopia." Dorland's at 648. Petitioners' expert, Dr. Marcel Kinsbourne, testified that he could not say, more likely than not, that esotropia was caused by the seizures. Tr. 149.

sodium atoms (sodium ions) into cells, which play a key role in a cell's ability to generate and transmit electrical signals.[9] In H.E.F.'s case, her SCN1A gene stops the translation of the protein before it is complete. According to the medical literature and animal models, this type of truncation mutation in the SCN1A gene has almost always been shown to be disease-causing.[10] Tr. 354. H.E.F. has a novel SCN1A gene mutation which has not been previously reported in literature as associated with Dravet syndrome or other severe forms of epilepsy. Pet. Ex. 26 at 48.

H.E.F.'s mother also underwent genetic testing and the results revealed that she has the same gene mutation as H.E.F. But Ms. Faoro is asymptomatic and shows no signs of Dravet syndrome. H.E.F.'s father and maternal grandmother were also tested and they do not have the gene mutation. Pet. Ex. 1 ¶ 113; Pet. Ex. 16 at 90; Pet. Ex. 28. To explain this phenomena, respondent proposes a theory of mosaicism (meaning the mutation is in some of the cells). Mosaicism, which is more fully discussed below, is the explanation proposed by respondent's expert for why Ms. Faoro is asymptomatic. Petitioners contend that respondent's theory that Ms. Faoro is mosaic is only speculation and has not been confirmed by any testing. Jt. Sub. at 3.

(2) Dravet Syndrome

Dravet syndrome is a rare condition with an incidence of 1:40,000 children.[11] Seventy to 80% of Dravet syndrome cases are caused by SCN1A mutations.[12] Ninety-five percent of these mutations are de novo.[13] Id. at 491. The gene which is affected by the mutation is in the alpha subunit of the SCN1A gene, which "encodes the voltage-dependent sodium channel ($Na_v1.1$)." Within the infant's brain, sodium channels evolve in the first six months of life. At birth, the human body relies on the $Na_v1.3$ sodium channel instead of the $Na_v1.1$ channel. Around three months of age, there is a natural transition to reliance on the $Na_v1.1$.sodium channel. The $Na_v1.1$. sodium channel functions to maintain a neurological balance in the brain and dysfunction of this channel can lead to seizures.[14]

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[9] Resp't Ex. C-40, Rilstone et al., Dravet syndrome: Seizure control and gait in adults with different SCN1A mutation, 53(8) Epilepsia 1421-1428 (2012).

[10] Resp't Ex. C-42, Harkin LE et al., The Spectrum of SCN1A-related infantile epileptic encephalopathies, 130 Brain 843-852 (2007).

[11] Pet. Ex. 30-C, Berkovic ASF et al., De novo mutations of the sodium channel gene SCN1A in alleged vaccine encephalopathy: a retrospective study, 5 Lancet Neurol 488-492 (2006); see also Resp't Ex. A-2.

[12] Resp't Ex. C-29, Marini C et al., SCN1A duplications and deletions detected in Dravet Syndrome: implications for molecular diagnosis. 50(7) Epilepsia 1670-1678, 1671 (2009).

[13] In this context, a "de novo mutation" means "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

[14] Resp't Ex. C-9, Oakley JC et al., Temperature- and age-dependent seizures in a mouse model of severe myoclonic epilepsy in infancy, 106(10) Proc. Nat'l Acad. Sci. USA 3994-99 (2009).

Dravet syndrome is also referred to as Severe Myoclonic Epilepsy of Infancy ("SMEI") and is an epilepsy syndrome that typically starts around six months of age.[15] Initial seizures may be accompanied by fever. Id. Development is generally normal at the onset of the disease, but 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[16] seizures in the first year of life, followed by myoclonic[17] seizures. In addition to developmental delay, the children may have an ataxic[18] gait.[19] The seizures are refractory to treatment. Id.

d. Chronology of H.E.F.'s Developmental Delay

The following is a brief summary of events that chronicle H.E.F.'s developmental delay. H.E.F. was born on August 28, 2007. At two weeks of age, September 4, 2007, Dr. White noted, H.E.F. "move[d] her arms and legs equally and focuse[d] on faces." Pet. Ex. 5 at 4. A few days later, on September 11, 2007, H.E.F. was noted to be "active" and "alert." Id. at 6. Again, on October 9, 2007, Dr. White noted that H.E.F. was active and alert. Id. at 8. At her two-month well-child visit on October 22, 2007, H.E.F. was documented as having normal growth and development. Id. at 11. In particular, she was able to raise her head, smile, respond to sound, follow faces, and vocalize. Id. On December 7, 2007, Dr. White again noted that H.E.F. was active and alert. Id. at 13. At approximately five months of age, on December 20, 2007, H.E.F.'s development continued to be assessed as normal. She was "cooing and laughing interactively and ha[d] a social smile . . . [she] was tracking with her eyes and maintain[ed] good head control. She [was] able to open her hands and grasp onto objects. She move[d] her arms and legs equally and lift[ed] her head at 90 degrees while in prone position. She [could] roll over from her front to back and bear weight on her legs." Id. at 14.

At approximately six months of age, on January 17, 2008, records from Mahaska Hospital state that H.E.F. displayed a social smile, rolled over by herself, and was babbling. Pet. Ex. 7 at 135. At approximately six and one-half months of age, on February 6, 2008, H.E.F. was noted as being active and alert and she had normal reflexes. Id. at 159, 163. At about nine and one-half months, on June 12, 2008, Dr. Dodson noted that H.E.F. babbled, had good head control, was socially responsive, turned to localized sound, was playful and alert, blew kisses, and had "no formal regression." Pet. Ex. 16 at 8-9.

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[15] Pet. Ex. 30-V, 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).

[16] Clonic is an adjective of the word "clonus" which is defined as "alternate muscular contraction and relaxation in rapid succession." Dorland's at 373.

[17] 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.

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

[19] Resp't Ex. C-2, Guerrini et al., Borderline Dravet syndrome: A useful diagnostic category?, 52(2) Epilepsia 10, 10 (2011).

At ten months of age, on July 23, 2008, at a Mayo Clinic appointment, H.E.F. was "able to drink a bottle easily with either hand," track objects and faces well, and move all four extremities." Pet. Ex. 16 at 17. Dr. Katherine Nickels noted that H.E.F. was developing normally. Pet. Ex. 19 at 18. However, given H.E.F.'s symptoms and history of seizure activity, Dr. Nickels suspected that she had Dravet syndrome. Id. Genetic testing at this time was pending. Id. On a routine visit to the Mayo Clinic on August 19, 2008, approximately two weeks before her one-year birthday, H.E.F. was noted as being alert and interactive and could pull to stand, cruise, crawl, and sit independently. Pet. Ex. 16 at 24-25. Dr. Nickels did not note any concerns regarding H.E.F.'s development at this time. Id.

On January 9, 2009, at 16 months of age, during a visit to the Mayo Clinic, H.E.F. was noted to be "making progress" developmentally. Pet. Ex. 16 at 32. She was alert and interactive, could walk, run, crouch, use a fork and spoon, participate in pretend play and follow commands. Id. at 32-33. At this visit, H.E.F.'s development was placed at 15 months. However, she did not have a pincer grasp which was a nine-month old milestone. Id. H.E.F.'s development began to regress. Records dated January 16, 2009, when H.E.F. was approximately 17 months of age, reflect that her "development [had] been slow" and that she was at the nine or ten months developmental stage. Id. at 48. Later, on July 27, 2009, at 23 months, Dr. Nickels noted that H.E.F. was "alert" and interactive," but she did not say any "recognizable words." Id. at 97.

On November 23, 2009, at two years and three months of age, Dr. Nickels noted that H.E.F. was progressing developmentally. She responded to her name, understood "no," could easily climb, could say approximately 15 words, and was able to draw lines with a crayon. Pet. Ex. 16 at 102. On June 2, 2010, at two years and nine months of age, H.E.F. was alert and interactive, used two-word phrases, followed objects with her eyes, could reach for objects, and had "good resistive strength" and a stable gait. Id. at 118. She was able to run, but not well, and could not catch a ball or combine words. Id. at 120.

H.E.F.'s diagnosis on July 11, 2013 (at almost 6 years of age) was that H.E.F. had Dravet syndrome and "developmental delay, ataxia, dysmetria, and behavioral control consistent with Dravet syndrome comorbidities." Pet. Ex. 16b at 5-6. H.E.F. was alert and interactive, had good climbing skills, clearly combined approximately four words, but again had an unstable gait. Id.

III. Procedural History

Petitioners filed their petition on October 15, 2010. Respondent filed her report pursuant to Vaccine Rule 4(c) on March 28, 2011. Petitioners filed four expert reports from Dr. Barbara Burton and one from Dr. Marcel Kinsbourne. Respondent filed two expert reports from Dr. Rajesh Sachdeo and two from Dr. Gerald Raymond. In total, the parties filed approximately 72 medical texts and articles. The parties also filed pre-hearing briefs.

A two-day hearing was held on June 3-4, 2014. Ms. Faoro testified on the first day of the hearing, and was present during the entire hearing. Drs. Burton and Kinsbourne testified on behalf of petitioners and Drs. Sachdeo and Raymond testified on behalf of respondent.

A post-hearing status conference was held on June 26, 2014, to discuss the issue of having all of Ms. Faoro's biological children tested for the SCNIA gene mutation. With the consent and agreement of Ms. Faoro, the parties worked together to obtain familial genetic testing.[20] On May 20, 2015, petitioners' counsel filed a status report confirming receipt of the results of the genetic testing of Ms. Faoro's six other biological children, and reported that the results were "negative for the specific mutation tested." Petitioners filed the SCNIA Family-Specific Test Report as exhibit 43. Following this filing, the undersigned ordered the parties to file a joint status report by July 2, 2015, stating whether either party wanted to file a supplemental expert report to address the significance of the findings of the genetic tests. Order dated May 26, 2015; Order dated June 1, 2015. On July 10, 2015, the parties filed a joint status report declining the opportunity to file supplemental expert reports regarding the additional genetic test results. On July 13, 2015, an order was issued confirming that the record was now complete for purposes of determining entitlement.

However, on August 3, 2015, respondent filed a motion for leave to file a supplemental report from Dr. Raymond and additional literature on the basis that respondent had additional relevant evidence. In the motion, respondent stated that on July 31, 2015, Dr. Raymond had learned of an SCN1A mutation database hosted by the Institute of Neurosciences, Guangzhou Medical University, in China. Dr. Raymond stated that he had not known of the database at the time of the hearing. "Upon searching this database, Dr. Raymond learned of additional evidence, including medical literature, related to the specific SCN1A mutation at issue in this case." Respondent's Motion to File Additional Evidence, Aug. 3, 2015, at 1. Petitioners objected to respondent's motion as untimely and because it was perceived as a way for respondent to introduce additional argument about the evidence which the court had not solicited. See Petitioners' Response to Motion To File Additional Evidence, Aug. 3, 2015, at 1.

On August 12, 2015, a status conference was held to discuss the dispute. Respondent stated that the database information was new information, available only as of 2015, and was not available to her experts at the time of the hearing in this case in June 2014. Respondent also clarified that one of the articles identified in her motion was a study conducted by the Mayo Clinic involving a patient that was later identified to be H.E.F. Petitioners confirmed that H.E.F. was the individual involved in this study. Respondent explained that the article stated that H.E.F's specific genetic mutation was classified as a disease-causing mutation, and that Dr. Raymond's supplemental report would discuss the significance of this article. After discussion, the parties agreed to work together to redact the portions of Dr. Raymond's supplemental report considered by petitioners to constitute argument, i.e., not a factual discussion of the additional evidence, and agreed to file the redacted report and medical literature, including the link to the SCN1A database referenced by Dr. Raymond. On August 13, 2015, respondent filed the redacted supplemental report of Dr. Raymond and two additional medical articles.[21] See Resp't

[20] The parties cooperated to obtain genetic testing of H.E.F.'s siblings which took approximately 10 months to complete. See Status Reports, filed August 11, 2014; September 12, 2014; October 14, 2014; November 21, 2014; December 29, 2014; and May 20, 2015.

[21] The undersigned notes that the outcome of this decision would have been the same even if Dr. Raymond's supplemental report and the additional information had not been considered.

Ex. I, I-1 and I-2. The Meng article[22] referenced in Dr. Raymond's report provides the cite for the SCN1A database identifying 1257 mutations. H.E.F.'s mutation is listed in this database.[23]

IV. 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 their 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 H.E.F. suffered a "Table Injury"—i.e., an injury listed on the Vaccine Injury Table—corresponding to a vaccine that she received, or (2) that H.E.F. suffered an injury that was actually caused by the vaccine (or vaccines) she 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

[22] Resp't Ex. I-2, Meng H. et al., The SCN1A Mutation Database: Updating Information and Analysis of the Relationships among Genotype, Functional Alteration, and Phenotype, 36 Hum Mutat 573-80 (2015).

[23] http://www/gzneurosci.com/scn1adatabase/

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 H.E.F. suffered a Table injury, they must prove that a vaccine H.E.F. received caused her injury. To do so, they must establish, by preponderant evidence: (1) a medical theory causally connecting a vaccine and H.E.F.'s injury ("Althen Prong One"); (2) a logical sequence of cause and effect showing that a vaccine was the reason for her injury ("Althen Prong Two"); and (3) a showing of a proximate temporal relationship between a vaccination and her injury ("Althen Prong Three"). Althen, 418 F.3d at 1278; § 300aa–13(a)(1) (requiring proof by a preponderance of the evidence).

Another important aspect of the causation-in-fact case law under the Vaccine Act concerns the factors that a special master should consider in evaluating the reliability of expert testimony and other scientific evidence relating to causation issues. In Daubert v. Merrell Dow Pharm., Inc., 509 U.S. 579 (1993), the Supreme Court listed certain factors that federal trial courts should utilize in evaluating proposed expert testimony concerning scientific issues. In Terran v. Sec'y of Health & Human Servs., 195 F.3d 1302, 1316 (Fed. Cir. 1999), the Federal Circuit ruled that it is appropriate for special masters to utilize Daubert's factors as a framework for evaluating the reliability of causation-in-fact theories presented in Program cases.

B. Causation Theory

The first issue presented is whether H.E.F.'s December 28, 2007 vaccinations can and did cause her injury. Jt. Sub. at 3. As an initial matter, it must be clarified that the parties do not dispute that H.E.F. was born with a mutation of her SCN1A gene and that the vaccinations at issue did not cause her gene mutation. Id. at 1. Rather, the parties dispute whether the vaccinations caused H.E.F. to develop a seizure disorder, i.e., Dravet syndrome and the resulting complications. The undersigned finds that they did not.

(1) Althen Prong One: Petitioners' Medical Theory

Under Althen Prong One, petitioners must set forth a medical theory explaining how the vaccines H.E.F received could have caused her injuries. 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 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, but it must be informed by "sound and reliable medical or scientific explanation." Knudsen 35 F.3d 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. Marcel Kinsbourne

Dr. Marcel Kinsbourne is currently a tenured professor of clinical psychology for graduate students at The New School, University of New York. Tr. 120. He received his medical degree from Oxford University in 1955. Tr. 122. Dr. Kinsbourne then studied neurology, general pediatrics, and pediatric neurology until 1964. Pet. Ex. 31A at 1-2. Dr. Kinsbourne came to the United States in 1967 and became an Associate Professor of Pediatrics and Neurology at Duke University Medical Center in Durham, N.C. Id. at 2. He has held teaching positions in pediatrics and neurology at the University of Toronto, Ontario, Duke, Harvard Medical School, Boston University, and Tufts University. Id. at 3. In 1992, Dr. Kinsbourne became a professor in cognitive studies at Tufts University, and in 1995, he assumed his current position. Id. The last time Dr. Kinsbourne saw patients in significant numbers was in 1981. Tr. 126. Since then, he has devoted his time to research and teaching. Tr. 127. He describes himself as a pediatric neurologist with a special interest in behavioral disorders, including autism. Tr. 127. Dr. Kinsbourne is board-certified in pediatrics and has authored a number of books and hundreds of medical articles. Tr. 129. Dr. Kinsbourne concedes that he is not a geneticist, but he states that he is conversant in neurogenetics to the extent he is able to "understand the findings, evaluate them, and apply them to patient care." Tr. 128. Dr. Kinsbourne has been retained as an expert in two other SCN1A cases in the Program. In both of those cases, entitlement to compensation was denied. Tr. 137.

To explain why Ms. Faoro has the same genetic mutation at H.E.F. but is asymptomatic, Dr. Kinsbourne proposes a "second hit" theory. Pet. Ex. 30 at 7. According to Dr. Kinsbourne, the SCN1A genetic mutation creates a "susceptibility" in an individual. Id. Whether the genetic mutation triggers the seizure disorder "depends on the occurrence of a 'second hit' in [the] gene-environment interaction." Id. Petitioners' theory in this case is that the environmental second hit is the vaccination.

According to Dr. Kinsbourne, environmental triggers can include vaccines, viruses and bacterial infections. Tr. 175-76. He states that the DTaP vaccine "often causes fever and it also can cause a proinflammatory cascade that causes seizures." Id. at 177. "Fever is a potent trigger of seizures" in Dravet syndrome. Pet. Ex. 30 at 6. Dr. Kinsbourne states that the interaction of the DTaP vaccine, which causes fever or inflammation, combined with the genetic susceptibility of the individual can trigger an earlier onset and can increase the severity of Dravet syndrome. Id. Thus, when either of these two mechanisms caused by vaccination, fever and an inflammatory process, occurs in a vulnerable child (i.e., genetic susceptibility due to the SCN1A genetic mutation), Dravet syndrome may be triggered. As a result, Dr. Kinsbourne states that disease onset is earlier and the clinical course is more severe (more severe phenotype[24]).

[24] Phenotype is "the observable morphological, biochemical, and physiological characteristics of an individual, either in whole or with respect to a single or a few traits, as determined by a combination of the genotype and the environment." Dorland's at 1431.

According to Dr. Kinsbourne, the SCN1A genetic mutation is known to lower an infant's seizure threshold due to a fever. Tr. 143. Dr. Kinsbourne cites an article by Ceulemans et al.[25] for the proposition that a fever may trigger seizures in children with Dravet syndrome. Id. Dr. Kinsbourne also cites an article by Tro-Baumann et al.,[26] involving a study of 70 patients with Dravet syndrome who also have SCN1A mutations. In that study, Dr. Kinsbourne explains that 27% of those patients had seizures after receiving vaccinations. "Two thirds of the events (seizures) occurred in the context of fever." The authors found that "seizures after vaccination are a common feature in [Dravet syndrome]." Pet. Ex. 30 at 5. Dr. Kinsbourne explains that a child's febrile reaction to the DTaP vaccine may induce neurochemical changes that lower the seizure threshold and provoke the susceptibility [in a child] to seizures." Pet. Ex. 30 at 7.

Dr. Kinsbourne explains that vaccines, like infections, may "cause the release of proinflammatory cytokines, including interleukin 1 beta (IL-1β) as part of a reaction by the innate immune system." Pet. Ex. 30 at 7. Citing an article by Vezzani and Baram,[27] Dr. Kinsbourne states that IL-1β has a "well-documented propensity to cause seizures." Id. The proinflammatory cytokines "either get through to the brain or stimulate similar cytokines being developed in the brain, and those can cause inflammation in the brain locally and trigger seizures" in a susceptible or vulnerable child. Tr. 142, 144.

In support of his theory about potential environmental triggers, Dr. Kinsbourne cites six articles.[28] Tr. 178. Although he concedes that none of these articles address the role of vaccines, Dr. Kinsbourne states that these articles make the point that the SCN1A genetic mutation is not the "complete explanation of the epileptic condition . . . and one has to think of other factors that might also be involved . . . genetic or environmental or both." Tr. 178. A review of these articles shows they were published more than 10 years ago (in 2004 and 2005). The article by Mulley, et al.[29] suggests a polygenic[30] syndrome may be at play when a child with SMEI inherits an SCN1A mutation from an unaffected parent. Id. at 538. The Mulley authors also state that disease severity may be explained by the type of mutation (i.e., truncating) and the position of the mutation. Id. In the Rhodes article,[31] the authors "speculate that the severe neurological

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[25] Pet. Ex. 30-F, Ceulemans B., et al., Severe myoclonic epilepsy in infancy: Toward an optimal treatment, 7 Nature Reviews Neuroscience 583-90 (2006).
[26] Pet. Ex. 30-V, Tro-Baumann B., et al., A retrospective study on the relation between vaccination and occurrence of seizures in Dravet syndrome, 52 Epilepsia 175-78 (2011); also filed as Respondent's Exhibit C-36.
[27] Pet. Ex. 30-W, Vezzani A. and Baram TZ, New roles for interleukin-I Beta in the mechanisms of epilepsy, 7(2) Epilepsy Curr 45-50 (2007);
[28] Pet. Ex. 30-C (Wallace); Pet. Ex. 30-E (Burgess); Pet. Ex. 30-E (Caspi and Moffet); Pet. Ex. 30-R (Rhodes); Resp't Ex. C-17 (Kimura)(also filed as Pet. Ex. 30-L); Resp't Ex. C-7 (Mulley).
[29] Pet. Ex. 30-O, Mulley JC et al., SCN1A mutations and epilepsy, 25 Hum Mutat 535-42 (2005); see also Resp't Ex. C-7.
[30] Polygenic is defined as "pertaining to or determined by the action of multiple different genes." Dorland's at 1489.
[31] Pet. Ex. 30-R, Rhodes TH et al., Nonactivating voltage-gated sodium channels in severe myoclonic epilepsy of infancy. Proceedings of the National Academy of Sciences, USA 1010:11147-52.

consequences of SMEI are caused by a combination of sodium channel dysfunction (either gain or loss of function) with predisposing genetic or developmental factors that lead to a great chance of neuronal injury." Pet. Ex. 30-R at 5. The authors, however, do not suggest or even speculate that vaccines play a role in the development of Dravet syndrome or other epilepsies associated with SCN1A mutations.

Dr. Kinsbourne also relies on the Sell and Menassian[32] commentary to the Berkovic study published in The Lancet Neurology in 2006. The authors of the commentary applaud the effort of the work by Berkovic and his colleagues in studying SCN1A mutations and questioning whether the mutation is a "predisposing factor waiting to be triggered by fever or other stress." Id. at 466. Sell and Menassian acknowledge that the question requires more study. They also point out that complications of infections are "much higher than those associated with vaccination" and suggest that prophylactic treatment with antipyretics to prevent fever may be required to prevent reactions to vaccines. Id.

In his expert report, Dr. Kinsbourne also cites the McIntosh study[33] in which the authors found that DTaP vaccination "triggered a significantly earlier onset of seizures in infants with SCN1A gene mutations." Pet. Ex. 30 at 6. In that study, the patients were divided into two groups, one that had seizures within two days of vaccination (vaccination-proximate), and the other group that had seizures not temporally associated with vaccine administration (vaccination-distant). The mean age of the child for seizure onset was "18.4 weeks in the vaccination-proximate group and 26.2 weeks in the vaccination-distant group." Id. The onset difference between the two groups was approximately eight weeks. Based on the difference in onset, Dr. Kinsbourne opines that a vaccine "alters the course of seizures in children with SCN1A gene mutation." Id. Although he relies on the McIntosh study, Dr. Kinsbourne criticized the authors' conclusion that there was "no difference between the two groups, vaccination-proximate and vaccination-distant," with regard to "intellectual regression or [] disability." Id. He believes the authors misinterpreted the data due to the small sample size (14 patients), resulting in misleading information or a false negative finding. Id.

b. Petitioners' Expert, Dr. Barbara K. Burton

Dr. Burton is a medical geneticist who currently practices at the Ann & Robert H. Lurie Children's Hospital of Chicago, which is affiliated with the Northwestern University School of Medicine. Tr. 47. She attended medical school at Northwestern University Feinberg School of Medicine, and completed a residency in pediatrics. Dr. Burton then completed a two-year fellowship in medical genetics at Children's Memorial Hospital. She is board-certified by the American Board of Pediatrics and the American Board of Medical Genetics, with subspecialties in clinical genetics and clinical biochemical genetics. Pet. Ex. 36 at 2. Dr. Burton is currently a Professor of Pediatrics at Northwestern University, a member of the Center for Genetic Medicine, and a Clinical Practice Director of the Division of Genetics at Children's Memorial

[32] Pet. Ex. 30-T, Sell E. et al., Demystifying vaccination-associated encephalopathy, 5 Lancet Neurology 465-66 (2006)

[33] Pet. Ex. 30-M, McIntosh et al., Effect of vaccination on onset and outcome of Dravet syndrome: a retrospective study, 9 Lancet Neurology 592-98 (2010); see also Resp't Ex. A-1.

Hospital. She serves as a director and consultant for a number of different clinics at Children's Memorial Hospital, including the Institute for Fetal Health, the PKU clinic, and the Marfan syndrome clinic. Id. at 2-3.

In her current position, Dr. Burton provides "care to patients and families who have birth defects or genetic disorders." Tr. 48. She orders diagnostic testing, provides genetic counseling, as well as ongoing medical care and treatment to her patients with certain genetic disorders. Tr. 48. Although Dr. Burton occasionally sees patients with Dravet syndrome for genetic counseling, or evaluation and diagnosis, she does not typically provide ongoing care and treatment for these patients, as they are usually followed by a pediatric neurologist. Tr. 49.

In addition to patient care and teaching, Dr. Burton also has a number of current research grants and contracts, and she has authored books, book chapters, and hundreds of articles and abstracts. See Pet. Ex. 36. Dr. Burton is licensed to practice medicine in Illinois. She has received numerous honors and awards over the course of her medical practice. Id.

Dr. Burton explained her view of the significance of an inherited mutation. She agrees that "specific mutations (changes) in [the SCN1A] gene are known to be associated with [Dravet syndrome], a condition that causes intractable seizures and developmental disabilities in children." Pet. Ex. 29 at 1. However, she states that "[m]ost disease-causing mutations in SCN1A that result in [Dravet syndrome] are de novo, meaning that they are not present in the parent. If a variant of unknown significance is detected in a parent who is clinically normal, it is typically concluded that the genetic change is not responsible for the patient's abnormalities and most likely represents a normal variant." Id.

Dr. Burton disagrees with respondent's explanation of mosaicism to explain why a mother with the same mutation as her child is asymptomatic, whereas the daughter has a severe form of disease caused by the mutation. She defines mosaicism as a situation where there is "more than one population of cells, just like if you have a mosaic tile pattern on the floor where there's more than one color of tiles … there's more than one type of cell… some cells have the mutation and some don't…. It's a mixed population of cells." Tr. 66. While Dr. Burton agrees that mosaicism is one theory "demonstrated in some families where there's been a normal parent," she states that there can also be other explanations. Tr. 67, 70. She states that there are genetic factors or "some other environmental factors" that may explain why a parent is normal, but the child has Dravet syndrome. Tr. 75. Dr. Burton warns against speculating that a parent is mosaic without additional evidence because there are "too many exceptions in genetics." Tr. 82.

Dr. Burton concedes that she is not an expert in the area of vaccine-induced brain injury or in vaccine-gene interactions, and she clarifies that she did not "come up with the vaccine" as a cause of H.E.F.'s condition. Tr. 89, 104-06. Nonetheless, Dr. Burton testified that the theory proposed by Dr. Kinsbourne, that vaccination could be an environmental trigger for the development of Dravet syndrome in a child with an underlying genetic vulnerability, sounds "very reasonable." Tr. 89, 95. She emphasized, however, that the issue was outside the scope of her expertise. Tr. 76-77.

c. Respondent's Expert -- Dr. Rajesh C. Sachdeo

Dr. Sachdeo is a neurologist who specializes in epilepsy, and he treats children and adults with seizure disorders. Tr. 208. He attended medical school at the Christian Medical College in India. After moving to the United States, Dr. Sachdeo completed his residency at Loyola University Medical Center. He obtained his subspecialty training in epilepsy through a fellowship at Rush-Presbyterian St. Luke's Medical Center in Chicago. Resp't Ex. A-6 at 2. Dr. Sachdeo is currently a Clinical Professor of Neurology at UMDNJ Robert Wood Johnson Medical School in New Jersey. Resp't Ex. A at 1. He is an attending physician at a number of hospitals, including the Robert Wood Johnson University Hospital and Princeton University Medical Center. Id. He is board-certified in neurology and neurophysiology. Id. Dr. Sachdeo has served on many committees and received a Humanitarian Award from the New Jersey Epilepsy Foundation. He is active in research and has conducted more than 50 studies on epilepsy. Dr. Sachdeo has authored book chapters and many articles in the area of his expertise. Id. He has an active clinical practice caring for children who have epilepsy, and over the course of his career has seen and treated approximately 40 to 50 patients with Dravet syndrome. Tr. 201. He currently follows 12 to 14 patients with Dravet syndrome. Tr. 201. Dr. Sachdeo has an active medical license in good standing in New Jersey. Resp't Ex. A-6 at 3.

Dr. Sachdeo disagrees with Dr. Kinsbourne's "second hit" theory, stating there is no proof that environmental factors cause Dravet syndrome. Tr. 230, 232. Likewise, he disagrees that vaccinations cause or significantly aggravate Dravet syndrome. Resp't Ex. A at 4. While Dr. Sachdeo agrees that a "vaccination might trigger earlier onset" of Dravet syndrome in children with the SCN1A mutation, he states that "there is 'no evidence that vaccination before or after disease onset affects outcome'" in patients with Dravet syndrome. Id. Dr. Sachdeo explains that there is extensive data showing that even when the onset of Dravet syndrome is temporally associated with vaccination, there is no difference in outcome or prognosis of the patient. Tr. 232. He testified that 20-30 years ago, there was a time when vaccinations may have been blamed for the disease onset in patients with Dravet syndrome, but now, there is universal acknowledgment by epileptologists[34] that the disease is caused by a gene mutation, not vaccination. Tr. 221, 232-33.

Dr. Sachdeo also disagrees with Dr. Kinsbourne's theory that vaccines function like infections or that they cause a proinflammatory process that causes or contributes to Dravet syndrome. Dr. Sachdeo testified that there is no evidence that vaccinations interact with the lower seizure threshold caused by the SCN1A mutation (Pet. Ex. 30 at 7) and thus trigger the seizure disorder. Tr. 233. He states that while fever, hot baths, or infection may all initiate seizures in children with Dravet syndrome, the time or cause of the initial seizure does not impact or affect the clinical course of the disease. Tr. 234. A child may have his first seizure two months earlier, but the earlier onset does not change the ultimate clinical course or prognosis. Tr. 265. Similarly, he states that there is no difference in patients who have seizure onset associated with vaccinations as opposed to those who do not. Tr. 266. Dr. Sachdeo states

[34] "A specialist in epileptology [the study, diagnosis, and treatment of epilepsy]." Dorland's at 634.

that none of these conditions cause the genetic disorder or the genetic susceptibility in a child. Tr. 236.

Dr. Sachdeo also cites the McIntosh[35] article to support his opinion. As stated earlier, in the McIntosh study, the seizure onset occurred approximately eight weeks earlier in the vaccination-proximate group. But there were no other statistically significant differences between the two groups regarding subsequent seizure types, intellectual function, or prognosis. Id. at 4.

d. Respondent's Expert -- Dr. Gerald V. Raymond

Dr. Gerald Raymond is a pediatric neurologist who specializes in neuropathology and genetics. He attended medical school at the University of Connecticut. Resp't Ex. F at 1. After medical school, Dr. Raymond completed a residency in pediatrics and neurology. Id. He then completed a fellowship in developmental neuropathology, 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 extensive clinical, instructional, and research experience in the fields of neurology, pediatrics, and genetics. See id. at 1-2, 9-10. Dr. Raymond has served as a peer reviewer and published numerous articles in these fields as well. See id. at 2-9.

Dr. Raymond explains that the SCN1A gene contains the recipe for the voltage-gated sodium channel, which is a series of "complex chemical reactions [that] move sodium from one side of a [cell] membrane to the other to change the polarity of the membrane." Tr. 312. The SCN1A gene, along with SCN1B gene, make up the $Na_v1.1$ channel "in the inhibitor interneurons of the hippocampus, the frontal lobes of the cortex, the cerebellum, the brain stem" and other areas of the brain. Tr. 312-14. The $Na_v1.1$ sodium channel is not significant at birth; the significant sodium channel in the first few months of life is $Na_v1.3$. Id. at 315. But after two to four months of age, the Na_v 1.3 evolves to the $Na_v1.1$ sodium channel. Id. Once the $Na_v1.1$ sodium channel becomes functional, the SCN1A mutation manifests and symptoms of Dravet syndrome are seen. Tr. 315-16. The alteration in sodium currents "has a profound effect on . . . excitatory/inhibitory imbalances." Tr. 361. The lack of a functioning SCN1A gene results in a "temperature-sensitive seizure disorder, temperature-sensitive channelopathy." Tr. 320.

Animal models, Dr. Raymond indicated, play an important role in helping to understand the pathogenesis of Dravet syndrome. During his testimony, Dr. Raymond referenced the Oakley article[36] which describes a study of mice that have an SCN1A gene mutation. Tr. 318-19. In that study, a mouse model was created with an abnormal deletion of one copy of the SCN1A gene. Id. At birth, these mice did not have seizures when exposed to heat. Tr. 319. As the mice aged, this changed. One group of mice was subjected to heat until seizures were provoked. Id. The other group was not exposed to temperature elevation, but still subsequently started to seize on their own. Id. Of particular interest to Dr. Raymond was the fact that the

[35] Pet. Ex. 30-M (McIntosh); see also Resp't Ex. A-1.

[36] Resp't Ex. C-9, Oakley JC et al., Temperature- and age-dependent seizures in a mouse model of severe myoclonic epilepsy in infancy, 106(10) Proc. Nat'l Acad. Sci. USA 3994-99 (2009).

animals had features typically seen in Dravet syndrome in humans, including gait problems and behavioral abnormalities. Id. According to Dr. Raymond, the mouse model "recapitulates the human disease with high fidelity." Tr. 317. The Oakley study shows that the animals with an abnormal SCN1A gene that did not have seizures initially, later (and spontaneously) developed a seizure disorder based upon the abnormal SCN1A gene mutation. Id. Dr. Raymond testified, "[i]f you leave them all alone, they will start to seize on their own." Id. Thus, in mice like in humans, the seizure disorder will develop without any trigger (like vaccinations).

Dr. Raymond disagrees with Dr. Kinsbourne's assertion that Dravet syndrome has wide variability in genetic expression, which according to Dr. Kinsbourne explains why Ms. Faoro is asymptomatic although she carries the same genetic mutation as H.E.F. Tr. 331. Dr. Raymond explained that, generally, variations in expressivity in SCN1A have not been seen. Id. If Ms. Faoro is asymptomatic and has the same gene mutation as H.E.F., then, according to Dr. Raymond, Ms. Faoro is likely mosaic. Id.

Dr. Raymond also disagrees with Dr. Kinsbourne's proposed theories of second hit (gene-environment) and vaccinations as similar to infections (immune-mediated response). Dr. Raymond testified that the SCN1A genetic alteration is the sole cause of H.E.F.'s Dravet syndrome and its sequela. Tr. 182; 340. The basis for Dr. Raymond's opinion is three-fold. First, current medical research and literature establishes that a "significant alteration in the [SCN1A] gene is sufficient" for the expression of Dravet syndrome. Tr. 328. Second, animal models show that if you alter or remove (knock out) one copy of the SCN1A gene, the result is Dravet syndrome (Oakley mice study discussed above). Third, the Berkovic[37] and McIntosh[38] studies show that febrile seizures following vaccination do not alter the outcome of Dravet syndrome. Tr. 328.

Dr. Raymond cites studies by Depienne,[39] Gennaro,[40] Marini,[41] and Morimoto[42] to discuss the theory of mosaicism, which he states explains the reason that a parent may be asymptomatic or mildly affected, but the child may have a more severe outcome, such as Dravet syndrome. Tr. 336. In the Depienne study, researchers used quantitative PCR[43] testing to learn that only a fraction of the parent's cells were affected. This study led to the discovery of mosaicism. Resp't Ex. C-18 at 5 (internal page 8). Mosaicism was confirmed in 12 of 19 cases and ranged from 0.04% to 85% in the blood cells. Id. Low level mosaicism was not detectable

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[37] Resp't Ex. A-2, Berkovic et al., De-novo mutations of the sodium channel gene SCNIA in alleged vaccine encephalopathy: a retrospective study, 5(6) Lancet Neurol. 488-92 (2006).
[38] Pet. Ex. 30-M (McIntosh); also filed as Respondent's Ex. A-1.
[39] Resp't Ex. C-18, Depienne C., et al., Parental Mosaicism Can Cause Recurrent Transmission of SCN1A Mutations Associated With Severe Myoclonic Epilepsy of Infancy, 27 (4) Hum. Mutat. 389 (2006).
[40] Resp't Ex. C-19, Gennaro E. et al., Somatic and germline mosaicisms in severe myoclonic epilepsy of infancy, 341(2) Biochem. Biophys. Res. Commun 489-93 (2006).
[41] Resp't Ex. C-29, Marini C. et al., SCN1A duplications and deletions detected in Dravet Syndrome: implications for molecular diagnosis. 50(7) Epilesia 1670-1678 (2009).
[42] Resp't Ex. C-21, Morimoto M. et al., SCN1A mutation mosaicism in a family with severe myoclonic epilepsy in infancy, 47(10) Epilepsia 1732-36 (2006).
[43] Polymerase Chain Reaction, Dorland's at 1399.

with standard techniques. Id. There was a correlation noted between the percentage of mosaicism and how severely affected the parent was. Parents with 18% mosaicism or less were unaffected, while those with 43% or more were increasingly affected the higher the percentage of mosaicism detected. Id. The researchers "hypothesize that a mosaic parent may be asymptomatic or less severely affected, depending on the number of mutation containing cells in [his or her] brain." Id.; Resp't Ex. E at 1. In the Scheff[44] paper presented by respondent, the author noted that "[a] recent carefully executed examination for the presence of SCN1A mosaicism showed that it is more frequent than previously appreciated."

In an article presented by respondent, the authors explained why testing for mosaicism can be difficult.[45] While recent technological advances have provided tools to assess mosaicism on a broader scale, detection of mosaicism still proves to be challenging. Id. Testing requires an analysis of ample cells within a given tissue. Because mosaicism may be tissue-specific or tissue-limited, the detection of mosaicism requires analysis of multiple tissues within an individual. The authors note that not all tissue are amenable to analysis and it is not always possible to predict which tissues may be affected. Id.

There are 1257 mutations that have been identified in the SCN1A gene.[46] The SCN1A mutation database[47] identifies "90 nonsense mutations that result in truncation with all resulting in a seizure disorder." Resp't Ex. E at 1. In this database, 94% of the mutations are de novo, and only 6% are inherited. Tr. 346. Dr. Raymond believes that all of the inherited cases are mosaic. Tr. 346.

Dr. Raymond disagrees with Drs. Kinsbourne's and Burton's assertion that a specific phenotypic expression explains why a mother is asymptomatic, but her child has a disease, although they share the same genetic mutation. Dr. Raymond explains that what was previously thought to be explained by "reduced expression and penetrance of disease-causing" genetic mutations is now explained by mosaicism. Resp't Ex. E at 1; Tr. 335. Dr. Raymond rejects the articles cited by Dr. Kinsbourne[48] as "older literature that can't be relied upon now." Tr. 335. Now, "mosaicism is the explanation for many of these families." Tr. 335. Dr. Raymond states that this is particularly true in mutations that cause "premature truncation of the protein . . . associated with severe epileptic phenotypes." Id.

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[44] Resp't Ex. C-39, Scheffer I., Diagnosis and long-term course of Dravet Syndrome, 16 Eur J Paediatr Neurol S5-S8 (2012).

[45] Resp't Ex. C-41, Spinner NB, A genomic view of mosaicism and human disease, 14(5) Nat. Rev. Genet. 307-20 (2013).

[46] Resp't Ex. I-2 (Meng).

[47] Researchers developed an online and freely available database containing all reported sequence variants in SCN1A (http://www.molgen.ua.ac.be/SCN1AMutations.) See Tr. 346; See Resp't Ex. C-16, Claes LR, et al., The SCN1A variant database: a novel research and diagnostic tool, 30(10) Hum. Mutat. E904-20 (2009).

[48] See Tr. 335 (Kimura (Pet. Ex. 30-L), Gennaro (Pet. Ex. 30-J), Mulley (Pet. Ex. 30-O), Burgess (Pet Ex. 30-D) and Wallace (Pet. Ex. 30-X)).

In summary, Dr. Raymond states that mosaicism is the only explanation for the situation where a parent and child share the same SNC1A mutation (in this case, where a mutation results in a "truncation of the protein"), and the parent is asymptomatic, but the child has Dravet syndrome. Resp't Ex. E at 2.

e. Evaluation of the Evidence

The undersigned finds that petitioners have failed to provide preponderant evidence to support their medical theory. None of the articles cited by Dr. Kinsbourne suggest that vaccines can cause Dravet syndrome or change the clinical course of Dravet syndrome. While some studies demonstrate an association between vaccination and fever, and thus the onset of seizures in children with Dravet syndrome, the current research and medical literature establishes that vaccination does not affect the prognosis or severity of Dravet syndrome. The animal models, as presented by Dr. Raymond, provide strong evidence that Dravet syndrome will develop with or without vaccination in children with the SCNIA mutation, and truncating mutations in the SCN1A gene, like the one identified in H.E.F., are associated with a more severe prognosis. Lastly, Dr. Raymond's testimony and supportive medical literature regarding mosaicism is very persuasive. Mosaicism is the best explanation for why a parent who has the SCNIA mutation may not be symptomatic, but her child, who inherited the same mutation has the disease.

(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 [H.E.F.'s] injury." Althen, 418 F.3d at 1278. This requires petitioners to show that the vaccines H.E.F. received actually caused her 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. Kinsbourne

Dr. Kinsbourne opines that the vaccinations that H.E.F. received on December 28, 2007, contributed to the development of her seizure disorder via the theories described above. Tr. 139; 153. He states that H.E.F.'s SCN1A mutation lowered her seizure threshold and predisposed her to having seizures. Tr. 152-153. The seizures that occurred following her receipt of vaccines on December 28, 2007, triggered the onset of her Dravet syndrome. Tr. 152. However, Dr. Kinsbourne could not say that H.E.F. would not have developed seizures had she not been vaccinated. Tr. 153. He also conceded that the vaccines H.E.F. received did not continue to cause her seizures after the onset because after that time, the vaccines "ha[d] no causal effect, in and of itself afterwards." Tr. 154. Instead, he stated that each seizure makes it more likely that there will be another seizure. Id.

Dr. Kinsbourne testified that once H.E.F. had the initial seizure, it then became much more likely that she would have additional seizures. Tr. 172. He also opines that the vaccinations caused H.E.F. to develop a more severe form of Dravet syndrome than she would have otherwise had. Tr. 190. The basis for his opinion is that H.E.F.'s mother has the mutation but not the disease. Based on the findings published in the McIntosh article, Dr. Kinsbourne opines that the vaccine caused H.E.F. to have an earlier onset of Dravet syndrome by two months. Tr. 190. Dr. Kinsbourne cites a commentary by Dr. Elinor Ben-Menachem to support his opinion that H.E.F.'s outcome would be different but for the vaccine. Tr. 196; Pet. Ex. 30-N.[49]

H.E.F. did have two focal[50] seizures following her vaccinations on December 28, 2007. These seizures lasted about two minutes each. Tr. 145; Pet. Ex. 7 at 94, 107. After the seizures, H.E.F. experienced Todd's paralysis[51] lasting approximately two hours. Tr. 145. The Todd's paralysis is thought to be caused by fatigue due to metabolic demands. Id. at 148. H.E.F. also had esotropia following her seizures. However, Dr. Kinsbourne testified that he could not say more likely than not that these findings (Todd's paralysis and esotropia) are evidence that H.E.F. suffered a brain injury as a result of the seizures. Tr. 149-50. Her MRI and EEG results were normal, which is typical of Dravet syndrome. Tr. 173.

Dr. Kinsbourne concedes that he has no clinical experience in diagnosing or treating children with Dravet syndrome. He has not treated children since the SCN1A genetic mutation was discovered. Tr. 162-63.

b. **Petitioners' Expert, Dr. Burton**

Dr. Burton testified that the purpose of her testimony was to explain that H.E.F.'s mutation has not been established as disease-causing and thus there is insufficient evidence that it is the "sole cause" of her disease. Pet. Ex. 29A at 1 (Supplemental Expert Report of Dr. Barbara Burton). Genetic testing of H.E.F. revealed a novel variant "referred to as c.2531T>G in exon 14 of one of [her] SCN1A genes." Pet. Ex. 29 at 1. Dr. Burton emphasized that the "variant had not been reported in the literature in any other patient" and therefore, "the pathogenicity" of the mutation has not been determined.[52] Id. The mutation could be disease-causing (pathogenic change) or a polymorphism (normal variation) without any effect on gene function (benign change). Id.; Tr. 65-66. H.E.F.'s mutation is predicted to "lead to a stop codon," which means that transcription of the gene stops at a certain point before completion. Tr. 67, 116. A stop codon mutation is analogous to a truncating mutation. Id. at 116. While Dr. Burton testified that H.E.F.'s mutation could either be pathogenic or a normal variation, she

[49] Pet. Ex. 30-N, McIntosh AM, et al., Vaccination and the onset of Dravet syndrome, 11 Epilepsy Currents 120-22 (2011).
[50] A focal seizure is a "partial" seizure. Dorland's at 1688.
[51] Todd's paralysis is defined as "hemiparesis or monoparesis lasting for a few minutes or hours, or occasionally for several days, after an epileptic seizure…" Dorland's at 1378.
[52] Prior to her testimony at the hearing, Dr. Burton reviewed the SCN1A database and did not find any other report of the same SCN1A genetic mutation as the type shared by H.E.F. and her mother. Tr. 113.

conceded that a truncating mutation (like H.E.F. has) is more likely than not to be a disease-causing mutation. Tr. 67, 115.

Once novel gene variants like H.E.F.'s are detected in studies, the parents are usually tested. Tr. 114. Testing was performed on H.E.F.'s parents which revealed that H.E.F.'s mother has the same genetic mutation as her daughter. However, H.E.F. has Dravet syndrome and her mother does not. Tr. 68. Because of this, Dr. Burton opines that the genetic mutation "is not responsible for the intractable seizures and developmental disabilities observed in [H.E.F.]." Pet. Ex. 29 at 2.

Although Dr. Burton agrees that the SCN1A mutation likely contributed to H.E.F.'s Dravet syndrome, she does not believe it is the "sole cause" of the child's condition. Pet. Ex. 29A at 1. According to Dr. Burton, the only way that the genetic mutation could be the sole cause of H.E.F.'s condition is if her mother has a de novo mutation that is mosaic. Tr. 82. Dr. Burton does not, however, believe that H.E.F.'s mother is mosaic because the genetic testing that has been performed does not show evidence of mosaicism. Tr. 67-68, 114. Dr. Burton also relies on the Depienne[53] article to support her proposition that generally, in genetic DNA testing, if at least 20 percent of the cells have the SCN1A mutation, the result would be reported as mosaicism. Tr. 70-72. Because Ms. Faoro's test results did not state that she was mosaic, Dr. Burton believes it is unlikely that Ms. Faoro is, in fact, mosaic.[54] Tr. 69-72. However, Dr. Burton goes on to explain that mosaicism cannot be completely ruled out. She states, for example, that if only a patient's blood is tested, but the abnormal gene is contained in the brain or some other tissue, the test would be negative for mosaicism even though the patient is mosaic. Tr. 69-70. Thus, mosaicism could not be completely ruled out in Ms. Faoro's case. Id.

Dr. Burton disagrees with Dr. Raymond's explanation that H.E.F.'s gene mutation is pathogenic based on the type and location of the mutation of the gene. Resp't Ex. C at 7. Dr. Raymond explains in his expert report that H.E.F's mutation creates a stop codon, which means that the codon stops reading or transcribing the gene at a certain point, and stops formation of the protein in her DNA (also known as a truncating mutation). According to Dr. Raymond, because of this stop codon mutation, H.E.F. is more likely to have a disease-causing mutation that results in a severe dysfunction of the protein encoded by her DNA and usually results in disease. Id.; Tr. 311. While Dr. Burton testified that protein-truncating mutations do not always cause disease, she admitted that it "usually" results in disease. Tr. 115.

Dr. Burton testified that expression of the gene mutation may vary based upon phenotype. Her opinion is based on results from studies[55] that show a wide range of phenotypic variability in family members with the same SCN1A mutation. Tr. 97-99. She states that individuals in the same family, with the same mutation, and who do not have mosaicism, can

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[53] Resp't Ex. C-18 (Depienne).

[54] More precise testing, TAQMAMA Quantification, which uses a technique to quantify the amount of a gene present, and to determine the percentages of normal versus mutated cells, was not done here. Tr. 72.

[55] Resp't Ex. C-10, Escayg et al., Sodium channel SCN1A and epilepsy: mutations and mechanisms, 51(9) Epilepsia 1650-58 (2010).

have a "different expression of that mutation." Tr. 95. In those families, Dr. Burton states that there must be "an explanation other than mosaicism for why one individual has nothing to show for the mutation and another has generalized epilepsy or some other phenotype." Id. Whether that explanation is "other genes or environmental influences, it [is] something other than mosaicism." Tr. 95.

Dr. Burton also relies upon an article by Escayg and Goldin[56] to support her argument that mosaicism is not the answer to the puzzle. In that article, the authors state that "family members with the same SCN1A mutation often display a wide range of seizure types and severities, suggesting that additional environmental or genetic facts likely influence clinical presentation." Resp't Ex. C-10 at 5 (internal page 1653); see Tr. 99; 103. Dr. Burton also references an article by Kimura et al.[57] for the same proposition, that "genetic or environmental factors other than SCN1A mutations may modify SMEI phenotypes." Resp't Ex. C-17 at 3 (internal page 425); see Tr. 100.

Dr. Burton testified that if it turns out that H.E.F.'s mother is not mosaic, then the SCN1A gene mutation cannot explain H.E.F's condition. Tr. 110. That would mean H.E.F's mother would have the gene mutation in every cell in her body and is asymptomatic. Thus, the mutation alone could not be the sole cause of H.E.F.'s Dravet syndrome. Id.

According to Dr. Burton, there is up to a 50% risk (per child) that Ms. Faoro would transmit the mutation to each of her children. Tr. 61. Thus, according to Dr. Burton, H.E.F.'s siblings are likely to have the mutation. However, the results of the children's genetic testing were all normal. Dr. Burton testified that this is either because they have not had any environmental trigger or Ms. Faoro is mosaic. Tr. 111. Dr. Burton agreed that if Ms. Faoro was mosaic, she would have a mix of cells that have the mutation and do not have the mutation, and that, probably, most of the cells in her brain do not have the mutation which is what has protected her from having any neurologic symptoms. Tr. 109. In addition, Ms. Faoro would have fewer cells in her ovary that have the gene mutation, and the risk of each of her children being born with the mutation would be less than 50%. Tr. 111.

To determine whether Ms. Faoro is mosaic, Dr. Burton testified that Ms. Faoro would have to undergo quantitative PCR and tissue biopsy testing. Tr. 108-09. If testing revealed that Ms. Faoro has the gene mutation in only a portion of her cells, it would mean that Ms. Faoro is mosaic. It would also mean that the gene mutation would not be present in many (or any) of Ms. Faoro's brain cells because she does not have an epilepsy disorder. Tr. 109. If Ms. Faoro is in fact mosaic, it also means that the gene mutation occurred the first time in her (i.e., de novo) and can be passed down to her offspring, which is what happened to H.E.F. Tr. 109. H.E.F. inherited the mutation from her mother and the mutation is contained in every cell in her body, including her brain. Id.

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[56] Resp't Ex. C-10, Escayg A. et al., Sodium channel SCN1A and epilepsy: Mutations and mechanisms, 51(9) Epilepsia 1650-1658 (2010).

[57] Resp't Ex. C-17, Kimura et al., A missense mutation in SCN1A in brothers with severe myoclonic epilepsy in infancy (SMEI) inherited from a father with febrile seizures, 27 Brain & Development 424-30 (2005).

c. Respondent's Expert, Dr. Sachdeo

Dr. Sachdeo opined that H.E.F.'s seizure disorder was a result of her Dravet syndrome, which by itself would have triggered her seizure disorder. Dr. Sachdeo stated that the vaccinations H.E.F. received had nothing to do with the development of her seizures, or the severity and outcome of her condition. Resp't Ex. A at 4-5; Tr. at 221. He testified that while the fever associated with her vaccines likely triggered the initial seizure, the vaccinations did not trigger H.E.F.'s underlying genetic disorder. Tr. 236, 284.

Dr. Sachdeo testified that H.E.F.'s clinical course was consistent with the expected course of Dravet syndrome. Tr. 227. He opined that H.E.F. began having symptoms of developmental delay at some point between 12 and 15 months, which is consistent with the clinical course of the disease. Tr. 227-228; 266. Even assuming that H.E.F. began having developmental delay at 9 ½ months of age (consistent with Ms. Faoro's testimony at the hearing), that onset too, would be consistent with the natural, clinical course of the disease. Tr. 229.

Based on his experience treating children with Dravet syndrome, Dr. Sachdeo testified that those children who respond well to medication early, tend to have a better prognosis. Tr. 265. He stated that the most important factor in determining prognosis is good seizure control through medication. Tr. 267. Based on H.E.F.'s medical records, Dr. Sachdeo testified that it took approximately a year to find medication that effectively controlled H.E.F.'s seizures. Tr. 268. Dr. Sachdeo stated that he was impressed with H.E.F.'s treatment, and he felt that she made good progress developmentally. Tr. 269. Dr. Sachdeo testified that H.E.F.'s seizures are well controlled and that her prognosis is good. Tr. 269.

d. Dr. Raymond

Dr. Raymond testified that H.E.F.'s SCN1A gene mutation is the "sole cause" of her seizure disorder. Tr. 299; 340. Her genetic mutation is described by Dr. Raymond as a "premature Stop codon" type mutation. Tr. 302. This type of mutation affects the "function of the protein." Tr. 310. Dr. Raymond explained that 90 to 99% of truncating SCN1A mutations are associated with Dravet syndrome or other severe temperature sensitive seizure disorders. Tr. 321; 327. Moreover, H.E.F.'s specific mutation has now been "uploaded into an international SCN1A mutation database (http://www/gzneurosci.com/scn1adatabase/); Resp't Ex. I.

H.E.F.'s SCN1A gene mutation takes the amino acid sequence TTA and takes it to TGA, and that "becomes a stop, so there's no further translation of additional protein." Tr. 324. Dr. Raymond stated that this results in haploinsufficeincy[58] of SCN1A and the voltage gated sodium channel $Na_v1.1$. Tr. 324. This "truncation mutation" and "haploinsufficeincy" are associated with severe phenotypes, which manifests in H.E.F. as a severe temperature-related seizure disorder. Tr. 326-27. A person needs two functioning copies of SCN1A. Tr. 260.

[58] "Haploinsufficiency" is defined as "the situation in which the contribution for a single copy of a normal allele, as in an individual carrying a heterozygous mutation or hemizygous at a particular locus, is inadequate to provide normal function." Dorland's at 820.

Haploinsufficiency occurs when a child receives one functioning copy of SCN1A from one parent, and a defective copy from the other parent. Tr. 359. The sodium currents in the voltage gated sodium channel are not sufficient to provide enough inhibitory current into the neurons to make the neurons function. The neurons are not carrying out their function and this results in an excitory/inhibitory imbalance, leading to a seizure disorder. Tr. 361.

Dr. Raymond opines that the theory of mosaicism is the most logical explanation for why H.E.F. has a seizure disorder, but her mother does not. If H.E.F.'s mother is mosaic, it means that she has the SCN1A gene mutation in some, but not all of her cells. Tr. 330-31. If the percentage of abnormal cells is not highly expressed in her mother's brain, then H.E.F.'s mother is not likely to have Dravet syndrome. Tr. 331. However, H.E.F.'s mother may still pass the gene mutation to her offspring who may inherit the full-blown disordered, like H.E.F. did. H.E.F. inherited the mutation from her mother and that mutation is contained in 100% of her cells. As a result, H.E.F. has Dravet syndrome. Tr. 332.

Dr. Raymond also explained that testing to verify whether H.E.F.'s mother is mosaic is currently not commercially available. Tr. 332, 378-81. However, he stated that circumstantial evidence could be established through testing Ms. Faoro's parents or her other biological children. Tr. 384. Ms. Faoro's mother tested negative for the gene mutation. Ms. Faoro's father passed away, but Ms. Faoro testified that her father did not have a seizure disorder. Tr. 13. Without results from Ms. Faoro's father, it cannot be confirmed if Ms. Faoro is mosaic. Tr. 384. Regarding Ms. Faoro's other biological children, Dr. Raymond explains that he did not believe that any of Ms. Faoro's other children have the SCN1A genetic mutation because they do not have clinical symptoms. Tr. 365. He explained that there is a risk of between zero and 50% for each pregnancy that Ms. Faoro's child would inherit the mutation, depending on the percentage of Ms. Faoro's affected cells. Tr. 359. If all of the other children are tested and none have the SCN1A gene mutation, this would be circumstantial evidence in support of Dr. Raymond's theory that Ms. Faoro is mosaic. Tr. 385. However, if a sibling was positive for the mutation, then that would be evidence that the SCN1A mutation is not the sole cause of H.E.F.'s Dravet syndrome. Tr. 385-86.

After the hearing, the children were all tested and the results confirmed that none of them have the SCN1A gene mutation. Pet. Ex. 43. Based upon Dr. Raymond's explanation above, this is circumstantial evidence that Ms. Faoro is mosaic.

Dr. Raymond disagrees that any environmental factor was at play here. He opined that no one has identified a specific environmental factor that causes or contributes to Dravet syndrome. Tr. 372. He states that his opinion is that H.E.F.'s gene mutation is the "sole cause of her Dravet syndrome…" Resp't Ex. I at 1.

e. Evaluation of Evidence

Petitioners have failed to prove by a preponderance of the evidence a logical sequence of cause and effect showing that the vaccines H.E.F. received caused her Dravet syndrome. First, it is undisputed that H.E.F. was born with the SCN1A gene mutation and the parties agree that her gene mutation was not caused by the vaccines. Second, H.E.F. did not sustain any permanent

brain injury after her initial seizures following vaccination. The initial seizure lasted two minutes, which was followed by Todd's paralysis of her arm which resolved. H.E.F. then had a second seizure lasting two minutes, again followed by Todd's paralysis, which again resolved. After being observed in the hospital, H.E.F. was discharged home. Her diagnostic studies, including the EEG, were all normal. H.E.F.'s physical and neurological exams were normal. Dr. Kinsbourne agrees that there was no evidence of brain injury after her first two seizures.

H.E.F received her vaccines at approximately four months of age (December 28, 2007). The first medical records that describe any type of development delay appear in H.E.F.'s records on January 9, 2009, when H.E.F. was approximately 16 months of age. This was approximately one year after the vaccines at issue were administered.[59]

Once H.E.F.'s treating physicians obtained the results of her genetic testing, they confirmed the presence of an SCN1A gene mutation and H.E.F. was diagnosed with Dravet syndrome. Once the genetic cause of H.E.F.'s illness was discovered, her diagnosis was clear. There is no indication in the record that any of H.E.F.'s treating physicians have diagnosed her with a vaccine-related injury after the results of her genetic tests were obtained and reviewed.

Petitioners' argument, that expression of the gene mutation may vary based upon phenotype, also fails. At the hearing, Dr. Burton testified that the evidence was insufficient to establish mosaicism. According to Dr. Burton, the only way that the genetic mutation could be the sole cause of H.E.F.'s condition is if her mother, Ms. Faoro, had a de novo (new) genetic mutation and was mosaic. Tr. 82, 110. Ms. Faoro's mother, H.E.F's grandmother, was tested and does not have the SCN1A gene mutation. Although Ms. Faoro's father could not be tested, Ms. Faoro testified that he did not have a seizure disorder. Tr. 13. After the hearing, testing was performed on Ms. Faoro's other biological children which revealed that none of them had the SCN1A mutation. These negative test results are strong circumstantial evidence that H.E.F.'s mother is mosaic. This strong evidence supports Dr. Raymond's theory of mosaicism. There is no basis for implicating the vaccinations as the cause in the face of this convincing evidence.

Lastly, petitioners failed to prove by preponderant evidence that Dr. Kinsbourne's theory (the vaccines affected the occurrence and severity of H.E.F.'s disease) is reliable. Dr. Kinsbourne did not provide any reliable testimony or medical literature to show that H.E.F's outcome would have been different had she not received the vaccines. The commentary cited by Dr. Kinsbourne to support his theory that the outcome of H.E.F.'s Dravet syndrome would be different, but for the vaccine, is not supported. Dr. Kinsbourne conceded that he has not treated children with Dravet syndrome. Both of respondent's experts have experience providing medical care to patients with Dravet syndrome. Respondent's experts testified that H.E.F.'s clinical course was, and continues to be, consistent with the expected course of Dravet syndrome. Respondent also provided medical literature to support her position that H.E.F.'s vaccines did not change the occurrence or severity of her clinical course of Dravet syndrome.

[59] Even assuming that H.E.F. had developmental delay at nine and one-half months of age, as testified to by her mother that would be more than five months after the vaccines were administered.

(3) Althen Prong Three: Timing

Under Althen Prong Three, petitioners must establish that H.E.F.'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. Kinsbourne

Dr. Kinsbourne opined that the vaccinations H.E.F. received on December 28, 2007, were a significant contributing factor to the onset of her Dravet syndrome, in part because she had her first seizure approximately seven hours after vaccination. Pet. Ex. 30 at 4, 7-8.

Dr. Kinsbourne submitted several articles in which 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,[60] 12 out of 28 children with SMEI had their first seizure within three days of the DTP vaccine. Pet. Ex. 30 at 4. In the Berkovic study,[61] 11 out of 14 children with the SCN1A gene mutation had their initial seizure within three days of vaccination. And in the Tro-Baumann study,[62] the authors reviewed information about 70 children diagnosed with Dravet syndrome and found that seizures occurred after vaccination in 19 of the children (27%).[63]

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[60] Pet. Ex. 30-Q, Nieto-Barrera J. et al., Severe myoclonic epilepsy in childhood. Epidemiologic analytic study, 30 Revista de Neurologica 620-24 (2000).

[61] Pet. Ex. 30-C, Berkovic ASF et al., De novo mutations of the sodium channel gene SCN1A in alleged vaccine encephalopathy: a retrospective study, 5 Lancet Neurol 465-66 (2006); see also Resp't Ex. A-2.

[62] Pet. Ex. 30-V (Tro-Baumann); see also Resp't Ex. C-36.

[63] Resp't Ex. C-36 at 176.

b. Petitioners' expert, Dr. Burton

Dr. Burton stated that she is not an expert in vaccine related injuries. Tr. 76, 89. Throughout the hearing, she emphasized that she did not reach any conclusions about whether H.E.F.'s injuries were vaccine related. Tr. 90. Even so, Dr. Burton testified that based on the temporal association of H.E.F.'s seizures to her vaccinations, it was reasonable to assume that there was a causal relationship. Tr. 90.

c. Respondent's Expert, Dr. Sachdeo

Dr. Sachdeo stated that a temporal relationship between seizures and vaccination may exist. However, he stated that this temporal relationship does not affect the outcome in patients with Dravet syndrome. Resp't Ex. A at 5. Dr. Sachdeo estimated that 30-40% of his patients with Dravet syndrome had their first seizure within 72 hours of a vaccination. Tr. 260. He has not, however, seen any differences between his patients who have their initial seizures in temporal association with vaccines, as compared to those who do not. Tr. 264-65. The biggest factor in predicting good outcomes, according to Dr. Sachdeo, is whether a child responds well to medication early in the course of their disease. Tr. 265.

d. Respondent's expert, Dr. Raymond

Dr. Raymond testified that following H.E.F.'s vaccination, she did experience temperature elevation followed by brief seizures. But he explained that this temporal association played "no aggravating or contributing role to her diagnosis of Dravet syndrome." Tr. 340. Dr. Raymond explained that fever, illness, and lack of sleep, are factors that may lower the seizure threshold but that these factors do not cause Dravet syndrome. Tr. 372. He stated that Dravet syndrome is caused by a genetic mutation. Tr. 339-40.

Dr. Raymond also cited the McIntosh study,[64] in which the authors 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.[65] Dr. Raymond also cited the Tro-Baumann article[66] for the same proposition.

e. Evaluation of the Evidence

The medical records show, and all of the experts agree, that H.E.F.'s initial seizure, or seizure onset, was within 24 hours of her four month vaccinations. 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").

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[64] Pet. Ex. 30-M, see also Resp't Ex. A-1.
[65] Resp't Ex. A-1 at 596.
[66] Resp't Ex. C-36.

Moreover, the McIntosh study shows that in children with Dravet syndrome, who have their initial seizures following vaccination, are no different than children who do not experience their first seizure in temporal relation with a vaccination. The clinical course and outcome are no different.

C. Standards of Adjudication - Significant Aggravation

The second issue presented by the parties is whether H.E.F.'s vaccinations significantly aggravated her pre-existing injury. Jt. Prehearing Sub. at 3. 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); see also W.C. v. Sec'y of Health & Human Servs., 704 F.3d 1352, 1357 (Fed. Cir. 2013) (holding that "the Loving case provides the correct framework for evaluating off-table significant aggravation claims"). 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 H.E.F.'s Condition Prior to Administration of the Vaccine?

The first step in the Loving test is to determine H.E.F.'s condition before she received the vaccinations at issue. H.E.F. was born with a mutation of her SCN1A gene. See Jt. Sub. at 1. The specific mutation here is a "premature Stop codon" mutation that affects the function of the protein. Tr. 310. Mutations of this type are associated with severe epilepsy and Dravet syndrome. Tr. 321,327.

Although H.E.F. was born with the SCN1A mutation, her physical and neurological examinations were all normal prior to her December 28, 2007 vaccinations. See Pet. Ex. 5 at 3, 7. She was healthy and did not have any seizures prior to the vaccinations.[67]

(2) Loving Prong 2: What is H.E.F.'s Current Condition (or Her 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 her vaccinations is most pertinent.

On December 28, 2007, approximately seven hours after her four month old immunizations, H.E.F. had her initial seizure which lasted about two minutes. Pet. Ex. 7 at 92. She had temporary paralysis of her right arm, but then regained full movement. Id. at 92-93. The results of the CT scan of her head and her lab work were normal. Id. at 95. H.E.F. had subsequent seizure activity at 2:00 am on December 29, 2007. Id. at 104. After this episode, H.E.F.'s left arm and leg were flaccid (Todd's paralysis) for approximately two hours. Again, the paralysis was temporary and H.E.F. regained full function. Id. at 105-07; Pet. Ex. 5 at 19. Pediatric neurologist Dr. Narawong diagnosed H.E.F. with a complex febrile seizure. Pet. Ex. 9 at 1-2.

Approximately two weeks later, H.E.F. had seizure activity, this time associated with illness. Pet. Ex. 7 at 115. The seizure was described similar to her prior episodes, as "twitching of the right side which affected both the arms and legs." Id. H.E.F.'s next episode of seizure activity occurred on February 6, 2008, and was a left-sided seizure lasting at least seven minutes. Id. at 159. H.E.F. then suffered another seizure, this time a "right sided partial complex seizure, which lasted approximately eight minutes." Id. at 152. H.E.F. continued to have seizures in April and May 2008, associated with illness and fever. Id. at 215, 219, 236; Pet. Ex. 10 at 26.

In June 2008, H.E.F. was referred to the Mayo Clinic for repeat episodes of "status epilepticus." Pet. Ex. 16 at 7. She was diagnosed with "epilepsy with tendency for recurrent prolonged seizures." Id. at 9. On July 23, 2008, H.E.F. was seen by Dr. Nickels at the Mayo Clinic and diagnosed with Dravet syndrome. Id. 18.

Several years later, on June 2, 2012, H.E.F. during a follow-up visit to the Mayo Clinic, neurologist Dr. Amy M. Martyanov stated that H.E.F. "has very classic Dravet's phenotype with prolonged seizures that are temperature sensitive." Pet. Ex. 16 at 120.

The evidence in the record indicates that H.E.F.'s current condition is consistent with that of a child who has the SCN1A gene mutation and Dravet syndrome. Like H.E.F.'s treating

[67] Medical records from the Mayo Pediatric Neurology Clinic erroneously note that H.E.F. has seizure activity prior to her four month immunizations. Pet. Ex. 17 at 24-25. However, Ms. Faoro clarified that this entry in the medical records was incorrect, and that H.E.F. did not have any seizures prior to December 28, 2007. Tr. 14.

neurologist, Drs. Sachdeo and Raymond (who both treat patients with Dravet syndrome) testified that H.E.F.'s clinical course is consistent with that of a child with Dravet syndrome.

(3) Loving Prong 3: Does H.E.F.'s Current Condition (or Condition after Vaccination) constitute a "Significant Aggravation" of her Condition Prior to Vaccination?

The next prong of the Loving test is to determine whether there is a "significant aggravation" of H.E.F.'s condition by comparing her condition before vaccination to her condition after vaccination. 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, H.E.F. had two brief seizures immediately after her December 28, 2007 vaccinations. Over time, H.E.F.'s condition deteriorated and she developed severe epilepsy and developmental delay. The undersigned must first make clear that there is no question that H.E.F.'s condition prior to and after her December 28, 2007 vaccination was worse. However, the question relevant to this prong of the Loving analysis is whether H.E.F.'s vaccination significantly aggravated her Dravet syndrome. In other words, is H.E.F.'s clinical course and outcome any different than it would have been if she 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) (affirming special master's finding that petitioner's condition was not inconsistent with the disease generally and not affected by the vaccinations).

As stated above, H.E.F.'s clinical course is consistent with Dravet syndrome. Dr. Kinsbourne, however, suggests that if H.E.F. had not received the vaccines on December 28, 2007, the onset of her Dravet syndrome would have been later; or that her developmental delay may been less severe. Pet. Ex. 30 at 6. All of these arguments fail, however, because Dr. Kinsbourne concedes that there is no way to predict what H.E.F.'s outcome would have been if she had not received the vaccines. Simply stating what "may" have happened is a matter of speculation and such a statement does not provide petitioners with preponderant evidence to support their theory. Tr. 192.

Alternatively, Dr. Kinsbourne cites the McIntosh study[68] to support petitioners' claim of significant aggravation. Dr. Kinsbourne states that earlier onset of seizures indicates that vaccines "alter the course of seizures" in children with Dravet syndrome. Pet. Ex. 30 at 6. Dr. Kinsbourne's conclusion, however, contradicts the conclusion of the authors in the McIntosh study who found that although vaccination might appear to trigger the onset of Dravet syndrome, there was no difference in the clinical outcome in patients with vaccination-proximate seizures.

Petitioners have failed to show by a preponderance of the evidence that the vaccinations significantly aggravated H.E.F.'s condition. She was born with the SCN1A and her clinical course developed consistent with that condition. The undersigned finds that the vaccinations would not have changed her clinical course and thus, the vaccinations did not significantly

[68] Pet. Ex. 30-M (McIntosh); see also Resp't Ex. A-1.

aggravate her preexisting condition. See Snyder/Harris v. Sec'y of Health & Human Servs., 553 Fed. Appx. 994 (Fed. Cir. 2014) (the Federal Circuit ruled that the special master was not arbitrary in finding that petitioners' expert failed to show that the child's outcome would have been different had he not received the vaccinations at issue.)

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

As set forth in section D(1) above, petitioners failed to establish by a preponderance of the evidence, a medical theory causally connecting H.E.F.'s condition, or any significant aggravation. Dr. Kinsbourne did not set forth any additional theories for petitioners' argument based on significant aggravation, apart from the theories addressed above. 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 H.E.F.'s Condition?

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

(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 D(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 H.E.F.'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 H.E.F.'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 Vaccine 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).

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 H.E.F.'s Dravet syndrome and resultant neurological injuries.

Compensation has been denied in similar cases 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. See 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. Deribeaux, 717 F.3d 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 that petitioners were entitled 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 a result of her SCN1A mutation and that the vaccine did not cause or aggravate her condition. Id.

In Deribeaux II, the special master specifically addressed the Althen prongs of causation and found that the SCN1A mutation was the "sole substantial factor" in causing 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.

Special masters have similarly 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),[69] 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 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 Federal Circuit upheld the special master's findings in Snyder v. Sec'y of Health & Human Servs., 553 Fed. Appx. 994, 999 (Fed. Cir. 2014), that the "Secretary proved by preponderant evidence its 'factors unrelated' defense by showing that the gene mutations were the sole cause of the disorders."

Two SCN1A cases were recently on review at the Court of Federal Claims. In both cases, the court upheld the special master's denial compensation to petitioners. In Santini v. Sec'y of Health & Human Servs., 122 Fed. Cl. 102 (2015), the court found that petitioners' expert failed to provide a medical theory linking the child's vaccination to his Dravet syndrome and affirmed the special master's decision denying compensation. Santini, 122 Fed. Cl. at 110. In Barclay, the court upheld that the special master's determination that the vaccine did not aggravate or worsen the child's genetic condition. Barclay, 122 Fed. Cl. at 199.

Likewise, in Barnette v. Sec'y of Health & Human Servs., 110 Fed. Cl. 34, 26 (2013), the special master's finding that the child's SCN1A mutation was the sole cause of her Dravet syndrome and related injuries was affirmed.[70] 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.

Here, respondent has put forth preponderant evidence establishing that H.E.F.'s SCN1A mutation, a factor unrelated to the administration of the vaccines, is the agent solely responsible causing her Dravet syndrome.

a. Althen Prong One: Respondent's Medical Theory

To prove Althen Prong One 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 H.E.F.'s Dravet syndrome and the resulting complications.

[69] 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 the decisions were affirmed by the Federal Circuit. Id.

[70] 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, like the petitioners in the present case, that the DTaP vaccination acted as an environmental trigger effected an earlier onset of her Dravet Syndrome. 110 Fed. Cl. at 38.

Respondent's expert, Dr. Raymond, explained the pathophysiology of Dravet syndrome.[71] 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 . . . . [There 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 Ex. C at 5.

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,[72] 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.[73] 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 her colleagues conducted a clinical study[74] on 60 patients with Dravet syndrome. Dr. Ceulemans concluded that there "is a strong argument favoring the genetic disorder itself as probably being the most important factor for developmental problems in these [Dravet syndrome] patients." Id. at 4.

In the McIntosh[75] 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

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[71] 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 Ex. C; see also the Brunklaus study, Resp't Ex. C-37.

[72] Resp't Ex. C-37, Brunklaus A., et al., Prognostic, clinical and demographic features in SCN1A mutation-positive Dravet syndrome,135 Brain 2329-30 (2012).

[73] Id.

[74] Pet. Ex. 30-F, Ceulemans B., et al., Overall management of patients with Dravet syndrome, 53 Developmental Med. & Child Neurology 19-23 (2011).

[75] Pet. Ex. 30-M (McIntosh); see also Resp't Ex. A-1.

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.

In the Harkin article[76] presented by respondent, the authors acknowledged that when there is a truncation mutation in the SCN1A gene, the likelihood of mutation being pathogenic is extremely high.

Here, respondent has established by a preponderance of the evidence that the SCN1A mutation is the sole cause of H.E.F.'s Dravet syndrome and the resulting neurological condition.

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 H.E.F.'s Dravet syndrome/SMEI and neurological injury.

H.E.F. developed Dravet syndrome as a result of her genetic mutation, not because she received vaccinations. According to Dr. Raymond, even assuming that H.E.F. had an earlier onset of her seizure disorder, this would not alter her clinical course or outcome. Tr. 328. As explained by Dr. Sachdeo, "H.E.F. . . . would have followed the same clinical course if she had not received any vaccines." Tr. 263. Dr. Raymond and Dr. Sachdeo rely on the McIntosh and Brunklaus articles, respectively, in support of their proposition.

Dr. Raymond also testified that H.E.F.'s SCN1A mutation is the "sole cause" of her seizure disorder, Dravet syndrome, developmental delay, and all of the other features of Dravet syndrome. Tr. 340. Both Dr. Raymond and Dr. Sachdeo testified that it is not necessary to invoke an environmental factor, like the vaccination, to explain H.E.F.'s condition. Tr. 161.

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. H.E.F.'s alleged injury is her Dravet syndrome and her resulting neurological complications. See Petr's' 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 H.E.F.'s first two seizures. H.E.F. did not manifest the criteria for Dravet syndrome for months after her first seizure, and so there is no temporal relationship between her vaccinations and the onset of her Dravet syndrome. Moreover, H.E.F. had no brain damage after the vaccination at issue. Therefore, while H.E.F. did not have an injury that was temporally associated with the vaccination at issue, her initial seizures were, in hindsight, a suspicious sign that she might develop Dravet syndrome, or the initial manifestation of her genetic mutation. That fact alone does not establish a vaccine-related injury.

Respondent's experts, on the other hand, state that H.E.F.'s clinical course, timing of the onset of her initial seizure and overall outcome were consistent with Dravet syndrome.

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[76] Resp't Ex. C-42, Harkin LE et al., The Spectrum of SCN1A-related infantile epileptic encephalopathies, 130 Brain 843-52, 849 (2007).

Therefore, the undersigned finds by a preponderance of the evidence that respondent has satisfied Althen Prong Three.

V. 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
Chief Special Master